SWOG CANCER RESEARCH NETWORK

May 1, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Mar. 30, 2021	AE-2387207
S1404 Melanoma	Apr. 02, 2021	AE-2807265 FU
S1609 Early Therapeutics	Apr. 08, 2021	AE-2970184
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

May 1, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Apr. 05, 2021	AE-2496602
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		
S2001 Gastrointestinal		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

April 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Mar. 09, 2021	AE-2725769
S1404 Melanoma	Mar. 11, 2021	AE-2168935
S1609 Early Therapeutics	Mar. 12, 2021	AE-2693707
S1616 Melanoma	Mar. 15, 2021	AE-2268658
	Mar. 19, 2021	AE-2617613 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

April 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Mar. 24, 2021	AE-2446105
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		
S2001 Gastrointestinal		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

Distribution Date: April 15, 2021
E-mailed Date: April 2, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) No review required

MEMORANDUM – Rave Charts Un-frozen

S1404 Rave charts will be un-frozen starting Monday, April 5, 2021. New data can be submitted, and outstanding queries can be addressed.

Please email melanomaquestion@crab.org with any questions.

This memorandum serves to notify the NCI, CIRB, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

Distribution Date: March 15, 2021
E-mailed Date: March 10, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) No review required

MEMORANDUM – Rave Charts Freeze

The above-referenced study needs to provide a clean dataset to the FDA. To this end, **S1404** Rave charts will be frozen starting Wednesday March 17, 2021. The only data that will be able to be submitted will be data to resolve outstanding queries. We expect the study to be unfrozen in April 2021.

New disease assessments and follow-up should be held for entry until the study is unfrozen.

Please email melanomaquestion@crab.org with any questions about resolving outstanding queries while the data are frozen.

This memorandum serves to notify the NCI, CIRB, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

March 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Feb. 05, 2021	AE-2186009 FU
S1404 Melanoma	Feb. 10, 2021	AE-2004610
S1609 Early Therapeutics	Feb. 16, 2021	AE-2188184 FU
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

March 1, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Feb. 04, 2021 AE-2858880 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

Distribution Date: February 15, 2021
E-mailed Date: February 8, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) No review required

MEMORANDUM – Database lock

The above-referenced study is quickly approaching a database lock and **all queries must be resolved by Friday, February 26, 2021**.

A weekly list of outstanding database queries will be provided to your site. Expect additional communication from the Statistics and Data Management Center regarding resolution of open queries.

Thank you for your urgent attention to this very important matter.

This memorandum serves to notify the NCI, CIRB, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

February 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma **S1800A** Lung **S1801** Melanoma **S2001** Gastrointestinal	Jan. 20, 2021 AE- 2970905 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

February 1, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jan. 04, 2021 AE-2388240 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

February 1, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Dec. 29, 2020	AE-2317411 FU
S1418/BR006 Breast	Jan. 04, 2021	AE-2575170 FU
S1512 Melanoma	Jan. 06, 2021	AE-2293049
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		
S2001 Gastrointestinal		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

January 15, 2021

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Dec. 07, 2020 AE-2144460 FU
S1404 Melanoma	Dec 15, 2020 AE-2354890 FU
S1609 Early Therapeutics	Dec. 21, 2020 AE-2990378 FU
S1616 Melanoma	Dec. 29, 2020 AE-2515208 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Nov. 19, 2020 AE-2354890

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Oct. 27, 2020	AE-2911487 FU
S1404 Melanoma	Oct. 28, 2020	AE-2736077 FU
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Oct. 27, 2020	AE-2751702 FU
S1418/BR006 Breast	Oct. 30, 2020	AE-2827113 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

November 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Oct. 22, 2020	AE-2728853
S1404 Melanoma	Oct. 22, 2020	AE-2802538 FU
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

November 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Oct. 19, 2020	AE-2673715
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

November 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Sep. 23, 20202 AE-2547521

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

November 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma **S1800A** Lung **S1801** Melanoma	Oct. 05, 2020	AE-2286191 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

October 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Sep. 03, 2020 AE-2916074 FU
S1404 Melanoma	Sep. 16. 2020 AE-2614718 FU
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

October 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Sep. 09, 2020	AE-2751702 FU
S1418/BR006 Breast	Sep. 16, 2020	AE-2587089 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A Lung		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

September 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Aug. 13, 2020	AE-2647268 FU
S1418/BR006 Breast	Aug. 13, 2020	AE-2262472
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

v

SWOG CANCER RESEARCH NETWORK

September 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Aug. 12, 2020	AE-2974719
S1418/BR006 Breast	Aug. 12, 2020	AE-2630992 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

September 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Aug. 12, 2020	AE-2974719
S1418/BR006 Breast	Aug. 12, 2020	AE-2630992 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

August 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Jul. 16, 2020	AE-2616960
S1404 Melanoma	Jul. 16, 2020	AE-2185741 FU
S1609 Early Therapeutics	Jul. 20, 2020	AE-2120164 FU
S1616 Melanoma	Jul. 20, 2020	AE-2662883 FU
	Jul. 27, 2020	AE-2120164 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

July 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jun. 24, 2020 AE-2357373 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

July 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Jun. 12, 2020	AE-2202036 FU
S1418/BR006 Breast	Jun. 25, 2020	AE-2897241 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

July 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	May 28, 2020	AE-2715356 FU
S1418/BR006 Breast	May 28, 2020	AE-2051652 FU
S1512 Melanoma	Jun. 01, 2020	AE-2202036 FU
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

Version Date: June 3, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION # 16

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Other: Additional Translational Medicine

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #16

The above-referenced protocol has been updated as follows to incorporate additional translational medicine details:

1. The Version Dates of the protocol and Model Consent Form have been updated. No additional changes were made to the Model Consent Form

2. Section 1.4 has been updated to include additional translational medicine objectives as outlined in Appendix 18.10.

3. Section 15.3: The URLs to the SWOG Biospecimen Bank have been updated.

4. Appendix 18.9 has been updated to clarify that the first two paragraphs of instructions are general banking information and the third paragraph is related to the translational medicine outlined in Appendix 18.8. Additional instructions have been added related to the translational medicine outlined in Appendix 18.10.

5. Appendix 18.10 has been added to include translational medicine details for ctDNA.

This memorandum serves to notify the NCI, and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Teresa Petrella, M.D. – CCTG
Karen Favata – Merck
Maria Edwards – PPD
TaNisha Evans – PPD

SWOG CANCER RESEARCH NETWORK

July 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	May 28, 2020	AE-2715356 FU
S1418/BR006 Breast	May 28, 2020	AE-2051652 FU
S1512 Melanoma	Jun. 01, 2020	AE-2202036 FU
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

May 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Apr. 23, 2020 AE-2876185

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

May 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Apr. 07, 2020 AE-2501580 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

April 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Mar. 19, 2020 AE-2267633
S1404 Melanoma	Mar. 23, 2020 AE- 2501580
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

April 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Feb. 25, 2020	AE-2204824 FU
S1418/BR006 Breast	Feb. 27, 2020	AE-2335647 FU
S1512 Melanoma	Mar. 9, 2020	AE-2107375
S1607 Melanoma	Mar. 11, 2020	AE-2475477 FU
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

Version Date: February 19, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION # 15

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) IRB Review only

Protocol changes
(√) Other: MK-3475 (pembrolizumab, NSC 776864) CAEPR update
(√) Informed Consent changes
(√) Patient notification required; instructions noted below

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #15

This revision has been prepared in response to an Request for Rapid Amendment (RRA) for MK-3475 (pembrolizumab, NSC 776864) from Dr. Elad Sharon (sharone@mail.nih.gov) received on February 14, 2020. The associated Action Letter for this RRA is attached. The above referenced protocol has been revised as follows:

1. The Version Date has been revised in the Protocol.

2. Section 3.3c: The MK-3475 (pembrolizumab) CAEPR has been updated to Version 2.5, December 27, 2019 as follows:

   Added New Risk
   - Rare but serious: Eye disorders - Other (Vogt-Koyanagi-Harada syndrome); Nervous system disorders - Other (non-infectious myelitis)

Model Consent Form Changes

1. The version date has been updated.

2. The MK-3475 (pembrolizumab) risk profile date has been updated to CAEPR Version 2.5, December 27, 2019.

3. Possible Side effects of MK-3475 (pembrolizumab) updates:

Added New Risk Rare, and Serious:

- **A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss**
- **Swelling of the spinal cord**

Provided further clarification:

- **A note was added, "Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time."**

Please note that the information provided below regarding patient notification and amendments to local consent forms reflect SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

Patient Notification and use of Consent Addendum:

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes.

Who must be informed?

- Patients currently receiving treatment with MK-3475 (pembrolizumab)

How must patients be notified?

- Notification must take place either via the attached Consent Addendum or via formal reconsent. After the change has been discussed with the patient, the patient must sign and date either the Consent Addendum or the *2/19/2020* version of the consent form.

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.

- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.

- Sites not using the NCI CIRB as their IRB of record: If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- It depends. If your site will utilize formal reconsent then local consent forms must be updated. If your site will not utilize formal reconsent then local consent forms need not be updated.

This study has been reviewed and approved by the NCI's Central Institutional Review Board (CIRB).

This memorandum serves to notify the NCI, and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **March 26, 2020**

FROM: Elad Sharon, MD, MPH, MD, Medical Officer, IDB, CTEP, DCTD, NCI
Jeffrey Moscow, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, Acting Associate Director, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for MK-3475 (pembrolizumab, NSC 776864)

TO: Investigators for CTEP-supported Studies Involving MK-3475 (pembrolizumab, NSC 776864)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with MK-3475, and to request all trials with MK-3475 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes MK-3475. See the accompanying list of CTEP trials with MK-3475.

In response to the new/modified risk information CTEP is requiring that all trials with MK-3475 be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on April 9, 2020** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Elad Sharon (sharone@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since MK-3475 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-29-2008-letter-to-dr-jeffrey-abrams/index.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

Action Letter

CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with MK-3475.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.5, December 27, 2019): ___
   Page Number(s): ____

   - Added New Risk:
     - Rare but Serious: Eye disorders - Other (Vogt-Koyanagi-Harada syndrome); Nervous system disorders - Other (non-infectious myelitis)

   PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.5, and associated risk information for the ICD, to the most recent CAEPR Version 2.4. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.4), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

- Added New Risk:
  - Rare: A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss; Swelling of the spinal cord

Action Letter

- Provided Further Clarification:
    - A note was added, "Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time."

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to MK-3475 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised MK-3475 CAEPR – Version 2.5, December 27, 2019

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 27, 2019[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your

name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for MK-3475

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes. Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 in your ICD.

Risk Profile for MK-3475 (pembrolizumab) (CAEPR Version 2.5, December 27, 2019)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: November 2018) will include the wording below:

"If you choose to take part in this study, there is a risk that the MK-3475 (pembrolizumab) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The MK-3475 (pembrolizumab) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 (pembrolizumab) in your ICD.

Action Letter

COMMON, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:

- Nausea
- Infection
- Loss of appetite
- Pain in back
- Joint stiffness
- Cough
- Swelling and redness of the skin

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Anemia which may require blood transfusion
- Pain in lymph nodes
- Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Pain in belly
- Sores in the bowels
- Chills, fever
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Fluid in the joints
- Pain in chest
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:

Action Letter

- A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss
- Swelling of the spinal cord
- Feeling of "pins and needles" in arms and legs
- Redness, pain or peeling of palms and soles

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body
- Swelling and redness of the eye
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin
- Damage to organs in the body when the body produces too many white cells
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs
- Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling
- Swelling or tenderness of blood vessels

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **For Lead Organizations, distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does <u>not</u> already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. The condensed risk profile is provided as guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. <u>Trials with a current CTEP status of **"Active"**</u>
   - Review and follow **<u>ALL</u>** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **<u>ONLY</u>** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment",** or **"Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG CANCER RESEARCH NETWORK

March 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Jan. 29, 2020 AE-2698260
S1404 Melanoma	Feb. 12, 2020 AE-2429564
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

March 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Feb. 26, 2020	AE-2385638 FU
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

March 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab (BMS-734016). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Jan. 28, 2020 AE- 2065903 FU
S1404 Melanoma	Jan. 29, 2020 AE- 2498627 FU
S1609 Early Therapeutics	Feb. 05, 2020 AE-2645695 FU
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

March 1, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma **S1800A** LungMap **S1801** Melanoma	Jan. 28, 2020	AE- 2137370 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

February 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Jan. 23, 2020 AE-2498627
S1404 Melanoma	Jan. 23, 2020 AE-2451202 FU
S1609 Early Therapeutics	Jan. 29, 2020 AE-2352376 FU
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

February 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Jan. 09, 2020	AE- 2866604 FU
S1418/BR006 Breast	Jan. 21, 2020	AE- 2291774 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

January 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Oct. 23, 2019 AE-2643876 FU
S1404 Melanoma	Dec. 10, 2019 AE- 2419396 FU
S1609 Early Therapeutics	Dec. 11, 2019 AE-2204017
S1616 Melanoma	Dec. 17, 2019 AE-2689454
	Dec. 18, 2019 AE-2966894
	Dec. 27, 2019 AE-2419396 FU
	Dec. 27, 2019 AE-2765584

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

January 15, 2020

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Dec. 17, 2019	AE- 2958164
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

Version Date: November 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: SWOG Operations Office (protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION # 14

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/213-8435
E-mail: S1404SCquestion@swog.org

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) IRB review only

Protocol changes
(√) Dose Modification changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #14

This revision has been prepared in response to the Request for Amendment (RA) from Dr. Elad Sharon (sharone@mail.nih.gov), dated October 15, 2019. The dose modification and toxicity management section for MK-3475 has been revised with information provided by the pharmaceutical collaborator. There will not be an action letter associated with this revision.

The above-referenced study has been updated as follows:

1. The Version Date of the protocol has been updated.

2. Section 8.4 Table 1: The MK-3475 (pembrolizumab) Dose Modification and Toxicity Management table has been replaced.
   a. General instructions were updated for clarification.
   b. Pneumonitis: The prophylactic antibiotics were moved from the monitoring column to the corticosteroid column.
   c. Nephritis: the toxicity title has been updated.
   d. Myocarditis: the toxicity title has been updated. The myocarditis grades, action, therapies, and monitoring have been simplified.
   e. All other immune-related AEs: Grade 3, or intolerable/persistent Grade 2 has been split to include different actions.
   f. Grade 4 toxicity for Diarrhea/Colitis was updated to Recurrent Grade 3 or Grade 4 toxicity.
   g. Footnote a-c: AST/ ALT grading definitions have been added.
   h. Footnote d: Clarification for the decision to withhold or permanently discontinue based on specific toxicities have been added.
   i. Footnote e: Guillain-Barre Syndrome, encephalitis, etc. events have been added as events that require discontinuation of MK-3475.

3. Section 8.4b, management of infusion reactions (formally: supportive care guidelines): this section has been deleted except for the management of infusion reactions. The supportive care guidelines are summarized in the new table in section 8.4a, Table 1. This section has been re-titled.

Model Consent Forms Changes

The version date has been updated. No other changes were made to the Model Consent Form.

This memorandum serves to notify the NCI, CIRB, and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

December 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Nov. 13, 2019 AE- 2535067 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Nov. 13, 2019	AE-2103794 FU
S1418/BR006 Breast	Nov. 18, 2019	AE-2305170 FU
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

December 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Nov. 01, 2019	AE- 2712465 FU
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

November 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Oct. 11, 2019	AE-2643876
S1404 Melanoma	Oct. 23, 2019	AE-2893320
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

November 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Sep. 30, 2019	AE 2169620 FU
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Dragnev, M.D.

SWOG CANCER RESEARCH NETWORK

October 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Sep. 20, 2019	AE-2302200 FU
S1418/BR006 Breast		
S1512 Melanoma		
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

October 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Aug. 28, 2019 AE- 2708319 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

September 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Aug. 21, 2019	AE-2708319 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

September 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Aug. 20, 2019	AE-2025089 FU
S1418/BR006 Breast	Aug. 20, 2019	AE-2129377 FU
S1512 Melanoma	Aug. 20, 2019	AE-2419922 FU
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

September 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Aug. 06, 2019	AE-2998486
S1404 Melanoma	Aug. 09, 2019	AE-2723343
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

Version Date: July 9, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #13

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #13

The above-referenced protocol has been updated as follows:

1. The Version Dates of the protocol and Model Consent Form have been updated.
2. Title Page: Dr. Grossmann's contact information has been updated.
3. Section 1.4 has been added as a translational medicine objective for banked tissue.
4. Section 9.1: The calendar footnote "d" has been updated to clarify "Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization".
5. Section 9.2: The calendar footnote "d" has been updated to clarify "Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization".
6. Section 9.3: The calendar footnote "d" has been updated to clarify "Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization".
7. Section 11.7.g: Added link to Section 18.8 for translational medicine details.
8. Section 15: The name of the Lab #201 has been corrected throughout.
9. Section 15: The URL for the specimen submission guidelines has been updated throughout.
10. Section 18.8 has been added for translational medicine on banked specimens.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Teresa Petrella, M.D. – CCTG
Karen Favata – Merck
Maria Edwards – PPD
TaNisha Evans – PPD

SWOG CANCER RESEARCH NETWORK

August 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jul. 09, 2019	AE-2788193 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

August 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma **S1800A** LungMap **S1801** Melanoma	Jul. 25, 2019	AE-2663946 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

August 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Jul. 02, 2019	AE-2052014 FU
S1404 Melanoma	Jul. 05, 2019	AE-2513425
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

August 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma **S1800A** LungMap **S1801** Melanoma	Jul. 12, 2019	AE-2947697 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

SWOG CANCER RESEARCH NETWORK

July 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jun. 12, 2019	AE-2178734 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

July 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Jun. 17, 2019	AE-2858668 FU
S1418/BR006 Breast	Jun. 19, 2019	AE-2242041 FU
S1512 Melanoma	Jun. 20, 2019	AE-2129377 FU
S1607 Melanoma		
S1800A LungMap		
S1801 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen L. Reckamp, M.D.
Konstantin H. Drognev, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

July 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jun. 07, 2019	AE-2305711 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

Distribution Date: July 1, 2019
E-mailed Date: June 21, 2019
Version Date: May 20, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma" Study Chairs: Drs. K.F. Grossmann and S.P. Patel

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to correct the patient notification requirements previously distributed with the Revision #12 (Version Date: 5/20/19) cover memorandum which was created in association with the Ipilimumab RRA received on May 8, 2019 from Dr. Howard Streicher and distributed on June 12, 2019. Additionally, instructions for consent amendment have been included below as they were not included in the Revision #12 cover memorandum.

Patient Notification:

Patients must be notified of the following **bolded** clarification to the Rare, and Serious Ipilimumab risks section.

> The previously included risk, "Swelling of the brain which may cause headache, blurred vision, stiff neck and/or confusion" (under Rare, and Serious) is now reported as **"Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck"** (under Rare, and Serious) and is now part of the "Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:" subsection.

Who must be informed?

- All patients who have been consented to the study and are currently receiving treatment with Ipilimumab (BMS-734016, MDX-010, YERVOY®).

How must patients be notified?

- Patients may be notified verbally, including notification via telephone. Documentation of notification must be maintained in the patient's chart.

What is the notification deadline and process?

- For patients currently receiving treatment with Ipilimumab (BMS-734016, MDX-010, YERVOY®):
  - Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.

-
    - Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.

Regulatory Considerations:

Do local consent forms need to be updated?

- Yes, local consent forms must be updated to include all the changes in this revision.

Please note that the information provided above regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

This memorandum serves to notify the NCI, CIRB, and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

Version Date: May 20, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase II Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma" Study Chairs: Drs. K.F. Grossmann and S.P. Patel

REVISION #12

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes

(√) Other: CAEPR Update for Ipilimumab
(√) Informed Consent changes
(√) Patient notification not required

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice. The protocol and informed consent form changes have been approved by the CIRB.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #12

S1404 has been revised with the following changes in response to the Rapid Request for Amendment (RRA) received on May 8, 2019 from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). The associated action letter is attached.

The above-referenced study has been updated as follows:

1. The Version Dates of the protocol have been updated.

2. **Section 3.2.c, Ipilimumab (MDX-010, NSCs 732442 and 720801)**: A revised CAEPR (Version 2.10, March 29, 2019) has been inserted.

Added New Risk:

- Rare but Serious: Nervous system disorders – Other (immune-mediated encephalitis)

Increase in Risk Attribution:

- Changed to Rare but Serious from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Peripheral motor neuropathy; Peripheral sensory neuropathy

Model Consent Forms Changes

1. The Version Dates of the consent have been updated.

2. **"What possible risks…"**: The following changes were made to the Ipilimumab risk section:

   Rare, and Serious Side Effects: "Swelling of the brain which may cause headache, blurred vision, stiff neck and/or confusion (under Rare) is now reported as Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck (under Rare) and is now part of the "Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:"

This memorandum serves to notify the NCI, CIRB and SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Teresa Petrella, M.D. – CCTG
Karen Favata – Merck
Maria Edwards – PPD
TaNisha Evans – PPD

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **June 20, 2019**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
Jeffrey Moscow, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Ipilimumab (MDX-010, NSCs 732442 and 720801)

TO: Investigators for CTEP-supported Studies Involving Ipilimumab (MDX-010, NSCs 732442 and 720801)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with ipilimumab, and to request all trials with ipilimumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes ipilimumab. See the accompanying list of CTEP trials with ipilimumab.

In response to the new/modified risk information CTEP is requiring that all trials with ipilimumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on July 8, 2019** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since ipilimumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/september-29-2008-letter-to-dr-jeffrey-abrams/index.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

Action Letter

CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with ipilimumab.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.10, March 29, 2019): ___
   Page Number(s): ____

   - Added New Risk:
     - Rare but Serious: Nervous system disorders - Other (immune-mediated encephalitis)

   - Increase in Risk Attribution:
     - Changed to Rare but Serious from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Peripheral motor neuropathy; Peripheral sensory neuropathy

   PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.10, and associated risk information for the ICD, to the most recent CAEPR Version 2.9. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.9), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

- Provided Further Clarification:
  - Swelling of the brain which may cause headache, blurred vision, stiff neck and/or confusion (under Rare) is now reported as Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck (under Rare) and is now part of the

Action Letter

"Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:"

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to ipilimumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Ipilimumab CAEPR – Version 2.10, March 29, 2019

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders - Other (immune-mediated encephalitis)[2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis,

iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for Ipilimumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes. Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab in your ICD.

Risk Profile for Ipilimumab (MDX-010) (CAEPR Version 2.10, March 29, 2019)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: November 2018) will include the wording below:

"If you choose to take part in this study, there is a risk that the ipilimumab (MDX-010) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The ipilimumab (MDX-010) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab (MDX-010) in your ICD.

Action Letter

Special precautions

Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:

Action Letter

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Confusion

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **For Lead Organizations, distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. The condensed risk profile is provided as guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment",** or **"Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG CANCER RESEARCH NETWORK

June 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	May 31, 2019	AE-2944611 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

June 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	May 21, 2019	AE-2169620 FU
S1418/BR006 Breast	May 24, 2019	AE-2989414 FU
S1512 Melanoma		
S1607 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

June 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Apr. 05, 2019	AE-2836139 FU
S1404 Melanoma	Apr. 25, 2019	AE-2587940 FU
S1609 Early Therapeutics	May 03, 2019	AE-2944611 FU
S1616 Melanoma	May 09, 2019	AE-2305711 FU
	May 14, 2019	AE-2494886 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

May 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Apr. 08, 2019	AE-2587940 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

April 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Mar. 25, 2019	AE-2085434 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

April 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Mar. 05, 2019	AE-2412891 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

April 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Mar. 05, 2019 AE-2205053 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

March 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Feb. 19, 2019 AE-2470874 FU
S1404 Melanoma	
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

March 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Jun. 26, 2018 Mfr Rpt #BMS-2017111224 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

February 15, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Jan. 15, 2019 AE-2080327
S1404 Melanoma	Jan. 22, 2019 AE-2425241 FU
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

February 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma	Jan. 17, 2019 AE-2954772 FU
S1418/BR006 Breast	Dec. 06, 2019 Mfr Rpt #1811USA003686 FU
S1512 Melanoma	
S1607 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

February 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Jun. 26, 2018	Mfr Rpt #BMS-2017111224 FU
S1404 Melanoma	Jul. 30, 2018	Mfr Rpt #BMS-21619580 FU
S1609 Early Therapeutics	Jan. 03, 2019	AE-2425241
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

February 1, 2019

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1404 Melanoma	Dec. 27, 2018	AE-2601682 FU
S1418/BR006 Breast	Dec. 31, 2018	AE-2954722 FU
S1512 Melanoma	Jan. 04, 2019	AE-2601682 FU
S1607 Melanoma	Jan. 04, 2019	AE-2954722 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG CANCER RESEARCH NETWORK

December 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Apr. 16, 2018	Mfr Rpt #BMS2017099064
S1404 Melanoma	Apr. 24, 2018	Mfr Rpt #BMS2017091143 FU
S1609 Early Therapeutics	May 11, 2018	Mfr Rpt #BMS2018035494 FU
S1616 Melanoma	Jun. 14, 2018	Mfr Rpt #BMS2018049605 FU
	Jun. 21, 2018	Mfr Rpt #BMS2017117354
	Jul. 02, 2018	Mfr Rpt #BMS2017088997 FU
	Jul. 03, 2018	Mfr Rpt #BMS2017008679 FU
	Jul. 06, 2018	Mfr Rpt #BMS2018052322 FU
	Aug. 24, 2018	Mfr Rpt #BMS2018071877 FU
	Aug. 31, 2018	Mfr Rpt #BMS2018072797 FU
	Sep. 19, 2018	Mfr Rpt #BMS-2018-078274 FU
	Sep. 21, 2018	Mfr Rpt #BMS2016091741
	Sep. 27, 2018	Mfr Rpt #BMS2018078883 FU
	Oct. 15, 2018	Mfr Rpt #BMS2018080341 FU
	Nov. 15, 2018	Mfr Rpt #AE-2409432 FU
	Nov. 20, 2018	AE-2464891 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Nov. 27, 2018 AE-2191532 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

December 1, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Apr. 18, 2018	Mfr Rpt #BMS-2018-032073
S1404 Melanoma	Apr. 19, 2018	Mfr Rpt #BMS2018025193 FU
S1609 Early Therapeutics	Oct. 25, 2018	AE-2625513 FU
S1616 Melanoma	Nov. 01, 2018	AE-2502278
	Nov. 06, 2018	AE-2100412
	Nov. 07, 2018	AE-2261176 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG CANCER RESEARCH NETWORK

December 1, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Nov. 02, 2018 AE-2712465 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

Version Date: October 10, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #11

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #11

The above-referenced protocol has been updated as follows:

1. The Version Dates of the protocol and Model Consent Form have been updated.

2. Section 11.5: In Table 6, the interim efficacy alpha level has been corrected from "0.009%" to "0.09%." This change is being made to correct a typographical error; there are no changes to the statistical information or design.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Teresa Petrella, M.D. – CCTG
Karen Favata – Merck
Maria Edwards – PPD
TaNisha Evans – PPD

SWOG CANCER RESEARCH NETWORK

November 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Oct. 17, 2018	AE-2625513 FU
S1404 Melanoma	Oct. 26, 2018	AE-2168260 FU
S1609 Early Therapeutics	Oct. 26, 2018	AE-2766447 FU
S1616 Melanoma	Oct. 31, 2018	AE-2186834 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

November 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Oct. 18, 2018 AE-2171964 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

November 1, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Sep. 27, 2018	AE-2766447 FU
S1404 Melanoma	Oct. 04, 2018	AE-2712450
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

October 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):	
S1400I Lung	Sep. 19, 2018	AE-2885110 FU
S1404 Melanoma	Sep. 24, 2018	AE-2337387
S1609 Early Therapeutics	Sep. 26, 2018	AE-2293643
S1616 Melanoma	Sep. 26, 2018	AE-2507891 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG CANCER RESEARCH NETWORK

October 15, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug MK-3475 (Pembrolizumab). Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1404 Melanoma	Mar.12, 2018 Mfr Rpt #1608LVA015694 FU
S1418/BR006 Breast	Apr. 03, 2018 Mfr Rpt #1610USA011750 FU
S1512 Melanoma	Apr. 12, 2018 Mfr Rpt #1509AUS005583 FU
S1607 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

4201 Medical Drive, Suite 250 | San Antonio, TX 78229 | OFFICE 210-614-8808 | FAX 210-614-0006

SWOG
Leading cancer research. Together.

Distribution Date: October 15, 2018
E-mailed Date: October 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to notify sites that S1404 is beginning the process to conduct an interim analysis of relapse-free survival. SWOG is requesting all sites to provide up-to-date follow-up via Rave and report any new relapses ASAP.

Please contact the Data Operations Office at melanomaquestion@crab.org if there are any questions or concerns on these submissions.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

October 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung	Sep. 05, 2018 AE-2851606 FU
S1404 Melanoma	Sep. 07, 2018 AE-2640851 FU
S1609 Early Therapeutics	Sep. 10, 2018 AE-2640851 FU
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

September 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report(s) have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access the safety report(s) via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

The safety report(s) pertain to the following study(ies):	Report(s):
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Aug. 29, 2018 AE-2116657

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in the report(s) if it is deemed necessary by your institution. Please append this notice and the report(s) to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

Distribution Date: September 15, 2018
E-mailed Date: September 12, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to notify sites that **S1404** is beginning the process to conduct an interim analysis of relapse-free survival. SWOG is requesting all sites to provide up-to-date follow-up via Rave and report any new relapses ASAP.

Please contact the Data Operations Office at melanomaquestion@crab.org if there are any questions or concerns on these submissions.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

September 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Aug. 02, 2018 AE-2579327 FU
S1404 Melanoma	Aug. 08, 2018 AE-2334160
S1609 Early Therapeutics	Aug. 15, 2018 AE-2664942 FU
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

September 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drugs MK-3475 (Pembrolizumab). Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Apr. 26, 2018 Mfr Rpt #1606USA006127 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Version Date: July 31, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #10

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
(√) Patient notification required: : See instructions below.
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #10

This revision has been prepared in response to the Request for Rapid Amendment (RRA)
received on July 17, 2108 and July 27, 2018 from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov, Dr. Jeffrey Moscow (jeffrey.moscow@nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov). The associated Action Letter is attached.

The following changes have been to the protocol and consent:

1. Title Page: The version dates of the protocol and model consent form have been updated.

2. Section 3.2.c: The CAEPR has been updated as follows:

- Added New Risk:
  - **Rare But Serious: Ataxia; General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS]); Generalized muscle weakness; Lymphocyte count decreased; Pericardial effusion; Psychiatric disorders - Other (mental status changes); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)**
  - Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Colonic ulcer; Gastrointestinal disorders - Other (gastroenteritis); Proctitis; Tumor lysis syndrome

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Weight loss

- Provided Further Clarification:
  - Endocrine disorders - Other (hypophysitis/ hypopituitarism) (CTCAE 4.0 language) is now reported as Hypophysitis and Hypopituitarism.
  - Endocrine disorders - Other (testosterone deficiency) (CTCAE 4.0 language) is now reported as Testosterone deficiency.
  - Nervous system disorders - Other (Guillian-Barre syndrome) (CTCAE 4.0 language) is now reported as Guillian-Barre syndrome.
  - Nervous system disorders - Other (myasthenia gravis) (CTCAE 4.0 language) is now reported as Myasthenia gravis.
  - Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC (CTCAE 4.0 language), is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.

3. Section 8.0: References to CTCAE version 4.0 have been changed to version 5.0.

4. The Model Consent Form has been updated as follows, under the section "What possible risks can I expect from taking part in this study?", possible side effects of Ipilimumab"

Added New Risk:

1. **Occasional: Difficulty eating**
2. **Rare: Severe illness with multiorgan failure; Fluid around heart; Confusion**

Increase in Risk Attribution:

3. **Changed to Occasional from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Weight loss**

Provided Further Clarification:

4. Pain in belly (under Occasional) is now reported as Pain (under Occasional).
5. Constipation (under Occasional) was previously reported as part of Blockage of the bowels which may cause constipation (under Rare).
6. Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional) is now reported as Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional).

7. Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare) is now reported as Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

Patient Notification and use of Consent Addendum:

SWOG has determined that the changes above that are **bolded** may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes. Notification must take place either via the attached Consent Addendum or via formal reconsent. After the changes have been discussed with the patient, the patient should sign and date either the Consent Addendum or 7/31/18 version of the consent form.

Who must be informed?

- Patients currently receiving drug/intervention; or
- All patients who have been registered to the study and received treatment with ipilimumab

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner.
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: This information should be communicated to patients already enrolled on study without waiting for IRB review/approval. This information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation. Per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- Local consent form must be updated only if the site plans to use the consent form rather than the Consent Addendum for the re-consent process.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE Karen Favata – Merck

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **August 30, 2018**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
Jeffrey Moscow, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Ipilimumab (MDX-010, NSCs 732442 and 720801)

TO: Investigators for CTEP-supported Studies Involving Ipilimumab (MDX-010, NSCs 732442 and 720801)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with ipilimumab, and to request all trials with ipilimumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes ipilimumab. See the accompanying list of CTEP trials with ipilimumab.

In response to the new/modified risk information CTEP is requiring that all trials with ipilimumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on September 13, 2018** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since ipilimumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

Action Letter

CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with ipilimumab.

In addition, as part of the implementation of version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE), the CAEPR list for ipilimumab, which was previously in CTCAE 4.0 language, has been migrated to CTCAE 5.0 language. However, there is no new or modified risk information for this agent other than what is outlined under the Specific Amendment Instructions section of this Action Letter.

Any reference to CTCAE 4.0 for adverse event reporting should also be updated to reference CTCAE 5.0 in the protocol amendment.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.9, December 20, 2017): ___
   Page Number(s): ____

   • The section below utilizes CTCAE 5.0 language unless otherwise noted.

- Added New Risk:
  - Rare But Serious: Ataxia; General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS]); Generalized muscle weakness; Lymphocyte count decreased; Pericardial effusion; Psychiatric disorders - Other (mental status changes); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)
  - Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Colonic ulcer; Gastrointestinal disorders - Other (gastroenteritis); Proctitis; Tumor lysis syndrome

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Weight loss

- Provided Further Clarification:
  - Endocrine disorders - Other (hypophysitis/ hypopituitarism) *(CTCAE 4.0 language)* is now reported as Hypophysitis and Hypopituitarism.

- Endocrine disorders - Other (testosterone deficiency) *(CTCAE 4.0 language)* is now reported as Testosterone deficiency.
- Nervous system disorders - Other (Guillian-Barre syndrome) *(CTCAE 4.0 language)* is now reported as Guillian-Barre syndrome.
- Nervous system disorders - Other (myasthenia gravis) *(CTCAE 4.0 language)* is now reported as Myasthenia gravis.
- Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC *(CTCAE 4.0 language)*, is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.9, and associated risk information for the ICD, to the most recent CAEPR Version 2.8. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.8), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

- Added New Risk:
  - Occasional: Difficulty eating
  - Rare: Severe illness with multiorgan failure; Fluid around heart; Confusion

- Increase in Risk Attribution:
  - Changed to Occasional from Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Weight loss

- Provided Further Clarification:
  - Pain in belly (under Occasional) is now reported as Pain (under Occasional).
  - Constipation (under Occasional) was previously reported as part of Blockage of the bowels which may cause constipation (under Rare).
  - Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional) is now reported as Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional).
  - Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare) is now reported as Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).

Action Letter

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to ipilimumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Ipilimumab (MDX-010) CAEPR – Version 2.9, December 20, 2017

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.9, December 20, 2017[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre

syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for Ipilimumab (MDX-010)

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes. Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab in your ICD.

Risk Profile for Ipilimumab (MDX-010) (CAEPR Version 2.9, December 20, 2017)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: October 2017) will include the wording below:

"If you choose to take part in this study, there is a risk that the ipilimumab (MDX-010) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The ipilimumab (MDX-010) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for Ipilimumab (MDX-010) in your ICD.

Action Letter

Special precautions
Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:

- Diarrhea, nausea
- Tiredness

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain
- Difficulty swallowing, eating
- Constipation, vomiting
- Weight loss, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.

- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

RARE, AND SERIOUS

In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Fluid around heart
- Severe illness with multiorgan failure
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion
- Confusion

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **For Lead Organizations, distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does <u>not</u> already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. The condensed risk profile is provided as guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. <u>Trials with a current CTEP status of **"Active"**</u>
   - Review and follow **<u>ALL</u>** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **<u>ONLY</u>** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG
Leading cancer research. Together.

August 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view the study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 03, 2018	Mfr Rpt #BMS2018025138 FU
S1404 Melanoma	Apr. 06, 2018	Mfr Rpt #BMS2018022896
S1609 Early Therapeutics	Apr. 10, 2018	Mfr Rpt #BMS2018014856
S1616 Melanoma	May 25, 2018	Mfr Rpt #BMS2018036045 FU
	May 25, 2018	Mfr Rpt #BMS2018044546
	Jul. 17, 2018	AE-2526855 FU
	Jul. 17, 2018	AE-2558282 FU
	Jul. 17, 2018	AE-2878901 FU
	Jul. 26, 2018	AE-2565135

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

August 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 13, 2018	Mfr Rpt #BMS2018027259
S1404 Melanoma	Apr. 27, 2018	Mfr Rpt #BMS2018003879 FU
S1609 Early Therapeutics	May 04, 2018	Mfr Rpt #BMS2018036536
S1616 Melanoma	May 09, 2018	Mfr Rpt #BMS2017117648 FU
	May 11, 2018	Mfr Rpt #BMS2018027560
	May 11, 2018	Mfr Rpt #BMS2018035494 FU
	May 21, 2018	Mfr Rpt #BMS2016109474 FU
	Jun. 07, 2018	Mfr Rpt #BMS2018045746 FU
	July 02, 2018	AE-2473827
	July 03, 2018	AE-2689539 FU
	July 09, 2018	AE-2141288 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

August 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drugs MK-3475 (Pembrolizumab). Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following studies:	Report:	
S1404 Melanoma	Jun. 28, 2018	AE-2976085 FU
S1418/BR006 Breast	July 09, 2018	AE-2033622 FU
S1512 Melanoma		
S1607 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

July 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 16, 2018	Mfr Rpt #21474036 FU
S1404 Melanoma	Apr. 20, 2018	Mfr Rpt #BMS2018033076 FU
S1609 Early Therapeutics	May 11, 2018	Mfr Rpt #BMS2017102388 FU
S1616 Melanoma	May 18, 2018	Mfr Rpt #BMS2018032663 FU
	Jun. 14, 2018	AE-2717621 FU
	Jun. 20, 2018	AE-2966434 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

July 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse events that occurred in association with the drugs MK-3475 (Pembrolizumab). Please access this safety report via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Jun. 21, 2018 AE-2712465 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

July 1, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

Protocol changes
(√) Data Submission / Forms changes

MEMORANDUM

The purpose of this memorandum is to inform sites of an update to the Master Forms set.

The following changes have been made to the following forms:

- **Adjuvant Melanoma Follow-up** The instructions have been updated to state "please submit at protocol-specified intervals after patient comes off treatment"
- **S1404** Adverse Events: Assessment has been updated to add 3 new bullet points in the instructions.
- **S1404 Baseline Laboratory Values** has added the Thyroid (T3, TSH, T4), and triglycerides to the form.
- **S1404** Disease Assessment Changed the date question to "Date of last disease assessment, or if no disease assessment was done, date of planned disease assessment"
- **S1404** Laboratory Values Added "Report ALL labs performed during this reporting period, including unscheduled labs." to the instructions and a new field was added to the paper form.
- **S1404** Onstudy: Laboratory Values, Albumin, Glucose, Sodium, Potassium, Bicarbonate (HCO3), and CO2 were added.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

June 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	May 22, 2018 AE-2350448 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

June 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475 (Pembrolizumab)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475 (Pembrolizumab). Please access this safety report via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	May 21, 2018 AE-2717115 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

swog.org

SWOG
Leading cancer research. Together.

June 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fair[illegible]
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	May 04, 2018 AE-2518803

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

Version Date: May 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) PARTICIPANTS

FROM: Danae Campos, Protocol Coordinator (dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #9

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Informed Consent changes
(√) Patient notification required (See instructions below)
(√) Other: Updated CAEPR

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #9

This revision has been prepared in response to the Request for Rapid Amendment (RRA) received on April 26, 2018 from Dr. Elad Sharon (sharone@mail.nih.gov). The associated Action Letter is attached.

The above-referenced study has been updated as follows:

1. The Version Date of the protocol and Model Consent has been updated.

2. Table of Contents: The page numbers have been updated.

3. **Section 3.3.c**: A revised CAEPR (Version 2.4, March 16, 2018) was inserted.

- Added New Risk:
  - Less Likely: Immune system disorders - Other (sarcoidosis)

- Rare but Serious: Immune system disorders - Other (acute graft-versus-host-disease); Metabolism and nutrition disorders - Other (diabetic ketoacidosis); Metabolism and nutrition disorders - Other (type 1 diabetes mellitus); Nervous system disorders - Other (non-infectious encephalitis); Nervous system disorders - Other (non-infectious meningitis); Palmar-plantar erythrodysesthesia syndrome

- Increase in Risk Attribution:
  - Changed to Less Likely from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Abdominal pain; Back pain; Cough; Hyponatremia

- Provided Further Clarification:
  - Footnotes have been reordered.
  - Footnote #2 has been updated and now reads: "Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care."
  - Footnote #3 has been added and reads: "Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants."
  - Thrombotic thrombocytopenic purpura, previously listed under the IMMUNE SYSTEM DISORDERS SOC (CTCAE 4.0 language), is now listed under the BLOOD AND LYMPHATIC SYSTEM DISORDERS SOC.
  - Endocrine disorders - Other (hypophysitis, hypopituitarism) (CTCAE 4.0 language) is now reported as Hypophysitis and Hypopituitarism.
  - Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC (CTCAE 4.0 language), is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.
  - Nervous system disorders - Other (Guillain-Barre syndrome) (CTCAE 4.0 language) is now reported as Guillain-Barre syndrome.
  - General disorders and administration site conditions - Other (generalized edema) (CTCAE 4.0 language) is now reported as Generalized edema
  - Renal and urinary disorders - Other (nephrotic syndrome) (CTCAE 4.0 l*anguage)* is now reported as Nephrotic syndrome

4. The following changes were made to the MK-3475 risk section on pages 13-15 of the model consent form.

- **Added New Risk:**
  - **Occasional: Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness**
  - **Rare: Feeling of "pins and needles" in arms and legs; Redness, pain or peeling of palms and soles; Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin; Damage to organs in the body when the body produces too many white cells; A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma; Inflammation of the brain**

(encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck

- **Increase in Risk Attribution:**
  - **Changed to Occasional from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain in back; Cough**

- **Decrease** in Risk Attribution:
  - Changed to Rare from Occasional: Reaction during or following a drug infusion which may cause fever, chills, rash

- **Provided** Further Clarification:
  - "Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional) is now reported as "Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional).

Please note that the information provided below regarding patient notification and amendments to local consent forms reflects SWOG's minimum requirements. Sites should refer to the policies/procedures of the IRB of record to determine whether they have any more stringent requirements.

Patient Notification and use of Consent Addendum:

SWOG has determined that the changes above that are bolded may affect a patient's willingness to participate in the study; therefore, SWOG requires that patients be notified of these changes. Notification must take place either via the attached Consent Addendum or via formal reconsent. After the changes have been discussed with the patient, the patient should sign and date either the Consent Addendum or the 5/1/18 version of the consent form.

Who must be informed?

- Patients currently receiving MK-3475

What is the notification deadline and process?

- Patients must be notified by their next scheduled visit or within 90 days after CTSU distribution of this revision, whichever is sooner
- Sites using the NCI CIRB as their IRB of record: CIRB has approved the attached Consent Addendum; therefore, the Consent Addendum may be utilized immediately to notify patients of these changes.
- Sites not using the NCI CIRB as their IRB of record: This information should be communicated to patients already enrolled on study without waiting for IRB review/approval. This information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation. Per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. If local IRB approval of the Consent Addendum is required before sites may utilize it, the site must still notify patients verbally prior to the notification deadline and notification must be documented in the patient chart. The site must then obtain patient signature on the Consent Addendum or updated consent form once the addendum and/or revised consent is locally approved.

Regulatory Considerations:

Do local consent forms need to be updated?

- It depends. If your site will use the consent addendum rather than reconsenting patients, you do not need to update your local consent.

An entire replacement protocol is attached. Please discard any previous versions of the protocol and attach this memorandum to the front of your copy of **S1404.**

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

Informed Consent Addendum Model for S1404

S1404 "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel."

The following information should be read as an update to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated below, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The following new risks have been identified:

- **Added New Risk**:
  - **Occasional**: **Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness**
  - **Rare:** **Feeling of "pins and needles" in arms and legs; Redness, pain or peeling of palms and soles; Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin; Damage to organs in the body when the body produces too many white cells; A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma; Inflammation of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck**

The following risks have been found to occur more often than originally thought:

- **Increase in Risk Attribution:**
  - **Changed to Occasional from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile):** **Pain in back; Cough**

Patient Signature and Date

By signing this form, I acknowledge that I have read the information above or had it read to me. I have discussed it with a member of the study team and my questions have been answered. I understand that I will be given a copy of this form.

Participant's signature_____

Date of signature_____

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **May 24, 2018**

FROM: Elad Sharon, MD, MPH, Medical Officer, IDB, CTEP, DCTD, NCI
Jeffrey Moscow, MD, Acting Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for MK-3475 (pembrolizumab, NSC 776864)

TO: Investigators for CTEP-supported Studies Involving MK-3475 (pembrolizumab, NSC 776864)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with MK-3475, and to request all trials with MK-3475 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes MK-3475. See the accompanying list of CTEP trials with MK-3475.

In response to the new/modified risk information CTEP is requiring that all trials with MK-3475 be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on June 7, 2018** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Elad Sharon (sharone@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since MK-3475 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with MK-3475.

In addition, as part of the implementation of version 5.0 of the Common Terminology Criteria for Adverse Events (CTCAE), the (CAEPR) list for MK-3475, which was previously in CTCAE 4.0 language, has been migrated to CTCAE 5.0 language. However, there is no new or modified risk information for this agent other than what is outlined under the Specific Amendment Instructions section of this Action Letter.

Any reference to CTCAE 4.0 for adverse event reporting should also be updated to reference CTCAE 5.0 in the protocol amendment.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.4, March 16, 2018): __
   Page Number(s): ____

   • The section below utilizes CTCAE 5.0 language unless otherwise noted.

   - Added New Risk:
     - Less Likely: Immune system disorders - Other (sarcoidosis)
     - Rare but Serious: Immune system disorders - Other (acute graft-versus-host-disease); Metabolism and nutrition disorders - Other (diabetic ketoacidosis); Metabolism and nutrition disorders - Other (type 1 diabetes mellitus); Nervous system disorders - Other (non-infectious encephalitis); Nervous system disorders - Other (non-infectious meningitis); Palmar-plantar erythrodysesthesia syndrome

   - Increase in Risk Attribution:
     - Changed to Less Likely from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Abdominal pain; Back pain; Cough; Hyponatremia

   - Provided Further Clarification:
     - Footnotes have been reordered.
     - Footnote #2 has been updated and now reads: "Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with

interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care."

- Footnote #3 has been added and reads: "Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants."
- Thrombotic thrombocytopenic purpura, previously listed under the IMMUNE SYSTEM DISORDERS SOC *(CTCAE 4.0 language)*, is now listed under the BLOOD AND LYMPHATIC SYSTEM DISORDERS SOC.
- Endocrine disorders - Other (hypophysitis, hypopituitarism) *(CTCAE 4.0 language)* is now reported as Hypophysitis and Hypopituitarism.
- Infusion related reaction, previously listed under the GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS SOC *(CTCAE 4.0 language)*, is now listed under the INJURY, POISONING AND PROCEDURAL COMPLICATIONS SOC.
- Nervous system disorders - Other (Guillain-Barre syndrome) *(CTCAE 4.0 language)* is now reported as Guillain-Barre syndrome.
- General disorders and administration site conditions - Other (generalized edema) *(CTCAE 4.0 language)* is now reported as Generalized edema
- Renal and urinary disorders - Other (nephrotic syndrome) *(CTCAE 4.0 language)* is now reported as Nephrotic syndrome

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.4, and associated risk information for the ICD, to the most recent CAEPR Version 2.3. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.3), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.

- Added New Risk:
  - Occasional: Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
  - Rare: Feeling of "pins and needles" in arms and legs; Redness, pain or peeling of palms and soles; Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin; Damage to organs in the body when the body produces too many white cells; A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma; Inflammation of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck

- Increase in Risk Attribution:
  - Changed to Occasional from Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution (i.e., added to the Risk Profile): Pain in back; Cough

Action Letter

- Decrease in Risk Attribution:
    - Changed to Rare from Occasional: Reaction during or following a drug infusion which may cause fever, chills, rash

- Provided Further Clarification:
    - "Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional) is now reported as "Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath." (under Occasional).

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to MK-3475 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised MK-3475 (pembrolizumab) CAEPR – Version 2.4, March 16, 2018

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, March 16, 2018[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events

potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3]Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Nephrotic syndrome; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for MK-3475 (pembrolizumab)

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. The condensed risk profile is provided as a guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes. Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 in your ICD.

Risk Profile for MK-3475 (CAEPR Version 2.4, March 16, 2018)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: October 2017) will include the wording below:

"If you choose to take part in this study, there is a risk that the MK-3475 (pembrolizumab) may not be as good as the usual approach for your cancer or condition at shrinking or stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The MK-3475 (pembrolizumab) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important things to know about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, and some may never go away.
- Some side effects may make it hard for you to have children.
- Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 (pembrolizumab) in your ICD.

COMMON, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:

- Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:

- Nausea
- Infection
- Loss of appetite
- Pain in back
- Joint stiffness
- Cough
- Swelling and redness of the skin

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Anemia which may require blood transfusion
- Pain in lymph nodes
- Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Pain in belly
- Sores in the bowels
- Chills, fever
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Fluid in the joints
- Pain in chest
- Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:

- Feeling of "pins and needles" in arms and legs
- Redness, pain or peeling of palms and soles

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.
- Swelling and redness of the eye
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin
- Damage to organs in the body when the body produces too many white cells
- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.
- Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Swelling or tenderness of blood vessels

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **For Lead Organizations, distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. The condensed risk profile is provided as guide to facilitate the inclusion of all risks listed in the current CAEPR. It should be used as written unless there is a compelling reason to add new language or reformat the list. If changes are made, please state, "The condensed risk profile has been modified" in the cover memo and specify the reasons in the Summary of Changes.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
   - Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG
Leading cancer research. Together.

Distribution Date: June 1, 2018
E-mailed Date: May 21, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C1[illegible]
PO Box 19024
Seattle, WA 98[illegible]09
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum

ATTENTION: Collection of PK/ADA samples was discontinued on December 11, 2017. All previously collected specimens must be shipped before June 1, 2018, after which PPD will no longer accept shipments and will close access to their web site PPD Clicks. Please remember to use the SWOG Specimen Tracking System to log any shipments in order to resolve any outstanding expectations.

ATTENTION: On **Thursday, June 7th at 11 AM PST/1 PM CT/2 PM EST**, the S1404 Study Team will be hosting a S1404 Site Education Webinar to provide an opportunity for sites unable to attend the Spring SWOG Group Meeting to receive updates provided at the Oishi Symposium, as well as to review the recently-released S1404 Data Entry and Specimen Submission Guidelines. An FAQ session with the S1404 Study Team is to follow. Attendance is capped at 250 call-in lines. Attendees at the same institution are encouraged to share a call-in line.

To sign-up for a call-in line, please complete the registration form at: https://www.surveymonkey.com/r/S1404SE

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

May 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 09, 2018	AE-2642375 FU
S1404 Melanoma	Apr. 13, 2018	AE-2530297 FU
S1609 Early Therapeutics	Apr. 19, 2018	AE-2262121 FU
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

May 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access these safety reports via the SWOG or CTSU website. On the SWOG website, view study's abstract page or the safety report link (https://www.swog.org/member-resources/safety-reports). On the CTSU website, view the drug safety notifications on the study's abstract page (www.ctsu.org).

This safety report s to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Apr. 27, 2018 AE-2536001

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

May 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 02, 2018	AE-2749166 FU
S1404 Melanoma	Apr. 03, 2018	AE-2422604 FU
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

April 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Mar. 20, 2018 AE-2478068 FU
S1404 Melanoma	Mar. 20, 2018 AE-2566785
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

April 15, 2018

TO: ALL NATIONAL CINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

Protocol Changes
(√) Data Submission / Forms changes

MEMORANDUM

The purpose of this memorandum is to notify sites of the following change to the **S1404** Step 2 Registration Worksheet in the master forms set: "Date Informed Consent Signed" was erroneously added on the last version. This has now been replaced with the correct wording: "Projected Start Date of Treatment".

The updated forms can be found on the SWOG website (www.swog.org) or the CTSU website (www.ctsu.org).

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C10
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

SWOG
Leading cancer research. Together.

April 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Mar. 01, 2018	AE-2307573
S1404 Melanoma	Mar. 12, 2018	AE-2478068 FU
S1609 Early Therapeutics	Mar. 13, 2018	AE-2168260
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

March 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jan. 18, 2018	Mfr Rpt #BMS2017109838 FU
S1404 Melanoma	Jan. 18, 2018	Mfr Rpt # BMS2016042059 FU
S1609 Early Therapeutics	Jan. 22, 2018	Mfr Rpt #BMS2017118667
S1616 Melanoma	Jan. 31, 2018	AE-2178112

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 1, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

Protocol changes
(√) Data Submission / Forms changes

MEMORANDUM

The purpose of this memorandum is to notify sites of the following changes:

1. Disease Assessment Form

A new "Disease Assessment" form will roll out starting with the release of **S1404** Revision #8. This form is intended to collect scan information associated with each disease assessment time point as described in the **S1404** Section 9.0 study calendars (please see footnote "k" for details). An associated "Source Documentation: Follow-Up" form will also roll out to collect associated disease scan reports. Both of these forms will be located in the new "Disease Assessment" folder in Rave.

2. Adjuvant Melanoma Follow-Up Form

The "Adjuvant Melanoma Follow-Up" form will now be located in the "Follow-Up" folder instead of the "Disease Assessment and Follow-Up" folder in Rave. This renaming is to avoid confusion with the new "Disease Assessment" form described above. Moving forward, this form should only be completed for patients who are off protocol treatment. Please see Section 14.4.j for the submission schedule for the "Adjuvant Melanoma Follow-Up" form.

"Adjuvant Melanoma Follow-Up" forms that have been completed prior to the release of **S1404** Revision #8 will now be located in the "Disease Assessment and Follow-Up (Old)" folder. No subsequent "Adjuvant Melanoma Follow-Up"

forms will roll out in this folder, and new “Adjuvant Melanoma Follow-Up” forms should be completed in the “Follow-Up” folder.

3. Cycle-specific Laboratory Values Forms

Please note that the “Laboratory Values” form instructions have been updated to include the following verbiage:

“If laboratory values were collected on Day 1 of the next cycle but prior to treatment, please include these laboratory values in this cycle.”

For any questions regarding these data entry requirements, please reach out to melanomaquestion@crab.org or call SWOG Data Operations at 206-652-2267.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Version Date January 10, 2018

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #8

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Scientific / Statistical Consideration changes
(√) Data Submission / Forms changes
(√) Editorial / Administrative changes

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #8

The above-referenced protocol has been revised.

1. The version date of the protocol and consent have been updated.

2. Title Page: The link for the guidance on Trial Master File has been updated.

3. Title Page: Dr. Grossmann's contact information has been updated.

4. The Table of Contents has been updated.

5. Section 1.1.d: The objective of comparing relapse-free survival among patients who are PD-L1 positive has been deleted.

6. Section 3.2c: The version date has been corrected to 2016 and not 2017.

7. Section 7.0: The instructions for viewing SWOG policy #38 have been updated.

8. Section 8.8: The instructions for viewing SWOG policy #38 have been updated.

9. Sections 9.1, 9.2, and 9.3: The link to the SWOG Best Practices document has been updated.

10. Sections 9.1, 9.2, and 9.3: A column for "Relapse/Recurrence" has been added and the procedures that were formerly in the "F/U post relapse" column have been moved to this new column to indicate they are to be done immediately after relapse/recurrence. The only follow up needed post relapse is described in footnote "d".

11. Section 11: The statistical considerations section has been updated from 4 to 3 primary objectives. Wording and tables in this section have been updated to reflect the new objectives.

12. Section 14.3.b: The instructions for viewing the CRA workbench from the SWOG website have been updated.

13. Section 14.3b: The last sentence has been added to clarify access for non-SWOG members.

14. Section 14.4.g: This section has been updated to include annual brain imaging.

15. Section 14.4.g: The **S1404** Disease Assessment Form has been added.

16. Section 14.4.k: The **S1404** Disease Assessment Form, **S1404** Cover Sheet for patient Completed Questionnaire, the **S1404** FACIT-BRM-FAC17-D, and the **S1404** EQ-5D-3L have been added and the last sentence has been clarified to submit the "adjuvant melanoma follow-up form" if the patient is no longer on protocol treatment.

17. Section 15.1.a: The instructions for viewing the CRA workbench from the SWOG website have been updated.

18. Section 15.1a: Access for non-SWOG members has been added to the first paragraph.

19. Section 15.3.b: The links for viewing the guidelines provided by the SWOG repository for Specimen Submission have been updated.

20. Section 15.3.d: The links for viewing the guidelines provided by the SWOG repository for Specimen Submission have been updated.

21. Section 15.4: A sentence has been added to state "As of 12/11/2017 PK/ADA Sampling has been discontinued.

22. Section 15.5.a.6: The guidance for submitting recurrence questionnaires has been clarified.

23. Section 15.5d: For clarification purposes, “relapse” has been added to the list of timepoints at which QOL instruments are to be administered.

24. Section 15.7: The link to view the **S1404** training has been updated.

This memorandum serves to notify the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

February 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jan. 11, 2018	AE-2712243 FU
S1404 Melanoma	Jan. 19, 2018	AE-2561969 FU
S1609 Early Therapeutics	Jan. 22, 2018	AE-2181990
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

February 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following studies:	Report:	
S1404 Melanoma	Jan. 11, 2018	AE-2683802
S1418/BR006 Breast	Jan. 16, 2018	AE-2084866 FU
S1512 Melanoma		
S1607 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

February 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Dec. 19, 2017 Mfr Rpt #BMS2017107338 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reporst if it is deemed necessary by your institution. Please append this notice and these repors to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

February 1, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 813/745-3437
E-mail: kenneth.grossmann@moffitt.org

IRB Review Requirements
(√) No review required

Protocol changes
(√) Data Submission / Forms changes

MEMORANDUM

The purpose of this memorandum is to inform sites of an update to the Master Forms set.

The **S1404** Laboratory Values Form has been updated to include clarified instructions and added options for labs "not done" and "check if no labs are required".

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

swog.org

SWOG
Leading cancer research. Together.

January 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

This safety report pertain to the following study:	Reports:
S1400I Lung	Nov. 15, 2017 Mfr Rpt #BMS2017083541 FU
S1404 Melanoma	Nov. 15, 2017 Mfr Rpt #BMS2017100848
S1609 Early Therapeutics	Nov. 21, 2017 Mfr Rpt #BMS2017070796 FU
S1616 Melanoma	Nov. 21, 2017 Mfr Rpt #BMS2017088917
	Nov. 30, 2017 AE-2651754 FU
	Dec. 18, 2017 AE-2553932 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reporst if it is deemed necessary by your institution. Please append this notice and these repors to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

January 15, 2018

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://www.swog.org/member-resources/safety-reports).

These safety reports pertain to the following studies:	Report:	
S1404 Melanoma	May 30, 2017	Mfr Rpt #1612JPN015218 FU
S1418/BR006 Breast	Nov. 17, 2017	Mfr Rpt #2016IN008423 FU
S1512 Melanoma	Dec. 05, 2017	AE-2648538 FU
S1607 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

December 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Nov. 17, 2017 AE-2530297

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

December 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma	Nov. 15, 2017 AE-2287685
S1418/BR006 Breast	Nov. 16, 2017 AE-2794586 FU
S1512 Melanoma	
S1607 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and his reportt to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

December 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Oct. 27, 2017 AE-2581180 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

December 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Nov. 01, 2017 AE-2609906

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and his reportt to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: December 1, 2017
E-mailed Date: November 21, 2017
Version Date November 8, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #7

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Editorial / Administrative changes
(√) Informed Consent changes
(√) Patient notification not required

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #7

The above-referenced protocol has been revised.

1. The version date of the protocol has been updated.

2. The Table of Contents has been updated.

3. Section 3.1c.3: Numbering has been added to the paragraph titled "Drug interactions".

4. Section 3.2.c: The version number and the version date of the CAEPR have been inserted.

5. Section 3.3l.3: The bulleting under this section has reverted to “a” and “b”, instead of “1” and “2”.

6. Section 5.1.p: The language “≥ 18 years of age” has been removed.

7. Section 7.4: Bullet points “e” and “f” have been inserted.

8. Section 7.6: The title has reverted to “Follow-up Period, End of Study”.

9. Section 9.3: The second page of the pembrolizumab calendar has been inserted.

10. Section 11.4: Reference 25 (previously reference 19) has been inserted.

11. Sections 11.7d and 11.7e: References 26 and 27 (previously reference 20) have been inserted.

12. Section 14.3.a: The last sentence beginning “Enter your valid…” has been reformatted as the second bullet point.

13. Section 17.0: References 25 and 26 have been inserted.

The following changes have been made to the Model Consent:

1. The version date has been updated.

2. In the section titled “What possible risks can I expect from taking part in this study?”, in the first table, the following changes have been made:

    - The drug name has been corrected from “Alfa 2 InterFERON 2b” to “interferon alfa 2b”.
    - “In children and adolescents: decreased height” has been deleted.
    - “Damage to the body by own immune system” has been changed to “Damage to the organs”.
    - “Damage to the muscles which may cause muscle pain, dark red urine” has been deleted.

This memorandum serves to notify the NCI.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

November 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Oct. 24, 2017 AE-2317077 FU
S1404 Melanoma	Oct. 25, 2017 AE-2769015 FU
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

November 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) No review required

Protocol changes
(√) Other – Funding Memorandum

MEMORANDUM

The purpose of this memorandum is to inform sites that the Funding Memorandum for the above-referenced study has been updated. The updated version is available on the protocol abstract page of the SWOG website (www.swog.org) and on the CTSU website (www.ctsu.org).

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

November 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-34[illegible]61[illegible] FAX

1100 Fairview Ave [illegible]th
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Sep. 28, 2017 AE-2581180 FU
S1404 Melanoma	Oct. 02, 2017 AE-2190200 FU
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Phyllis Diener – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

November 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following studies:	Report:
S1404 Melanoma	Sep. 25, 2017 AE-2275874
S1418/BR006 Breast	Sep. 29, 2017 AE-2646830
S1512 Melanoma	
S1607 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: November 1, 2017
E-mail Date: October 19, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

STATUS NOTICE

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) Closure – Permanent (Effective November 2, 2017)

PERMANENT CLOSURE

The purpose of this memorandum is to inform sites Step 2 (randomization) of the above-referenced study will be permanently closed to accrual **effective November 2, 2017** at 11:59 p.m. Pacific Time.

Closure to Step 1 (prestudy screening) was **effective August 15th**.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata

SWOG
Leading cancer research. Together.

Distribution Date: November 1, 2017
E-mailed Date: October 18, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to clarify the requirements for Institutional Review Board (IRB) approval and patient notification related to the Investigator Letter and Patient Information Letter distributed by e-mail on 10/3/17.

IRB Review Requirements

If the CIRB is the IRB of record, there is no need to submit to the local IRB. SWOG has submitted the letter to the CIRB and they have acknowledged. No additional IRB submission or review is required.

If the CIRB is not the IRB of record, then the local IRB of record must be notified of this information and sites should follow local IRB recommendations for informing patients.

Patient Notification Requirements

This information must be provided to patients currently on treatment within 10 days of distribution. Because CTSU distribution occurred on 10/9/17, this is the distribution date that will be used to calculate the deadline for informing patients. Therefore, all patients must be notified no later than 10/19/17.

Note that patients not currently on treatment need not be informed immediately; the information may be provided to them at their next regular visit.

Additionally, note that while the information states that the physician will contact the patient to provide more details, the intent is that this contact may occur during the next regularly scheduled visit.

cc: PROTOCOL & INFORMATION OFFICE
Karen Favata – Merck

SWOG
Leading cancer research. Together.

October 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Sep. 20, 2017 AE-2458073 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: October 15, 2017
Version Date June 24, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #6

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
(√) Patient notification not required

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice.

REVISION #6

The above-referenced protocol has been revised as follows.

1. The version date of the protocol has been updated on every page.

2. Page 1: The following language was added to the title page "This is an FDA Registration Trial. Additional site requirements include maintenance of a Trial Master File (https://swog.org/Visitors/QA/Documents/Guidance%20on%20FDA%20Inspection.pdf) and additional monitoring (see Appendix 18.6)".

3. Page 1: Vernon K. Sondak, M.D. has been added to the list of Study Chairs.

4. Page 1: Deleted space in E-mail: jmoon@fredhutch.org

5. Page 5: The instructions to submit site registration were updated with current contact information and template language.

6. Section 3.3c.1: The second to the last paragraph was updated to remove language that conflicts with Section 16.1. “If a male patient impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported and followed as described in Section 16.1i” has been deleted.

7. Section 3.3e: The paragraph for “how supplied” was updated to change the pH range to “5.2-5.8” and to include the info “supplied in Type I glass vials with a cap color of red, salmon, for blue”.

8. Section 4.0: This section has been revised to reflect the fact that patients with non-ulcerated T1b N1a disease are not eligible.

9. Section 5.1.a: The following sentence has been inserted: “Patients with non-ulcerated T1b N1a disease are not eligible.”

10. Section 7.1b1: Added footnote “*Dose rounding ± 10% is allowable per institutional standards.”

11. Section 8.2c: Leukopenia has been deleted from the list of toxicities to be monitored as this is not standard.

12. Section 8.4: Guidelines for dose modifications due to cardiac-related side effects have been added to the Dose Modifications table for MK-3475.

13. Section 8.4: updated Table 1- dose modifications as the previous version was outdated.

14. Section 8.4: updated Table 2- infusion reaction treatment guidelines as the previous version was outdated.

15. Section 9.1: On the first page of this section, the headings for the Induction Phase (“Days 1-5 (M-F) of Weeks 1-4)” and Maintenance Phase (“Days 1, 3, 5 (M, W, F) of Weeks 5-52)” have been revised for clarification. On the second page of this section, the URL for the SWOG Best Practices Guidelines has been corrected. Footnote “c”, toxicity notation has been removed as AE assessments will continue for all patients until 30 days after the last study drug administration. On the third page of this section, footnote “k” has been revised to allow a 4-week window around the timepoints for 6 months and annually. The “p” footnote has been revised to allow a 2-week window around the time points for submission of quality of life forms. Footnote “s” has been revised to include “Height is only required at baseline”.

16. Section 9.2: On the first page of this section, the row for “EKG, ECHO, CPK, & Troponins” has been updated to read as “Cardiac Function” and was moved from “Reg Step 1” to “C1W1”. Footnote “i” has been added to every “X” in the “Pregnancy Test” row. On the second page of this section, the URL for the SWOG Best Practices Guidelines has been corrected. On the third page, in the “c” footnote, instructions for the first year of follow-up have been inserted and toxicity notation has been removed as AE assessments will continue for all patients until 30 days after the last study drug administration. Footnote “k” has been revised to allow a 4-week window around the timepoints for 6 months and annually. The “r” footnote has been revised to allow a 2-week window around the time points for submission of quality of life forms. The “u” footnote has been revised for clarification of cardiac patients requiring cardiac function testing. The “t” footnote was revised to include “Height is only required at baseline”.

17. Section 9.3: On the first page of this section, a row for cardiac function tests has been added. On the second page of this section, the URL for the SWOG Best Practices Guidelines has been corrected. Footnote "c", toxicity notation has been removed as AE assessments will continue for all patients until 30 days after the last study drug administration. The "h" footnote has been revised to direct sites to footnote "v" for further clarification. Footnote "k" has been revised to allow a 4-week window around the timepoints for 6 months and annually. The "r" footnote has been revised to allow a 2-week window around the time points for submission of quality of life forms. The "t" footnote was revised to include "Height is only required at baseline". The "v" footnote has been inserted to indicate testing to be performed on cardiac patients.

18. Section 11.8: This section, formerly Section 11.7.g, has been expanded to provide additional details about the quality of life analyses.

19. Section 13.2: The Investigator/Site Registration section has been updated with current information.

20. Section 14.1: The Data submission schedule was updated with additional information on submission for clarification.

21. Section 14.4a: Changed "*Pathology report documenting histologic confirmation of malignant melanoma" to "Pathology reports documenting histologic confirmation and complete resection of all disease" for clarity.

22. Section 15.2d.1, 15.2d.2, 15.4d.1, and 15.4d.2: The URL for reordering supplies has been updated.

23. Section 15.2g: The following sentence has been inserted: "If there are any questions, please contact the SWOG Data Operations Center at (206) 652-2267".

24. Section 15.5d: In the first bullet, the first time point for administering quality of life questionnaires has been changed from "randomization" to "prior to Cycle 1" for clarification.

25. Section 15.6: The sentence "PET-CT, CT, and/or MRI images must be locally read and interpreted by the local site radiology service" has been deleted for clarification.

26. Section 17.0: References 23 through 28 have been added.

27. Section 18.4: The **S1404** Local Pathology Review Form has been corrected. It previously referred to blocks and slides. The new form correctly notes that unstained slides are required.

28. Section 18.6: This section was revised to add information about centralized risk-based monitoring and now includes a list of documents that must be uploaded into RAVE for the first two patients registered at each site. It also clarifies the differences among routine monitoring, risk-based monitoring, and on-site audits. The section title was updated to "QA Auditing and Monitoring".

The following changes have been made to the model consent forms.

1. The version date has been updated.

2. Under “possible side effects of MK-33475 (pembrolizumab)”, the first paragraph was deleted under direction from the NCI as this was duplicative information.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
Lam Calderon – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: October 15, 2017
E-mail Date: October 3, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) No review required

(√) Patient notification required

MEMORANDUM

Enclosed please find an "Investigator Letter" and a "Patient Information Letter" pertaining to recently-released results of melanoma studies. Note that each institution with patients registered to the study must respond and acknowledge its understanding of the actions it must take.

Investigators must notify their local Institutional Review Board (IRB) and must inform their patients of this information in the manner recommended by the local IRB. A "Patient Information Letter" is enclosed as a model for your use. While this letter need not be provided verbatim, the information in the letter must be provided in a manner recommended by the local IRB within 10 days after distribution of this memo. A discussion with the investigator can take place at the next scheduled visit. Documentation of this process must be stored in the patient's study record on site and will be subject to verification at the time of a Quality Assurance audit.

If the details of the "Patient Information Letter" are not completely implemented by local IRB's, we recommend at least that ALL patients who remain alive be notified of the study outcomes. It should be made clear to the patients who were registered to the trial, but are not currently receiving treatment, that they are only being informed because they were part of the trial. Patients no longer receiving treatment may be notified at their next scheduled visit.

We realize that there may be questions about this new information. Please contact Drs. Kenneth F. Grossmann, M.D., Ph.D. at 801/587-4735 or kenneth.grossmann@hci.utah.edu, Sapna Pradyuman Patel, M.D. at 713/792-2921 or S1404SCquestion@swog.org to seek any clarification or further details regarding follow-up on informing patients on the study.

Thank you for your cooperation and understanding in providing this new information to patients.

cc: PROTOCOL & INFORMATION OFFICE Shannon Meroney-Davis – Merck

SWOG
Leading cancer research. Together.

October 3, 2017

MEMORANDUM

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: Investigators with Patients Registered to **S1404**

FROM: Charles D. Blanke, M.D.

RE: **S1404** Patient Information

Enclosed please find an "Investigator Letter" and a "Patient Information Letter" pertaining to recent results of other melanoma studies.

We are asking you to do the following:

1. Acknowledge receipt of this information, submit the information to your IRB, and acknowledge your understanding of the actions you must take (listed below) by signing below and FAXing this letter back to the Operations Office (ATTN: Trina Fenning, 210/614-0006). **Only a single acknowledgement per institution is necessary.**

   I have submitted this information to my IRB.

   _____
   (Investigator Signature)

   _____
   (Print Name)

   _____
   (Print Institution Name)

2. Read the Investigator Letter.

3. Inform all living patients entered through your institution on this study of the information in the Patient Letter as directed in the Investigator Letter.

PC/dc

SWOG
Leading cancer research. Together.

October 3, 2017

TO: Participating Investigators, **S1404**

FROM: Kenneth F. Grossmann, M.D., Ph.D. – Study Chair
Sapna Patel, M.D. – Study Chair
Antoni Ribas, M.D. – Melanoma Committee Chair
Christopher Ryan, M.D. – Executive Officer
Charles D. Blanke, M.D. – Group Chair

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Investigator Letter

This letter is to inform you of new data that you will need to discuss with your patients who are participating on **SWOG S1404**: "*A Phase III Randomized Trial of Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High-Risk Resected Melanoma*". Two major studies of adjuvant therapy for melanoma (CheckMate-238 an COMBI-AD), presented at the European Society for Medical Oncology (ESMO) annual meeting and simultaneously published in the *New England Journal of Medicine*, have shown a relapse-free survival benefit in patients with melanoma.

CheckMate-238, the trial most analogous to **S1404** was reported by Jeff Weber et al and simultaneously published in the *New England Journal of Medicine.* This Phase III double-blind trial randomized 906 patients with resected stage III or IV melanoma to nivolumab (3mg/kg q2wks) or ipilimumab (10 mg/kg q3wks x 4 then q12 weeks) for one year. Patients were followed for a primary endpoint of relapse-free survival. At the first protocol mandated interim analysis at 18 months of follow-up, the 12-month rate of recurrence-free survival of 70.5% in the nivolumab group and 60.8% in the ipilimumab group (HR 0.65, 95% CI 0.51-0.03, P<0.001). Treatment-related grade 3 or 4 adverse events were reported in 14.4% of the patients in the nivolumab group and in 45.9% of those in the ipilimumab group. No overall survival benefit has been reported.

The link to the publication is available here:
http://www.nejm.org/doi/full/10.1056/NEJMoa1708539

The **COMBI-AD** trial, published by Georgina Long et al evaluated patients with completely resected, stage III melanoma with *BRAF* V600E or V600K mutations. In this double-blind, placebo-controlled trial, 870 patients were randomized to receive oral dabrafenib (150 mg po BID) plus trametinib (2 mg PO daily) or two matched placebo tablets. The primary endpoint was relapse-free survival. The estimated 3-year rate of relapse-free survival was 58% in the combination-therapy group and 39% in the placebo group (HR=0.47, 95% CI 0.39-0.58, P<0.001). The 3-year overall survival rate was 86% in the combination-therapy group and 77% in the placebo group, but this was a secondary endpoint in the trial and this result did

not cross the pre-specified interim analysis boundary for significance. The link to the publication is available here: http://www.nejm.org/doi/full/10.1056/NEJMoa1709030

A third study, **BRIM8** study (presented at ESMO; not yet published) investigated adjuvant treatment with vemurafenib (960 mg PO BID) vs placebo for one year in patients with fully resected, Stage IIC, IIIA, IIIB (Cohort 1), or IIIC (Cohort 2) V600E BRAF-mutated melanoma. In Cohort 1 (n=314), patients treated with vemurafenib had a significant improvement in disease-free survival (HR=0.54,95% CI 0.37-0.78, P=0.0010). In Cohort 2, there was a numerical improvement in DFS that was not statistically significant (HR=0.80, 95% CI 0.54-1.18, P=0.2598).

As yet, no significant overall survival benefit has been demonstrated for any of these agents in the trials presented in Madrid. It is still unknown how these new therapies will compare to pembrolizumab or to interferon, as no direct comparisons to either agent have been performed. Additionally, there are no data on nivolumab and dabrafenib/trametinib given more than 3 months after surgical resection of melanoma or following another adjuvant therapy when no relapse has occurred. Nivolumab and dabrafenib/trametinib are not FDA-approved for adjuvant therapy at this time.

As per the informed consent, you must discuss with your study participants any information that might influence their willingness to continue on the study. **For any patients who are currently undergoing treatment on SWOG S1404, please schedule an appointment to discuss these results**. For patients who have completed their treatment, this information should be shared at the next study visit. The attached "New Developments" sheet can be used to facilitate this discussion, and should be given to patients at the appointment. After your discussion with the patient, please ensure that this is appropriately documented in the medical record.

This information is being shared with the SWOG DSMB and the Central IRB. Pending their complete review, additional action may be required. SWOG will inform you if any additional action is needed.

Thank you again for your participation in **S1404**. We continue to believe that this is an important trial that has the potential to impact patient care for years to come.

New Developments:

In one study, called ***CheckMate-238***, two different immunotherapy drugs - nivolumab and ipilimumab, were compared for patients with stage 3 or 4 melanoma whose cancer had been totally removed by surgery. After 18 months of follow-up, 66.4% of patients treated with nivolumab were alive and free of recurrence, compared with 52.7% of patients who had received ipilimumab. In addition, patients receiving nivolumab had fewer serious side effects than those receiving ipilimumab. Interferon and Ipilimumab are the two treatment options on the control arm of your clinical trial, **S1404**, and they are currently FDA-approved standard of care options for high risk melanoma that has been surgically removed. Nivolumab is a PD1 inhibitor. Pembrolizumab is also a PD1 inhibitor. There are no current data comparing nivolumab to pembrolizumab.

Two additional studies looked at drugs that specifically target tumors that have an abnormality, or mutation, in a gene called *BRAF*. These studies did not evaluate patients who had stage 4 melanoma that has been surgically removed.

1) In the ***COMBI-AD*** study, two types of targeted therapy (dabrafenib and trametinib taken together) were compared to placebo for patients with stage 3 melanoma with a BRAF mutation following surgery to totally remove their cancer. Only 40-50% of patients with melanoma have BRAF mutations. After three years of follow-up, 58% of patients treated with dabrafenib and trametinib were alive and had no evidence of recurrence, compared with 39% of patients treated with placebo.
2) The ***BRIM8*** study compared one year of treatment with vemurafenib (a drug which also targets tumors that have a BRAF mutation) with placebo in melanoma patients with a BRAF mutation. This study showed a 46% reduction in the chance of recurrence for patients with earlier stage tumors (Stage 2C, 3A or 3B).

SWOG
Leading cancer research. Together.

PATIENT INFORMATION LETTER for

S1404, **"A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.**

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Dear SWOG **S1404** Participant:

You are receiving this letter because you have participated or are currently receiving treatment for high risk melanoma following surgical removal as part of a research study, ***SWOG S1404****: "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High-Risk Resected Melanoma*" that is sponsored by the National Cancer Institute (NCI).

New data have been reported in two separate melanoma studies (CheckMate-238 and COMBI-AD) that show two drug regimens to be potentially beneficial for use in your condition. One therapy regimen is specific for melanomas with a BRAF mutation (dabrafenib plus trametinib); and the other is nivolumab, an immune-based therapy. These drugs have been previously approved for use in more advanced stages of melanoma; they are not currently approved by the FDA for use in adjuvant stage 3 melanoma that has been removed by surgery. As in the **S1404** study, the adjuvant therapy treatments tested in these two studies were given within 3 months after the tumor has been surgically removed, and were aimed at reducing the chance that the cancer will come back. There is no data available to know what benefit these new therapies may have if given more than 3 months after surgery or if a different prior treatment regimen was given beforehand.

It is important to know that your tumor may or may not have the BRAF mutation, and that dabrafenib plus trametinib used in the COMBI-AD study have not been compared to any of the treatments in SWOG **S1404** and they were all given within 3 months of surgery for the melanoma. Your physician can provide you with information on the BRAF mutation status of your tumor.

Your physician will be contacting you in the near future to discuss these results in more detail.

We appreciate your participation in SWOG **S1404**.
Gratefully,

Kenneth F. Grossmann M.D., Ph.D.
S1404 Study Chair
Huntsman Cancer Institute
University of Utah

SWOG
Leading cancer research. Together.

October 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics **S1616** Melanoma	Sep. 14, 2017 AE-2468429

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Phyllis Diener – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

September 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Aug. 21, 2017 AE-2794586

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
David McFadden – Merck
Kelly Morrissey– Merck
Sandra Souza– Merck
Lam Calderon– Merck

SWOG
Leading cancer research. Together.

September 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Aug. 17, 2017 AE-2236698 FU
S1404 Melanoma	Aug. 25, 2017 AE-2486541
S1609 Early Therapeutics	
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Phyllis Diener – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

September 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:	
S1404 Melanoma	Jul. 20, 2017	AE-2339481
S1418/BR006 Breast	Jul . 24, 2017	Mfr Rpt #1612FRA000618 FU
S1512 Melanoma	Jul. 26, 2017	AE-2789854
	Jul. 28, 2017	AE-2108709
	Jul. 28, 2017	Mfr Rpt #2016IN007827 FU
	Aug. 01, 2017	AE-2481834
	Aug. 04, 2017	AE-2608931

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
David McFadden – Merck
Kelly Morrissey– Merck
Sandra Souza– Merck

SWOG
Leading cancer research. Together.

September 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Dec. 22, 2016 AE-2957042
S1404 Melanoma	Mar. 24, 2017 AE-2921421
S1609 Early Therapeutics	Jul. 24, 2017 AE-2231448 FU
S1616 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Phyllis Diener – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

August 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Jul. 17, 2017	AE-2157148 FU
S1404 Melanoma	Jul. 17, 2017	AE-2829845 FU
S1609 Early Therapeutics		
S1616 Melanoma		

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

August 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Jun. 21, 2017 Mfr Rpt #2017IN001602 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

August 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of an update to the Master Forms set. The **S1404** Eligibility Checklist, Initial Registration has been corrected on Page 3, Section 5.1o. "SGPT (AST)", now reads (SGPT (ALT).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: August 1, 2017
E-mail Date: July 28, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

STATUS NOTICE - UPDATED

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) Closure – Partial Permanent Effective August 15, 2017

PARTIAL PERMANENT CLOSURE: UPDATED

The purpose of this memorandum is to inform sites that the Partial Permanent Closure has been postponed. The closure will be effective August 15th rather than August 1st.

Step 1 (prestudy screening) will be permanently closed to accrual effective August 15, 2017 at 11:59 p.m. Pacific. All patients who have consented must be registered to Step 1 (prestudy screening) prior to 11:59 p.m. Pacific on August 15th in order to be eligible to participate. This closure does not apply to Step 2 (randomization).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

July 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

STATUS NOTICE

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Status Change
(√) Closure – Partial Permanent Effective August 1, 2017

PARTIAL PERMANENT CLOSURE

The purpose of this memorandum is to inform sites that Step 1 (prestudy screening) of the above-referenced study has reached its accrual goal and will be permanently closed to accrual **effective August 1, 2017** at 11:59 p.m. Pacific Time.

All patients who have consented must be registered to Step 1 (prestudy screening) prior to 11:59 p.m. PT on August 1st in order to be eligible to participate. This closure does not apply to Step 2 randomization.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza – Merck

SWOG
Leading cancer research. Together.

July 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	May 26, 2017	Mfr Rpt #BMS2017043793
S1404 Melanoma	May 26, 2017	Mfr Rpt #BMS2014004304 FU
S1609 Early Therapeutics	Jun. 26, 2017	AE-2829845 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

July 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of the **S1404** Tips for Data and Specimen Submission guide that is now available on the SWOG protocol abstract page. The referenced form is attached.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza – Merck

S1404 TIPS FOR DATA AND SPECIMEN SUBMISSION

S1404 is a REGISTRATION TRIAL! The data from this trial will be used to support an application to the FDA for the approval of MK-3475 (Pembrolizumab) in advanced melanoma. This means there is an increased potential for an FDA inspection of your site. Extra diligence in the submission of data, both in terms of timeliness and quality is critical. (See Protocol Section 14 for data submission schedule).

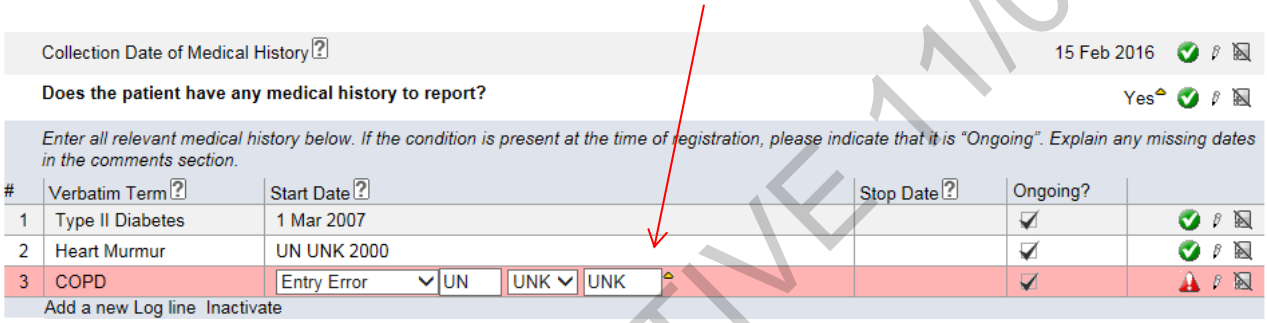
Below are some tips and common mistakes for data and specimen submission.

RAVE® DATA SUBMISSION/ENTRY ISSUES

Non-Conformant Data

Non conformant data are data that do not meet the criteria for data submission. This prevents data from being submitted, which results in overdue expectations!

Example: **Baseline Medical History Form.** Unknown *Month* and *Date* are acceptable; however, the form requires *at least* a valid year in the start/stop dates.



Collection Date of Medical History 15 Feb 2016

Does the patient have any medical history to report? Yes

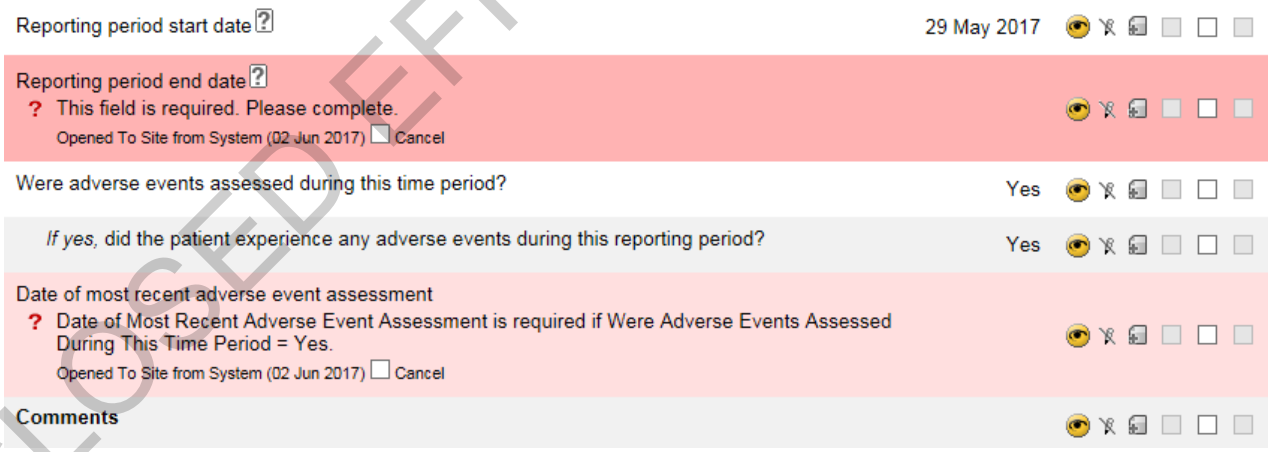
Enter all relevant medical history below. If the condition is present at the time of registration, please indicate that it is "Ongoing". Explain any missing dates in the comments section.

#	Verbatim Term	Start Date	Stop Date	Ongoing?
1	Type II Diabetes	1 Mar 2007		☑
2	Heart Murmur	UN UNK 2000		☑
3	COPD	Entry Error / UN / UNK / UNK		☑

Add a new Log line Inactivate

System Query

Specific fields in Rave are set up to require data. When those fields are left blank, the system will generate a query for the missing information. Like non-conformant errors, queries from the system will prevent the data from being transferred, which results in overdue expectations for your site.



Reporting period start date 29 May 2017

Reporting period end date
? This field is required. Please complete.
Opened To Site from System (02 Jun 2017) Cancel

Were adverse events assessed during this time period? Yes

If yes, did the patient experience any adverse events during this reporting period? Yes

Date of most recent adverse event assessment
? Date of Most Recent Adverse Event Assessment is required if Were Adverse Events Assessed During This Time Period = Yes.
Opened To Site from System (02 Jun 2017) Cancel

Comments

General Data Errors/Data Submission Tips

- **Source Documentation: Baseline**
  - Date of Procedure is the date the test was done, NOT the date the document is uploaded or date of the report.

- **Treatment Form**
  - Refer to form instructions for expected units
  - Reporting period start/end dates: The end date of one cycle = start date of the next cycle. (one day overlap)
  - Date of last contact should be the last time you had contact with the patient WITHIN the cycle you are reporting.
  - Wait until the END OF CYCLE to start data entry and submit form.
- **S1404 Concomitant Medication form**

  The concomitant Medication Form is designed to capture any non-protocol medications a patient takes while on treatment. An Adverse Event (AE)-specific concomitant medication form is generated if/when it's indicated that treatment is received for an immune-related adverse event.

Instructions: Please complete if patient receives any non-protocol therapy. If patient received a glucocorticoid to treat immune-related adverse events, record the dose and start and stop dates of the initial high dose and start and stop dates of the steroid taper on separate lines. List each medication on a separate line, even if given concurrently. If patient stops a medication and then restarts at a later date, list each occurrence on a separate line.

#	Concomitant Agent Name	Start Date	Stop Date	Ongoing?	Dose	Units of Measure	Route of Administration	
1	Prednisone	1 Mar 2016	5 Mar 2016	☐	40	mg	Oral	
2	Prednisone	6 Mar 2016	8 Mar 2016	☐	20	mg	Oral	
3	Prednisone	9 Mar 2016	11 Mar 2016	☐	10	mg	Oral	

Add a new Log line Inactivate

- **S1404 Adverse Event (AE) Reporting**
  - AEs should be reported in each cycle during which they occur, not just in the beginning/ending cycle. They should only be resolved at the end of cycle.
  - There are extra fields on the AE Report form to capture additional data (Onset and Resolution dates, Action taken, Outcome, Immune related? Treatment Received? AdEERS Report Ticket Number)
  - *Onset date* and *Resolution date* correspond to the specific CTCAE (4.0) grade, not the AE overall
  - If AE is ongoing, you must add the AE to the next cycle form
  - A resolution date only needs to be entered in the cycle during which the AE resolves, not in each cycle the AE occurred.

Instructions:

- Report adverse events occurring up until the next cycle of treatment begins.
- If an adverse event changes grade during the reporting period, report each grade as a separate event. If an adverse event resolves and then recurs at the same or different grade, report each event separately.
- To report ongoing adverse events, provide the AE start date and mark the AE as "ongoing" on each eCRF until the event is resolved. On the last cycle that the AE is seen, provide the AE end date.
- Do not code a condition existing prior to registration as an adverse event unless it worsens.
- Indicate if the adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥24 hours.
- Submit the Concomitant Medications form documenting treatment received for any immune-related adverse events.
- Follow instructions in Section 16.0 of the protocol for expedited reporting requirements on this study.
- Record any expedited adverse events that were reported using Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). If the AdEERS report was amended, please amend the data on this adverse event form.
- Category lists may not include all adverse events from that category.

#	Verbatim term	CTC adverse event term	CTCAE (4.0) grade	CTC adverse event attribution code	Onset date	Resolution date	Action taken	Outcome of AE	Hospitalization *(at least 24 hours)*	Is the AE immune-related?	Treatment received for this AE?	AdEERS Report Ticket Number	
1	Fatigue	Fatigue	1	Probable	6 Oct 2015	–	Dose Not Changed	Not Recovered/Not Resolved	☐	No	No	_	
2	Anemia	Anemia	2	Probable	6 Oct 2015	7 Dec 2015	Dose Not Changed	Recovered/Resolved	☐	No	No	_	
3	Anemia	Anemia	4	Probable	7 Dec 2015	–	Drug Withdrawn	Not Recovered/Not Resolved	☐	No	No	_	

Add a new Log line Inactivate

MANAGING YOUR DATA

SWOG Expectation Report: An Expectation is a reminder for the submission of study data, specimens, source docs, etc. Expectations with a defined due date are posted at the time the patient is registered (typically baseline forms and specimens). Other expectations are dynamic and are based on the timing of the patient's treatment cycle (typically Treatment, Adverse Event and Follow-Up Tumor Assessment Forms). The Expectation Report includes those Expectations that are overdue as well as those that are coming due in the near future to help with planning patient visits and follow-up reminders.

SWOG Query Report: Data Coordinators, Study Chairs, Auditors and Monitors post queries based in Rave® on their review of your data. System queries and non-conformant data notices are automatically posted based on your data and subsequent edit checks. Forms with system queries or non-conformant data are not submitted to the SWOG database and thus Expectations for forms with these queries will not be resolved until the data are corrected. It is important to address all queries in a timely manner.

CTSU Reports: Delinquent Data and Query Reports available at the DQP tab on the CTSU. These are additional tools to help manage your site's data. The specifications for these reports differ from the SWOG reports. For a summary of the differences please review the presentation available under the News section (dated May 5, 2017) on the Home page of the CRA Workbench.

The SWOG Reports and Presentation are available on the CRA Workbench:

https://crawb.crab.org/txwb/Default.aspx - For SWOG members; use SWOG roster ID and password.

https://crawb.crab.org/TXWB/ctsulogon.aspx - For non-SWOG members; use your CTEP-IAM userid and password.

REMINDERS:

All specimens must be logged into the SWOG Specimen Tracking System (STS) regardless of where specimens are shipped

If patient consents to the future use of optional specimens, it becomes a REQUIREMENT to collect and submit the specimens

Common errors in specimen submission for S1404:

- Specimens shipped but not logged into STS
- Specimens logged into STS but not shipped
- Specimens that were missed (site error or patient refused) where "Notify the Specimen cannot be submitted" is NOT logged in STS
- Specimen Labeling issues
    - Required information on specimen label is missing
        - *Frozen Liquids:* Must be labeled with registration number, collection date, patient initials, and specimen type.
        - *Formalin-fixed paraffin-embedded* specimens (blocks or slides) must be labeled with registration number, collection date, patient initials, block number, pathology ID number (SPID/accession # and tissue type (ex: primary)
    - Information on specimen label does not match packing list (ex: collection date on packing list doesn't match collection date on specimen label)
    - Paraffin tissue specimens not labeled with tissue type (ex: primary or metastatic)
- Specimen Quality Issues
    - Received at incorrect temperature
        - Insufficient amount of dry iced used when shipping, causing thawed specimens
    - Slides received broken, cracked or leaking (ex: vials filled too full, liquid expands when frozen, causing specimen to leak from vial)
- Missing paperwork
    - Pathology Report
        - All paraffin tissue submissions require submission of accompanying pathology report
        - Surgical Pathology ID/Accession number and collection date must be visible
    - STS packing list
- Batch shipments
    - Batch shipments should be limited to a maximum of 4 or 5 patient's samples per shipping container

  Per Lab:
    - Large shipments are more likely to have other submission errors (labeling issues, more likely to be thawed)
    - If a shipment gets lost in transit, or held up, the number of lost or unusable specimens is less.

BEFORE YOU SHIP

✓ Log specimens into STS

✓ Verify labels on all specimens match the packing list from STS

✓ Verify all necessary paperwork is included

- Packing list
- Pathology report (paraffin items only)
- Registration number is included on all paperwork

Common errors in specimen submission -Continued

- ✓ Pack your specimens according to the season
  - Summer months (*April --September):
    - Frozen specimens: Include plenty of dry ice to prevent specimens from thawing
    - Ambient specimens: include a cold pack
  - Winter months (*October – March):
    - Frozen specimens: Include plenty of dry ice to prevent specimens from thawing
    - Ambient specimens: insulate well (wrap in bubble wrap or something similar) to prevent specimens from freezing

CONTACT INFORMATION FOR LABS, TRIAD and the SWOG STATISTICAL AND DATA MANAGEMENT CENTER

- **Lab #201: SWOG Biospecimen *(Specimens for Banking)***
  Phone: 614-722-2865Email: bpcbank@nationwidechildrens.org
  *Only ambient blood and bone marrow specimens can be received at the SWOG Bank on Saturdays. Frozen and paraffin specimens can only be shipped Monday-Thursday.
  **The SWOG Bank also recommends shipping specimens FedEx Priority Overnight. All other shipping methods can delay receipt of specimens.
- **Lab #218: Central Laboratory/LabCorp Clinical Trials *(REQUIRED Submission of slides for PD-L1)***
  Phone: Contact the SWOG Data Operations: 206-652-2267
- **Lab #219 MK3475-053 PPD Central Lab (for PK and ADA) specimens *(for patients randomized to the MK-3475 arm)***
  Phone: 800-323-2996
  Email***:siteservices.us@ppdi.com***
- **Questions regarding image submissions, including TRIAD**
  SWOG1404@irocohio.org or call IROC Ohio at 614-293-2929

Contact your Data Coordinator or Central Monitor:

Data Coordinator E-mail: **MelanomaQuestion@crab.org** **Phone: (206) 652-2267**

Central Monitor E-mail: **centralmonitorquestion@crab.org**

Next page is a chart from STS showing the specimen or material type and specified laboratories listed for the S1404 Protocol

Step 2 of 3: Choose the specimen that you are logging from the list below.

Study Number: S1404

Registration Step	Submission Timepoint	Specimen or Material Type			Lab
1	Baseline, Pre-Randomization	Tissue from primary site	Unstained Slides	PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Pre-Randomization	Tissue from local site	Unstained Slides	PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Pre-Randomization	Regional Node	Unstained Slides	PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Pre-Randomization	Tissue from distant site	Unstained Slides	PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Re-Submission	Tissue from primary site	Unstained Slides	Re-Submission PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Re-Submission	Tissue from local site	Unstained Slides	Re-Submission PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Re-Submission	Regional Node	Unstained Slides	Re-Submission PD-L1-Evaluation	218 - LabCorp Clinical Trials
1	Baseline, Re-Submission	Tissue from distant site	Unstained Slides	Re-Submission PD-L1-Evaluation	218 - LabCorp Clinical Trials
2	Baseline, Prior to starting treatment	Tissue from distant site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from distant site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from distant site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from primary site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from primary site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from primary site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from local site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from local site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Tissue from local site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Regional Node	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Regional Node	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Regional Node	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Blood	Serum	1 ml serum vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Blood	Buffy coat	1 ml buffy coat vials from 3 10 mL whole blood tub	201 - SWOG Specimen Repository
2	Baseline, Prior to starting treatment	Blood	Plasma	1 ml plasma vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, MK-3475 arm, prior to starting treatment	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to starting treatment	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to Dose 2 (wk 4), Cycle 1	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to Dose 2 (wk 4), Cycle 1	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to Dose 2 (wk 10), Cycle 2	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to Dose 2 (wk 10), Cycle 2	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, Prior to starting treatment, Cycle 3	Blood	Serum	1 ml serum vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, Prior to starting treatment, Cycle 3	Blood	Buffy coat	1 ml buffy coat vials from 3 10 mL whole blood tub	201 - SWOG Specimen Repository
2	Other, Prior to starting treatment, Cycle 3	Blood	Plasma	1 ml plasma vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, MK-3475 arm, prior to Dose 3 (wk 19), Cycle 3	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to Dose 3 (wk 19), Cycle 3	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, Prior to starting treatment, cycle 4	Blood	Serum	1 ml serum vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, Prior to starting treatment, cycle 4	Blood	Buffy coat	1 ml buffy coat vials from 3 10 mL whole blood tub	201 - SWOG Specimen Repository
2	Other, Prior to starting treatment, cycle 4	Blood	Plasma	1 ml plasma vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, MK-3475 arm, prior to starting tx (wk 25), Cycle 4	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to starting tx (wk 25), Cycle 4	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to starting tx (wk 49), Cycle 6	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, MK-3475 arm, prior to starting tx (wk 49), Cycle 6	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, Off protocol treatment for any reason	Blood	Serum	1 ml serum vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, Off protocol treatment for any reason	Blood	Buffy coat	1 ml buffy coat vials from 3 10 mL whole blood tub	201 - SWOG Specimen Repository
2	Other, Off protocol treatment for any reason	Blood	Plasma	1 ml plasma vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, 30 days after discontinuing MK-3475	Blood	Serum	Serum for PK at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, 30 days after discontinuing MK-3475	Blood	Serum	Serum for ADA at -70 Celsius	219 - PPD for PK/ADA Analysis
2	Other, Disease Recurrence	Tissue from distant site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from distant site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from distant site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from primary site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from primary site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from primary site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from local site	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from local site	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Tissue from local site	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Regional Node	Blocks	If Block available preferred over USLID	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Regional Node	Unstained Slides	May substitute. for block	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Regional Node	Stained Slides	H & E stained slide	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Blood	Serum	1 ml serum vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Blood	Buffy coat	1 ml buffy coat vials from 3 10 mL whole blood tub	201 - SWOG Specimen Repository
2	Other, Disease Recurrence	Blood	Plasma	1 ml plasma vials from 3 10 mL whole blood tubes	201 - SWOG Specimen Repository

SWOG
Leading cancer research. Together.

July 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 24, 2017	Mfr Rpt #BMS2017008679 FU
S1404 Melanoma	Apr. 24, 2017	Mfr Rpt #BMS2017024663
S1609 Early Therapeutics	May 10, 2017	AE-2620571
	May 11, 2017	Mfr Rpt #BMS2017018533
	May 15, 2017	Mfr Rpt #BMS2016090658 FU
	Jun. 02, 2017	AE-2879477

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

July 1, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:	
S1404 Melanoma	Mar. 28, 2017	Mfr Rpt #1702FRA011159
S1418/BR006 Breast	Mar. 30, 2017	Mfr Rpt #1610ESP009590 FU
S1512 Melanoma	Apr. 03, 2017	Mfr Rpt #2017IN001602 FU
	Apr. 05, 2017	Mfr Rpt #2016IN006836
	May 03, 2017	Mfr Rpt #1704USA014650
	May 05, 2017	Mfr Rpt #2017IN003503
	May 22, 2017	Mfr Rpt #1705FRA007621 FU
	May 22, 2017	Mfr Rpt #2017IN004029
	Jun. 02, 2017	AE-2717115

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

June 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutics	May 23, 2017 AE-2157148

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

June 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma	May 26, 2017 AE-2709452
S1418/BR006 Breast	May 31, 2017 AE-2292082 FU
S1512 Melanoma	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: June 15, 2017
E-mailed Date: June 2, 2017
Version Date May 8, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #5

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
(√) Expedited review allowed

Protocol changes
(√) Informed Consent changes
  (√) Patient notification required – Consent Addendum enclosed
(√) Other: Updated MK-3475 (pembrolizumab) CAEPR

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice. If local approval is not granted within 30 days, accrual must be suspended until approval is obtained.

Sites not using the NCI CIRB*:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes in this revision are effective upon approval by the local IRB; however, any changes to eligibility become effective 6 weeks after distribution of this notice. If local approval is not granted within 6 weeks, accrual must be suspended until approval is obtained.

REVISION #5

The above-referenced study has been updated as follows:

This revision has been prepared in response to the Request for Rapid Amendment (RRA) for MK-3475 (pembrolizumab, NSC 776864) from Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), Dr. Meg Mooney (mooneym@ctep.nci.nih.gov), and Dr. Elad Sharon (sharone@mail.nih.gov) on April 25, 2017. The associated action letter is attached.

1. The version date of the protocol and model consent form has been updated.

2. Table of Contents: The page numbers have been updated.

3. Section 3.3c: The CAEPR for MK-3475 (pembrolizumab), Version 2.2, April 20, 2016 has been replaced with Version 2.3, March 9, 2017. The section has been updated as follows:

   - Added New Risk:
     - Rare But Serious: Toxic epidermal necrolysis

   - Provided Further Clarification:
     - Footnote #2 has been added to Toxic epidermal necrolysis and it reads; "Immune-mediated adverse reactions have been reported in patients receiving MK-3475. Adverse events potentially related to MK-3475 may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475, administration of corticosteroids and supportive care."

4. The following changes have been made to the MK-3475 (pembrolizumab) Risks in the Model Consent Form:

   - Increased in Attribution:
     - Changed to Occasional from Rare: Reaction during or following a drug infusion which may cause fever, chills, rash

   - Provided Further Clarification:
     - The following statement was added (under Occasional and Rare): "MK-3475 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:"
     - Pain is now reported as 1) Pain in lymph nodes; 2) Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness; 3) Pain in the belly; 4) Pain or swelling of joints; 5) Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine; and 6) Pain in the chest (all under Occasional).
     - Pain and swelling of thyroid is now reported as Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting (under Occasional).
     - Swelling of the body which may cause shortness of breath is now reported as 1) Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly; 3) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (all under Occasional); and 4) Swelling or tenderness of blood vessels (under Rare).
     - Damage to the bone which may cause loss of motion is now reported as Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional).
     - Blisters on the skin, itching, acne, rash, skin changes, hives (under Occasional) and Severe skin rash with blisters and can involve inside of

mouth and other parts of the body (under Rare) are now reported as Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives (under Occasional).

- Heart failure which may cause shortness of breath, swelling of the ankles, cough or tiredness is now reported as Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankle and body (under Rare).
- 1) Weakness and paralysis; 2) Muscle weakness; and 3) Feeling of "pins and needles" in arms and legs are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, leg" (under Rare).
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling (under Rare).

Despite CTEP's assessment that the changes outlined in item number 4 constitute changes to risk presentation and not new risk information, SWOG requires that patients be notified of these changes, as the updated presentation includes risk information that could affect a patient's willingness to participate in the study. Patients must be notified of these changes by signing the attached Consent Addendum (Version Date 5/8/17). Patients must sign the Consent Addendum at their next scheduled visit, or within 90 days of CTSU distribution of this revision, whichever is sooner. Sites do not need to wait for local IRB approval before notifying patients of these changes. All patients who are consented prior to local implementation of this revision must sign the Consent Addendum.

5. The following additional changes have been to the consent form to abide by the template language provided in the Request for Rapid Amendment:

    - A bullet has been added under "What possible risks can I expect from taking part in this study" to read "You may be asked sensitive or private questions which you normally do not discuss
    - After the second paragraph, the stand-alone sentence under "What possible risks can I expect from taking part in this study" has been revised to read, "There is also a risk that you could have side effects from the study drug(s)/study approach".

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **June 1, 2017**

FROM: Elad Sharon, MD, MPH, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for MK-3475 (pembrolizumab, NSC 776864)

TO: Investigators for CTEP-supported Studies Involving MK-3475 (pembrolizumab, NSC 776864)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with MK-3475, and to request all trials with MK-3475 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes MK-3475. See the accompanying list of CTEP trials with MK-3475.

Although there is modified risk information for MK-3475, the added risk is very similar to a risk that was already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD). In this case, (1) toxic epidermal necrolysis is associated with the previously identified risk, rash maculo-papular, on the ICD.

When changes such as these are made to the ICD (i.e., changes as to how risk information is presented and/or additional clarifying information), it is not necessary to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the IRB. For this requested amendment, patient enrollment may continue before the IRB reviews and approves such changes to the ICD; however, changes to the ICDs cannot be implemented until they are approved by the IRB. An amendment that includes the new version of the CAEPR for MK-3475 and this additional clarification of risks in the ICD must be included in a protocol amendment as outlined in this Action Letter and per the time-lines specified.

In response to the new/modified risk information CTEP is requiring that all trials with MK-3475 be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on June 15, 2017** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Elad Sharon (sharone@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since MK-3475 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for

studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with MK-3475.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.3, March 9, 2017): ___
   Page Number(s): ____

- Added New Risk:
  - Rare But Serious: Toxic epidermal necrolysis

- Provided Further Clarification:
  - Footnote #2 has been added to Toxic epidermal necrolysis and it reads; "Immune-mediated adverse reactions have been reported in patients receiving MK-3475. Adverse events potentially related to MK-3475 may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475, administration of corticosteroids and supportive care."

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.3, and associated risk information for the ICD, to the most recent CAEPR Version 2.2. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.2), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Increased in Attribution:
  - Changed to Occasional from Rare: Reaction during or following a drug infusion which may cause fever, chills, rash

Action Letter

- Provided Further Clarification:
    - The following statement was added (under Occasional and Rare): "MK-3475 may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:"
    - Pain is now reported as 1) Pain in lymph nodes; 2) Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness; 3) Pain in the belly; 4) Pain or swelling of joints; 5) Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine; and 6) Pain in the chest (all under Occasional).
    - Pain and swelling of thyroid is now reported as Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting (under Occasional).
    - Swelling of the body which may cause shortness of breath is now reported as 1) Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly; 3) Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath (all under Occasional); and 4) Swelling or tenderness of blood vessels (under Rare).
    - Damage to the bone which may cause loss of motion is now reported as Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional).
    - Blisters on the skin, itching, acne, rash, skin changes, hives (under Occasional) and Severe skin rash with blisters and can involve inside of mouth and other parts of the body (under Rare) are now reported as Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives (under Occasional).
    - Heart failure which may cause shortness of breath, swelling of the ankles, cough or tiredness is now reported as Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankle and body (under Rare).
    - 1) Weakness and paralysis; 2) Muscle weakness; and 3) Feeling of "pins and needles" in arms and legs are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, leg" (under Rare).
    - Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling (under Rare).

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to MK-3475 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised MK 3475 CAEPR – Version 2.3, March 9, 2017

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab, NSC 776864).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, March 9, 2017[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypophysitis, hypopituitarism)[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infusion related reaction		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (immune thrombocytopenic purpura)[2]		
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475. Adverse events potentially related to MK-3475 may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475, administration of corticosteroids and supportive care.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain;

Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (generalized edema); Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Renal and urinary disorders - Other (nephrotic syndrome); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for MK 3475

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for MK 3475 in your ICD.

Risk Profile for MK-3475 (pembrolizumab) (CAEPR Version 2.3, March 9, 2017)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The MK-3475 (pembrolizumab) used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 (pembrolizumab) in your ICD.

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:

- Nausea
- Infection
- Loss of appetite
- Joint stiffness
- Swelling and redness of the skin

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Anemia which may require blood transfusion
- Pain in lymph nodes
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness
- Pain in belly
- Pain or swelling of the joints
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Pain in chest
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting
- Diarrhea
- Sores in the mouth which may cause difficulty swallowing
- Chills, fever
- Reaction during or following infusion of the drug which may cause fever, chills, rash
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly
- The body's reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet
- Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath
- Fluid in the joints
- Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:

Action Letter

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body
- Swelling and redness of the eye
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling
- Swelling or tenderness of blood vessels

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

3. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
   - The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
   - You may include additional non-Action Letter related changes (any type) in your amendment response.

Action Letter

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

Informed Consent Addendum Model for S1404: Testing MK-3475 (Pembrolizumab)Compared to Standard Treatment for High Risk Resected Melanoma

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

S1404 *A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma.*

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

The purpose of a consent addendum is to:

- *Inform patients of any significant new findings developed during the course of participation that may have a bearing on their willingness to continue in the study.*
- *Inform patients of specific changes (rather than having them sign a modified consent). The addendum will facilitate discussion since the changes/new findings are the focus of the document.*

This consent addendum has been prepared for patients currently registered to S1404 and/or receiving the study drug pembrolizumab.

The following information should be read as an addition to the original Consent form that you read and signed at the beginning of the study. Unless specifically stated otherwise in the following paragraphs, all information contained in that original Consent Form is still true and remains in effect. Your participation continues to be voluntary. You may refuse to participate, or may withdraw your consent to participate at any time, and for any reason, without jeopardizing your future care at this institution or your relationship with your study doctor.

New or additional information

The way that risk information is explained has recently changed. Please note that while the way the information is explained has changed, the risks related to pembrolizumab have not changed, except as specifically noted below. The following changes have been made to the risk tables for pembrolizumab:

In the Occasional, Some may be Serious section:

1. **The table has been reformatted for clarity. As part of this reformatting, the following sentence was added as a heading: "MK-3475 (pembrolizumab) may cause**

your immune system to attack normal organs and cause side effects in parts of the body. These problems may include but are not limited to."

2. **Pain has been changed to:**
    - **Pain in lymph nodes**
    - **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include diarrhea or increase in bowel movements, blood in your stools, or dark, tarry, sticky stools, severe belly pain or tenderness.**
    - **Pain in belly**
    - **Pain or swelling of the joints**
    - **Pain in chest**

3. **Pain; Swelling of the body which may cause shortness of breath; and Damage to the bone which may cause loss of motion have all been changed to:**
    - **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**

4. **Pain and swelling of thyroid has been changed to:**
    - **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior, decreased sex drive, weight loss or weight gain, excessive thirst or urine, dizziness or fainting**

5. **Swelling of the body which may cause shortness of breath has been changed to:**
    - **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting, drowsiness, pain in the right upper belly.**
    - **Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**

The following 2 items used to be reported as "Rare, and Serious," but are now reported as "Occasional, Some may be Serious":

6. **Reaction during or following a drug infusion which may cause fever, chills, rash.**

7. **Blisters on the skin, itching, acne, rash, skin changes, hives; and Severe skin rash with blisters and can involve inside of mouth and other parts of the body have been changed to:**
    - **Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives**

In the Rare, and Serious section:

1. **The following sentence was added as a heading: "MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in parts of the body. These problems may include but are not limited to."**

2. **Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness has been changed to Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.**

3. **Swelling of the body which may cause shortness of breath has been changed to Swelling or tenderness of blood vessels**

4. **Weakness and paralysis; Muscle weakness; Feeling of "pins and needles" in arms and legs has been changed to Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet, weakness of the arms, legs**

5. **Kidney damage which may require dialysis has been changed to Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling**

The tables provided below are the most current risk tables for pembrolizumbab. These tables show the most common and the most serious side effects that researchers know about related to pembrolizumab. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS **In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:**
• **Tiredness** •
OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:**

- **Nausea**
- **Infection**
- **Loss of appetite**
- **Joint stiffness**
- **Swelling and redness of the skin**

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Anemia which may require blood transfusion**
- **Pain in lymph nodes**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness**
- **Pain in belly**
- **Pain or swelling of the joints**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Pain in chest**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting**
- **Diarrhea**
- **Sores in the mouth which may cause difficulty swallowing**
- **Chills, fever**
- **Reaction during or following infusion of the drug which may cause fever, chills, rash**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly**
- **The body's reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet**
- **Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Fluid in the joints**
- **Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives**

RARE, AND SERIOUS **In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:**
MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • **Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body.** • **Swelling and redness of the eye** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.** • **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.** • **Swelling or tenderness of blood vessels**

My Signature Agreeing to Take Part in the Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study *and any additional studies where I circled 'yes'*.

Participant's signature_____

Date of signature_____

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

June 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Apr. 06, 2017	Mfr Rpt #BMS2017024625
S1404 Melanoma	Apr. 11, 2017	Mfr Rpt #BMS2017029521
S1609 Early Therapeutics	Apr. 11, 2017	Mfr Rpt #BMS2016066540 FU
	May 12, 2017	AE-2161738

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

May 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Mar. 30, 2017	Mfr Rpt #BMS2016111478 FU
S1404 Mel	Apr. 03, 2017	Mfr Rpt #BMS2017010125
S1609 Early Therapeutics	Apr. 05, 2017	Mfr Rpt #BMS2017026423
	Apr. 05, 2017	Mfr Rpt #BMS2017025083

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

May 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Apr. 25, 2017 AE-2904061

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Shannon Meroney-Davis – Merck
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

May 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutic	Apr. 11, 2017 AE-2994466 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org
swog.org

May 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Mar. 31, 2017 Mfr Rpt #2017IN000676 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Giovanna Kinahan – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification require- see details below
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to remind sites that the PPD kit ordering system being used to order kits for specimen submissions for PD-L1 testing (Section 15.2) and PK and ADA testing (Section 15.4) for this study has transitioned to the Preclarus Site Portal (http://preclaruslabdata.ppdi.com). **Effective March 31, 2017, all sites are required to use the Preclarus Site Portal to place subsequent kit orders.** If your site has not already obtained an active Preclarus Site Portal account, you are encouraged to do so at this time to avoid unnecessary kit ordering delays. As noted in the memorandum distributed on February 15, 2017, the following information is provided to accommodate the transition:

Prior to accessing Preclarus:

Each Site Coordinator should have received an e-mail from PPD about Preclarus with an activation link. The Site Coordinator will need to activate their site and grant access to any others requiring this access to the portal for the site to begin using this database.

If you have trouble accessing Preclarus:

Sites should contact preclaruslabdata@ppdi.com if they have not received an activation link, if they are unable to find the activation link, or if the activation link has expired. For general help in using the portal, sites should contact the Help Desk either by phone at 859/781-8877 (Option 1: Investigator Help Desk, Option 2: Supplies) or by e-mail at siteservices.us@ppdi.com.

Preclarus portal training:

PPD asks that Sites follow the below process for Training on the new Investigator Site Portal:

- **Step 1**: Review the Promo Video Link (approximately 20 minutes): https://www.youtube.com/watch?v=49Kirdp7XXU
- **Step 2**: Review the (2) training videos that walk through the process (approximately 20 minutes total):
  - Video 1: https://www.youtube.com/watch?v=omyL__7oFpU
  - Video 2: https://youtu.be/34g-GmczCz4

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Ahmad Tarhini, M.D., Ph.D. – ECOG-ACRIN
Teresa Petrella, M.D. – CCTG
TaNisha Evans – PPD
Marian Hansen – LabCorp

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

April 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Feb. 28, 2017 Mfr Rpt #BMS2017010889
S1404 Melanoma	Mar. 01, 2017 Mfr Rpt #BMS2016085259 FU
S1609 Early Therapeutic	Mar. 02, 2017 Mfr Rpt #BMS2016085054 FU
	Mar. 24, 2017 AE-2921421
	Mar. 28, 2017 Mfr Rpt #BMS2017020499 FU
	Apr. 03, 2017 Mfr Rpt #BMS2017021208 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by

your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

April 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutic	Mar. 03, 2017 AE-2093875

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

April 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Mar. 16, 2017 AE-2648538

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck
David McFadden – Merckp
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1400I Lung **S1404** Melanoma **S1609** Early Therapeutic	Feb. 23, 2017 AE-2728211

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org
swog.org

March 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Feb. 08, 2017 Investigator Notification

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck
David McFadden – Merckp
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

March 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Inclusion of social security numbers on Registration Worksheets

MEMORANDUM

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

MEMORANDUM

The hard copies of the Registration Worksheet for the following studies have been updated to be consistent with their RAVE counterparts to include the (optional) collection of Social Security Number. This collection is helpful to verify survival information with the National Death Index in cases where patients have been lost to follow-up.

S0820 (Reg-1)
S1206
S1207
S1313
S1314
S1316
S1318 (Reg-1)
S1320
S1400
S1403
S1404 (Reg-1)
S1605

Updated Registration Worksheets for the above-noted studies are found in the forms set of each study and can be accessed from their respective abstract pages (www.swog.org).

cc: PROTOCOL & INFORMATION OFFICE-CTEP
PROTOCOL & INFORMATION OFFICE-DCP

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Jan. 25, 2017 Mfr Rpt #BMS2017004099
S1404 Melanoma	Feb. 06, 2017 AE2568911
S1609 Early Therapeutic	

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reporst to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org
swog.org

March 1, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Feb. 10, 2017 AE-2331406

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck
David McFadden – Merck
Tanja Obradovic – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification require- see details below
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of a change to the PPD kit ordering system being used to order kits for specimen submissions as outlined in Sections 15.2d and 15.4d. Currently, the protocol instructs sites that initial orders will be placed via the SWOG Specimen Tracking System (SpecTrack), and then subsequent orders will be placed via https://sites.ppdi.com/. However, PPD is currently in the process of transitioning away from this kit ordering portal, and expects for it to be inactive by the end of February 2017. Initial orders will still be placed via SWOG SpecTrack, but **sites are instructed to use PPD's new Preclarus portal to place all subsequent kit orders**. The portal can be accessed at http://preclaruslabdata.ppdi.com.

Please note that all other specimen submission instructions outlined in the protocol remain the same – this change only affects subsequent kit orders outlined in Sections 15.2d and 15.4d. The protocol will be updated to replace the current kit ordering information with Preclarus portal kit ordering instructions with the next available protocol revision.

Prior to accessing Preclarus:

Each Site Coordinator should have received an e-mail from PPD about Preclarus with an activation link. The Site Coordinator will need to activate their site and grant access to any others requiring this access to the portal for the site to begin using this database.

If you have trouble accessing Preclarus:

Sites should contact preclaruslabdata@ppdi.com if they have not received an activation link, if they are unable to find the activation link, or if the activation link has expired.

For general help in using the portal, sites should contact the Help Desk either by phone at 859/781-8877 (Option 1: Investigator Help Desk, Option 2: Supplies) or by e-mail at siteservices.us@ppdi.com.

Preclarus portal training:

PPD asks that Sites follow the below process for Training on the new Investigator Site Portal:

- **Step 1**: Review the Promo Video Link (approximately 20 minutes): https://www.youtube.com/watch?v=49Kirdp7XXU

- **Step 2**: Review the (2) training videos that walk through the process (approximately 20 minutes total):
    - Video 1: https://www.youtube.com/watch?v=omyL__7oFpU

Video 2: https://youtu.be/34g-GmczCz4

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification require- see details below
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites of the *potential* requirement to close local accrual to the above-referenced study in response to the CTEP Action Letter distributed on February 2, 2017.

CTEP has updated the standard language included in their Action Letters to require immediate suspension of accrual to active studies until the revision incorporating the changes outlined in the Request for Rapid Amendment and Action Letter have been incorporated into the protocol/consent and approved by both CTEP and the IRB of record. CTEP and CIRB have approved this revision (Revision #4) for this study.

Sites whose IRBs of record have already reviewed and approved Revision #4 (including sites utilizing CIRB as the IRB of record) DO NOT need to suspend local accrual.

Any site not utilizing CIRB and whose IRB of record has not approved Revision #4 MUST suspend local accrual until the IRB of record has approved Revision #4.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse event that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:	
S1400I Lung	Dec. 21, 2016	Mfr Rpt #BMS2016102751 FU
S1404 Melanoma	Jan. 11, 2017	Mfr Rpt #BMS2016111478
S1609 Early Therapeutic	Jan. 13, 2017	Mfr Rpt #BMS2016109074 FU
	Jan. 18, 2017	Mfr Rpt #BMS2016031599 FU
	Jan. 19, 2017	AE-2077443

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reporst to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local

policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza – Bristol Myers Squibb

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org
swog.org

February 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Jan. 17, 2017 AE-2792541

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: February 15, 2017
E-mailed Date: February 2, 2017
Version Date January 19, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Danae Campos, Protocol Coordinator (E-mail: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #4

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required – see instructions at the end of memo
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice. If local approval is not granted within 30 days, accrual must be suspended until approval is obtained.

Sites not using the NCI CIRB*:* Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. The changes in this revision are effective upon approval by the local IRB; however, any changes to eligibility become effective 6 weeks after distribution of this notice. If local approval is not granted within 6 weeks, accrual must be suspended until approval is obtained.

REVISION #4

The above-referenced study has been updated as follows:

This revision has been prepared in response to the Request for Rapid Amendment (RRA) for Ipilimumab (MDX-010) (NSC 732442 & 720801) from Dr. Howard Streicher (streicherh@mail.nih.gov), Dr. James Zwiebel (zwiebelj@ctep.nci.nih.gov), and Dr. Meg Mooney (mooneym@ctep.nci.nih.gov) on January 4, 2017. The associated action letter is attached.

1. The version date of the protocol and model consent form has been updated.

2. Table of Contents: The page numbers have been updated.

3. Section 3.2c the CAEPR for Ipilimumab, Version 2.7 June 28, 2015 has been replaced with Version 2.8, December 28, 2016. The section has been updated as follows:

   - Added New Risk:
     - Rare but Serious: Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)
   - Increase in Risk Attribution:
     - Changed to Rare but Serious from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution: Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)
   - Decrease in Risk Attribution:
     - Changed to Rare but Serious from Less Likely: Infections and infestations - Other (aseptic meningitis)
   - Provided Further Clarification:
     - The following footnote #4 was added: “Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.”
   - Footnotes have been renumbered.

4. Section 8.3: The following note was added to the beginning of Sections 8.3b, 8.3c, and 8.3d, “ **NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis.” Section 8.3e “Dose Modification and Management for Cardiomyopathy Myocarditis” was added and the subsequent section was renumbered.

5. Section 9.2: “EKG, ECHO, CPK & Troponins” were added at baseline and the start of each cycle, with a corresponding note (u), indicating “For patients with history of CHF or who are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs should have an EKG and ECHO at baseline and at the start of each cycle, as clinically indicated. Patients who have evidence at baseline (or subsequently) of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, ECHO cardiogram, as clinically indicated.”

Patients currently receiving Ipilimumab and patients who sign a consent form prior to local implementation of the revised consent form must be informed of the changes that are in **bold** font. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

6. The following changes have been made to the Ipilimumab Risks in the Model Consent Form:

- **Added New Risk:**
  - **Occasional: Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [the term above is a clinical manifestation of lab values not previously listed on the risk list]**
- **Increase in Risk Attribution:**
  - **Changed to Rare from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution (i.e. added to risk profile): A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**
- Provided Further Clarification:
  - Rash (under Common); Itching, Hives, Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional); and Severe skin rash with blisters and peeling which can involve mouth and other parts of the body (under Rare) are now reported as Skin: itching; rash, blisters including inside the mouth (can be severe); hives (under Common).
  - Pain is now reported as Pain in belly and Pain or swelling of the joints.
  - Constipation (under Occasional) is now reported as Blockage of the bowels which may cause constipation (under Rare).
  - Swelling of the body which may cause shortness of breath is now reported as part of 1) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional); 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly (under Occasional); 4) Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion (under Rare); and 5) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
  - Chills and Reaction during or following infusion of the drug are now reported as Reaction during or following a drug infusion which may cause fever, chills, rash.
  - Damage to organs leading to prolonged hospitalization is now reported as part of 1) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath; and 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
  - Difficulty eating, Abnormal movement of the facial muscles, and Weakness and paralysis are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
  - Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.

- A tear or hole in the stomach that may require surgery (under Rare) is now reported as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin is now reported as Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Headache is now reported as part of Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- The following statement was added (under Common, Occasional, and Rare): “Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body.”

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **February 1, 2017**

FROM: Howard Streicher, MD, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Ipilimumab (MDX-010, NSCs 732442 and 720801)

TO: Investigators for CTEP-supported Studies Involving Ipilimumab (MDX-010, NSCs 732442 and 720801)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with ipilimumab, and to request all trials with ipilimumab be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes ipilimumab. See the accompanying list of CTEP trials with ipilimumab.

In response to the new/modified risk information CTEP is requiring that all trials with ipilimumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on February 15, 2017** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since ipilimumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a

Action Letter

CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

On August 30, 2016, the FDA requested that CTEP 1) revise the ICD for all clinical trials that are investigating the use of ipilimumab and BMS-936558 (nivolumab) and ipilimumab to include the event of myocarditis, and 2) revise all protocols investigating ipilimumab and nivolumab and ipilimumab to include additional monitoring and management for myocarditis.

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with ipilimumab.

Risk Mitigation Plan

- Protocols will be revised to provide more specific guidelines for cardiac toxicities.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) Specific Protocol Revisions to Address Risk Mitigation Plan: (insert section and page # as appropriate)

- Provide more specific guidelines for cardiac toxicities, including the stipulations listed below:
  - Add on study evaluation of cardiac function including EKG and ECHO cardiogram for any patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs as clinically indicated.
  - For patients with evidence of CHF, MI, cardiomyopathy, or myositis cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram.
  - Drug modification table for cardiomyopathy myocarditis should be included in the appropriate section
    - Drug will be held for grade 2 cardiac dysfunction pending evaluation
    - Drug will be permanently discontinued for grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur
    - Treatment with steroids as clinically indicated
    - Add the table as follows in the treatment modification and AE management section

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.

Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Consult algorithm for more details. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

3) Revision of the Protocol CAEPR:

Protocol Section(s) for Insertion of Revised CAEPR (Version 2.8, December 21, 2016): ___
Page Number(s): ____

- Added New Risk:
  - Rare but Serious: Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)

- Increase in Risk Attribution:
  - Changed to Rare but Serious from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution: Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)

- Decrease in Risk Attribution:
  - Changed to Rare but Serious from Less Likely: Infections and infestations - Other (aseptic meningitis)

- Provided Further Clarification:
  - The following footnote #4 was added: "Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT."
  - Footnotes have been renumbered.

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.8, and associated risk information for the ICD, to the most recent CAEPR Version 2.7. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.7), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

Action Letter

4) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed form. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Occasional: Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting [the term above is a clinical manifestation of lab values not previously listed on the risk list]

- Increase in Risk Attribution:
  - Changed to Rare from Also Reported on Ipilimumab Trials But With Insufficient Evidence for Attribution (i.e. added to risk profile): A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma

- Provided Further Clarification:
  - Rash (under Common); Itching, Hives, Rash which may cause fever and swollen, red, painful bumps in the skin (under Occasional); and Severe skin rash with blisters and peeling which can involve mouth and other parts of the body (under Rare) are now reported as Skin: itching; rash, blisters including inside the mouth (can be severe); hives (under Common).
  - Pain is now reported as Pain in belly and Pain or swelling of the joints.
  - Constipation (under Occasional) is now reported as Blockage of the bowels which may cause constipation (under Rare).
  - Swelling of the body which may cause shortness of breath is now reported as part of 1) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath (under Occasional); 2) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine (under Occasional); 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly (under Occasional); 4) Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion (under Rare); and 5) Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body (under Rare).
  - Chills and Reaction during or following infusion of the drug are now reported as Reaction during or following a drug infusion which may cause fever, chills, rash.
  - Damage to organs leading to prolonged hospitalization is now reported as part of 1) Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine; 2) Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath; and 3) Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.

Action Letter

- Difficulty eating, Abnormal movement of the facial muscles, and Weakness and paralysis are now reported as Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Kidney damage which may require dialysis is now reported as Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- A tear or hole in the stomach that may require surgery (under Rare) is now reported as Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness (under Occasional).
- Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin is now reported as Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.
- Headache is now reported as part of Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
- The following statement was added (under Common, Occasional, and Rare): "Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body."

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to ipilimumab is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised Ipilimumab CAEPR – Version 2.8, December 21, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Ipilimumab (MDX-010, NSCs 732442 and 720801)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.8, December 21, 2016[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypopituitarism/hypophysitis)[2]		
	Endocrine disorders - Other (testosterone deficiency)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction		
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Neutrophil count decreased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
	Facial nerve disorder		
	Headache		
	Nervous system disorders - Other (Guillain-Barre syndrome)[2]		
	Nervous system disorders - Other (myasthenia gravis)[2]		
	Trigeminal nerve disorder		

Action Letter

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 4.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receiving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage,

Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Dyspepsia; Dysphagia; Gastrointestinal hemorrhage[6]
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; Weight loss; White blood cell decreased
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia, Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for Ipilimumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for ipilimumab in your ICD.

Risk Profile for Ipilimumab (CAEPR Version 2.8, December 21, 2016)

Special precautions Side effects of ipilimumab may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**
COMMON, SOME MAY BE SERIOUS In 100 people receiving ipilimumab, more than 20 and up to 100 may have:
• Diarrhea, nausea • Tiredness Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to: • Skin: itching; rash, blisters including inside the mouth (can be severe); hives

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving ipilimumab, from 4 to 20 may have:

- Abnormal heartbeat
- Hearing loss
- Swelling and redness of the eye
- Pain in belly
- Difficulty swallowing, vomiting, loss of appetite
- Fever
- Dehydration
- Pain or swelling of the joints
- Reaction during or following a drug infusion which may cause fever, chills, rash
- Low blood pressure which may cause feeling faint

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.
- Problem of the muscle, including inflammation, which can cause muscle pain and severe muscle weakness sometimes with dark urine.
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.

Action Letter

RARE, AND SERIOUS
In 100 people receiving ipilimumab , 3 or fewer may have:

- Bleeding
- Blockage of the bowels which may cause constipation
- Swelling of the brain which may cause headache, blurred vision, stiff neck, and/or confusion

Ipilimumab may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma
- Heart problems including inflammation and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.
- Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does <u>not</u> already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. <u>Trials with a current CTEP status of **"Active"**</u>

- Review and follow **<u>ALL</u>** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **<u>ONLY</u>** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy.
- Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR

3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239

503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229

210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101

206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109

206-667-4623
206-667-4408 FAX

swog.org
swog.org

January 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Dec. 13, 2016 Mfr Rpt #20161N007612 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

January 15, 2017

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Danae Campos, Protocol Coordinator (Email: dcampos@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(√) Other: Updated Funding Memorandum

MEMORANDUM

The purpose of this memorandum is to inform sites that the **S1404** Funding Memorandum has been updated on the protocol abstract page of the SWOG website (www.swog.org) and CTSU (www.ctsu.org).

Please note that participating sites are eligible to receive funds for Quality of Life submissions as indicated in Section 15.5 of the protocol. For patients registered to Step 2 and participating in QOL on or prior to 8/3/2016, these funds will be provided through federal sources. Sites must enter the Step 2 registration date into OPEN to trigger this payment. For patients registered to Step 2 after 8/3/2016, funds are being provided through non-federal sources

and payment will be automatically triggered by the submission/upload of the required QOL forms into Medidata Rave.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski - Merck
Lam Calderon - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(X) Other: **:** Updated Eligibility Checklist-Step1 (**S1404** Master Forms Set)

MEMORANDUM

The purpose of this memorandum is to inform sites that the "Eligibility Checklist-Step 1" in the **S1404** Master Forms Set has been updated to be congruent with Revision #3 changes. The revised Master Forms Set is accessible from the protocol abstract page of the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski - Merck
Lam Calderon - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
(X) Other: **:** Spanish Translated Model Consent Form (Revision 3, 9/28/16) and Certificate of Translation available

---

MEMORANDUM

The purpose of this memorandum is to indicate that the Spanish-translated version of the Model Consent Form for Revision 3 (version 9/28/16) has been approved by the NCI CIRB, and the Spanish MCF and Certificate of Translation are now accessible from the protocol abstract page at www.swog.org.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski - Merck
Lam Calderon - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

December 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:	
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma	Nov. 15, 2016	AE2990099

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org
swog.org

November 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:	
S1404 Melanoma **S1512** Melanoma	Oct. 13, 2016	Mfr Rpt #2016IN006422

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Joan Puchalski – Merck
Lam Calderon – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

November 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites that the **S1404** Master Forms Set has been updated to be congruent with Revision #3 changes, distributed on 11/1/2016. The revised Master Forms Set is accessible from the protocol abstract page of the SWOG website (www.swog.org) and CTSU (www.ctsu.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Jean Puchalski
Lam Calderon - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to clarify to sites and potential auditors that although a requirement to complete and submit the Eligibility Checklist was added with Amendment #1 (dated 2/19/16), distributed on 4/15/2016, the revised Eligibility Checklist was not actually made available until distribution of the new Master Forms Set on 9/15/16.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: November 1, 2016
CTEP Submission Date September 28, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #3

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
(√) Eligibility changes
(√) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required – see instructions at the end of memo
( ) Scientific / Statistical Consideration changes
(√) Specimen Submission changes
( ) Data Submission / Forms changes
(√) Editorial / Administrative changes
( ) Other:

REVISION #3

1. Title Page, Page 1: The version date of the protocol and model consent form has been updated. The e-mail address for Drs. Grossmann and Patel has been changed to S1404SCquestion@swog.org and has been updated throughout the protocol. The P.O. Box for the SWOG Statistical Center has been updated.

2. Table of Contents, Pages 3-4: The Table of Contents has been updated.

3. CTSU Table, Page 5: The section regarding regulatory and monitoring procedures for CTSU sites has been removed.

4. Section 1.3c, Page 7: "and FACIT-D" has been added.

5. Section 2.0, Page 11: Information regarding the FACIT-D has been added to the first paragraph.

6. Section 3.0, Page 12: In the second paragraph under "Investigator's Brochures" the information for accessing IBs from the Pharmaceutical Management Branch has been updated.

7. Section 3.2c, Pages 16-20: The CAEPR has been updated from Version 2.6, July 8, 2014 to Version 2.7, June 28, 2015. The following changes have been made:

   Added New Risk
   - Rare but Serious: Immune system disorders – Other (GVHD in the setting of allotransplant)
   - Also Reported on Ipilimumab (MDX-010) Trials But With Insufficient Evidence for Attribution: Alopecia

8. Section 3.3g, Page 28: Information regarding procedures for reporting temperature excursion has been added.

9. Section 5.0, Page 31: "…42, or 90" has been added to the last sentence of the second paragraph.

10. Section 5.1d, Page 31: "node-positive" has been added to the third sentence.

11. Section 5.1e, Page 32: The following has been added as the third sentence, "This must be documented by having a pathologist sign the **S1404** Local Pathology Review form (see Section 18.4) prior to Step 1 registration.

12. Section 5.1j, Page 32: "While on this protocol" has been changed to "after Step 2 registration".

13. Section 5.1l, Page 32: In the second sentence, "plus a CT of the neck if patient has a primary melanoma of the head and neck" has been removed. The third and fourth sentences have been added for clarification regarding neck imaging. "imaging" has been added to the last sentence.

14. Section 5.1m, Page 32: This section was previously under 5.1l and has been made a separate eligibility criterion for clarification. Subsequent sections have been renumbered accordingly. "within 90 days prior to registration" has been added to the first sentence.

15. Section 5.1o, Page 33: "or" after "SGOT (AST)" has been changed to "and".

16. Section 5.2c, Page 35: This new criterion has been added to clarify that no tests or exams are required to be repeated for Step 2 registration.

17. Section 7.1a, Page 36: "triglycerides and thyroid function tests (T3, TSH, and T4)" has been removed from the second sentence.

18. Section 7.1b.1, Page 37: Under "Self Administration of Subcutaneous Doses", "the **S1404** Patient Diary – Interferon alfa-2b (Section 18.3)" has been replaced with "compliance documentation (Section 7.3) for self-administered doses".

19. Section 7.1b.2, Pages 37-38: Under "Induction Therapy", "Weeks 1-10;" has been added and a "*" and footnote regarding dose rounding have been added to the table. Under "Maintenance Therapy", "Weeks 25-145;" has been added to the table in the schedule column, "12 doses" has been changed to "11 doses" in the schedule column, and a "*" and footnote regarding dose rounding have been added to the table.

20. Section 7.1c, Page 38: In the second sentence of the fifth paragraph, "Sponsor" has been changed to "Study Chairs".

21. Section 7.2, Pages 38-39: The first paragraph has been moved from the bulleted list and the following has been added, "must be completed at least 1 day prior to starting ipilimumab or MK-3475 and must be completed at least 7 days prior to starting interferon.". The second paragraph has been revised from "…therapies during the screening and treatment phases of this trial" to "therapies after registration to Step 1 and through completion of protocol therapy.".

22. Section 7.3, Page 39: In the first sentence, "on the **S1404** protocol abstract page of the SWOG website (www.swog.org)" has been replaced with "in Section 18.3".

23. Section 8.2b, Page 40: Information has been added to allow dose modifications outside of the guidelines prescribed in Section 8.2 for patients receiving interferon. These non-prescribed modifications are allowed at the discretion of the treating physician, providing the modification is due to HDI-related toxicity, and the treating physician feels that the modification is in the patient's best interest, after consideration of patient safety and overall clinical status. Any such modifications must be documented on the **S1404** Treatment Form.

24. Section 8.3a, Page 42: At the end of the third paragraph, "4 weeks before or after any dose of ipilimumab" has been changed to "1 week before or after any dose of ipilimumab".

25. Section 8.3b, Page 43: The reference to "Section 5.5.1.1.3" has been removed as it is not applicable.

26. Section 8.3c, Page 43: In the first sentence of the first paragraph, the spelling has been corrected for "corticosteroids".

27. Section 8.4a, Page 44: In the first paragraph, "should" has been changed to "must". The following has been added as the third paragraph, "NOTE: Due to the possible effect of treatment with MK-3475 on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) within 1 week before or after any dose of MK-3475."

28. Section 8.5, Page 49: "on the **S1404** Concomitant Medication Form" has been added to the first sentence.

29. Section 8.7, Page 49: The following has been added as the last sentence: "Document on the **S1404** Concomitant Medication Form".

30. Section 9.1, Pages 50-52:
Calendar: The "Induction Phase" box has been modified to only cover the columns for Weeks 1-4 and the "Maintenance Phase" box has been modified to cover the columns for Weeks 5-49. The second column under "C5" has been corrected to "W 43" and the column under "C6" has been corrected to "W 49". "and FACIT-D" has been added to the second row under "FORMS FOR QOL STUDIES". On the fourth row under "LABORATORY", "or" has been replaced with "and". On the 6th row under "LABORATORY", the "g" footnote has been replaced with "a". On the 8th row under "LABORATORY", "free" was added to T_3 and T_4. An "X" has been added to the Pre-study screening column for triglycerides and free T_3, TSH, and free T_4 and an "X" has been removed from the Cycle 1 Week 1 column for these rows. On the Interferon alfa-2b row, "→" has been replaced with "X" from Week 5 – Week 49. In the second NOTE below the table, the link to the SWOG guidelines has been updated.

Footnotes: In "a" and "c", "AST or ALT" has been changed to "AST and ALT". In "b", "13" has been changed to "15". In "c", the following has been added as the second sentence, "The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up.". In "g", "albumin, glucose, and electrolytes" and "within 3 days prior to the start of study treatment" have been removed and "at screening" has been added. In "k", the following has been added as the last sentence, "MRI of the brain is required for patients with progressive disease.". In "j", "or unknown primary with disease in the axilla" has been added. In "p" and "q", "FACIT-D" has been added. In "r", "at screening" has been added.

31. Section 9.2, Pages 53-55:
Calendar: Cycle 2 has been moved under "Induction" and over the columns for Weeks 7 and 10. Subsequent cycles have been renumbered. "FACIT-D" has been added to the second row under "FORMS FOR QOL STUDIES". On the fourth row under "LABORATORY", "or" has been replaced with "and". On the 6th row under "LABORATORY", the "g" footnote has been replaced with "a". On the 8th row under "LABORATORY", "free" was added to T_3 and T_4. An "X" has been added during Week 4 and Week 10 for rows 1, 2, and 4-6 under "LABORATORY". An "X" has been added to the Screen column for triglycerides and free T_3, TSH, and free T_4 and an "X" has been removed from the Cycle 1 Week 1 column for these rows. An "X" has been added to the 8th row under "LABORATORY" at Week 37. On the "Ipilimumab" row, the "X" at Week 13 has been removed. In the second row under "X-RAYS AND SCANS", the X under "End of treatment" has been removed. In the second row under "SPECIMEN SUBMISSION", the X under "Reg Step 1" has been moved to "Reg Step 2". In the second NOTE below the table, the link to the SWOG guidelines has been updated.

Footnotes: In "a" and "c", "AST or ALT" has been changed to "AST and ALT". In "b", "13" has been changed to "15". In "c", "then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (-/+ 2 weeks) if the patient is < 2 years from study entry" has been removed and the following has been added as the second sentence: "The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up.". In "g", "albumin, glucose, and electrolytes" and "within 3 days prior to the start of study treatment" have been removed and "at screening" has been added. In "k", the following has been added as the second to last sentence: "MRI of the brain is required for patients with progressive disease.". In "j", "or unknown primary with disease in the axilla" has been added. In "o", "at screening" has been added. In "r" and "s", "FACIT-D" has been added.

32. Section 9.3, Pages 56-58:
Calendar: In the "ON TREATMENT" box, "Each cycle consists of 2 infusions" has been replaced with "The first two cycles consist of 2 infusions, subsequent cycles consist of 4 infusions". "FACIT-D" has been added to the second row under "FORMS FOR QOL STUDIES". On the 4th row under "LABORATORY", "or" has been replaced with "and". On the 6th row under "LABORATORY", the "g" footnote has been replaced with "a". On the 8th row under "LABORATORY", "free" was added to T_3 and T_4. An "X" has been added to the Screen column for triglycerides and free T_3, TSH, and free T_4 and an "X" has been removed from the Cycle 1 Week 1 column for these rows. In the third row under "SPECIMEN SUBMISSION", the X under "Reg Step 1" has been moved to "Reg Step 2". In the second NOTE below the table, the link to the SWOG guidelines has been updated.

Footnotes: In "a" and "c", "AST or ALT" has been changed to "AST and ALT". In "c", the following has been added as the second sentence, "The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up.". In "g", "albumin, glucose, and electrolytes" and "within 3 days prior to the start of study treatment" have been removed and "at screening" has been added. In "k", the following has been added as the last sentence, "MRI of the brain is required for patients with progressive disease.". In "j", "or unknown primary with disease in the axilla" has been added. In "o", "at screening" has been added. In "q", a duplicative "before" has been removed and "first infusion Cycle 3 (Week 19)" has been changed to "third infusion Cycle 3 (Week 19)". In "r" and "s", "FACIT-D" has been added.

33. Section 10.1, Page 59: The first bullet regarding appearance of a new melanoma in-situ or Stage I melanoma has been added.

34. Section 11.5, Pages 62 and 64: In the second sentence of the 4th paragraph, "alpha=0.25%" has been replaced with "alpha=0.125%". In Table 3, the "Year 3 interim efficacy" and "Year 4 interim efficacy" alpha levels have been changed to "0.125%".

35. Section 11.7g, Pages 66-67: Information regarding the FACIT-D has been added to the first, third, fifth, and seventh paragraphs in this section.

36. Section 13.1, Page 67: "3 business days prior to submission of specimens…" has been changed to "7 business days prior to submission of specimens…".

37. Section 13.2, Page 68: Under "Requirements for site registration", the following has been added as the third bullet, "Verification of training completion (see Section 15.7)".

38. Section 14.4h, Page 73: "**S1404** FACT-BRM" has been changed to "**S1404** FACIT-BRM-FACIT-D". In the last paragraph, "For the first two patients enrolled at each site" has been added, "Follow-Up Form" has been changed to "Other form", and a note about additional submissions has been added.

39. Section 15.1a, Page 74: The address for Lab #201 has been removed.

40. Section 15.2a, Page 75: "along with" and "a copy of the **S1404** Local Pathology Review Form (Appendix 18.4)" have been removed.

41. Section 15.2c, Page 75: A note regarding kit expiration has been added to the end of this section.

42. Section 15.2d, Page 75: In first paragraph of subsection 1, the last three sentences have been revised to clarify the process for ordering supplies from PPD. The second paragraph has been added for clarification. In subsection 2, "the following" has been removed from the first sentence and "After reordering" has been added to the second sentence.

43. Section 15.2e, Page 76: In subsection 2, "PPD-GCL" has been changed to "kit". Subsections 7 and 15 have been bolded. In subsection 15, "PPD-GCL" has been removed and "from kits" has been added. In subsection 16, "and frozen gel packs/wraps" has been added, "the **S1404** Local Pathology Form and 3) the packing slip generated by" has been removed, and "the SWOG Online Specimen Tracking System" has been replaced with "the SWOG Specimen Tracking System Packing List".

44. Section 15.2f, Page 77: Shipping instructions following the bulleted list have been replaced with a new bulleted list and LabCorp (Lab #218) contact information has been removed. A note regarding the alternate study ID number and bullet referring to the PPD Laboratory Manual have been added.

45. Section 15.3a, Page 77: "Do NOT submit specimens for banking to LabCorp." has been added.

46. Section 15.3b.1, Page 78: The second bullet has been changed from "Progression/relapse" to "Relapse".

47. Sections 15.4d, 15.4f, and 15.4g, Pages 79-80: Information related to kit ordering, sample collection and preparation procedures, and shipping instructions has been updated for clarification.

48. Section 15.5a, Page 81: Subsection 6 has been added to address the process once a patient has completed on-treatment questionnaires and immediately has disease recurrence.

49. Section 15.5c, Page 82: "and FACIT-D" has been added to the first sentence of this section.

50. Section 15.5d, Page 82: "and FACIT-D" has been added to the first sentence of this section. The first bullet has been changed from "Baseline" to "Randomization" and in the second bullet, "Weeks 1 and" has been removed.

51. Section 15.7, Page 83: This section has been added to include information regarding the mandatory site training that must be completed prior to patient registration.

52. Section 16.1h.2, Page 89: The first paragraph has been revised to include current instructions for submission of supporting documentation.

53. Section 17, Page 92: Reference 22 has been added.

54. Section 18.6, Page 108: Under "On Site Monitoring" in the first bullet, "the second course" has been changed to "six weeks" and the following sentence has been added, "No off-site monitoring is required if the first onsite monitoring visit is scheduled within 4 months of the second patient registration."

55. Model Consent Form, Page 3: The study title has been revised to include "Either".

56. Model Consent Form, Page 6: In the second bullet under "What extra tests…", "two questionnaires" has been replaced with "three questionnaires" and the estimated time to complete questionnaires has been corrected from "about 20 minutes" to "about 10 minutes".

57. Model Consent Form, Page 8: The "Possible Side Effects of interferon alfa-2b" tables have been updated as follows:

- Added New Risk:
  - COMMON, SOME MAY BE SERIOUS: weight loss.
  - OCCASIONAL, SOME MAY BE SERIOUS: low blood pressure; change in skin color, numbness or pain in fingers and toes; diabetes; internal bleeding, which may cause black tarry stool, blood in vomit; blurred vision with chance of blindness, visual loss; bleeding of the eye; blockage of the lungs or lung collapse; damage to the blood vessel in lungs; blood clot.

- Risk increased in occurrence
  - Moved from RARE, AND SERIOUS to COMMON, SOME MAY BE SERIOUS: anemia which may require blood transfusions.
  - Moved from RARE, AND SERIOUS to OCCASIONAL, SOME MAY BE SERIOUS: abnormal heartbeat; allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat.

- Risk decreased in occurrence
  - Moved from COMMON, SOME MAY BE SERIOUS to OCCASIONAL, SOME MAY BE SERIOUS: confusion.

- Risk modified
  - COMMON, SOME MAY BE SERIOUS: "fever, chills" has been removed from "flu-like symptoms including fever, chills, body aches, muscle pain" and added as a separate bullet.
  - OCCASIONAL, SOME MAY BE SERIOUS: "heart failure which may cause…" has been changed to "heart failure or attack which may cause..."; "stroke" has been changed to "stroke, coma".

- Risk deleted
  - COMMON, SOME MAY BE SERIOUS: changes in taste.
  - OCCASIONAL, SOME MAY BE SERIOUS: swelling and redness at the side of the medication injection which may cause paralysis, weakness; severe skin rash with blisters and can involve inside of mouth and other parts of the body.

58. Model Consent Form, Page 9: The "Possible Side Effects of Ipilimumab" tables have been updated as follows:

- Added New Risk:
  - COMMON, SOME MAY BE SERIOUS: rash
  - RARE, AND SERIOUS: damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, or dry skin* (*This is applicable for patients who have undergone a stem cell transplant).

- Risk decreased in occurrence
  - Moved from COMMON, SOME MAY BE SERIOUS to OCCASIONAL, SOME MAY BE SERIOUS: rash which may cause fever and swollen, red, painful bumps in the skin.

59. Model Consent Form, Page 13: In the last sentence of the “Reproductive risks” paragraph, “(barrier method plus hormonal method)” has been changed to “two barrier methods, barrier method plus hormonal method, or barrier method plus IUD)”.

60. Model Consent Form, Page 16: Under “What is involved”, in subsection 1 “Cycle 5” has been corrected to “Cycle 4” in the last sentence.

61. Model Consent Form, Page 19: “(or legally authorized representative)” has been removed.

Patients currently receiving interferon alfa-2b and patients currently receiving ipilimumab must be informed of the increased risks described in item #57 and #58, respectively. The manner by which this notification takes place is at the discretion of the local IRB. At a minimum the patient must be notified at the next visit and this process must be documented in the patient chart

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

September 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S1404 Melanoma	Aug. 17, 2016 AE2836143

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

September 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform participating institutions that the Master Form Set has been updated on the protocol abstract page of the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

August 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform participating institutions that the Site Manual and Protocol Refreshment Sheet (Imaging) has been updated on the protocol abstract page.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

July 15, 2016

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Reports:
S1404 Melanoma	Jun. 17, 2016 Mfr Rpt #2016IN003519 Jun. 27, 2016 Mfr Rpt #AE-2337114

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

Distribution Date: July 15, 2016
E-mailed Date: July 6, 2016

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  (√) Patient notification required of changes to Model Informed Consent in Revision #2
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to give sites additional information regarding Revision #2 that was distributed on 6/27/16.

CTEP considers that the Model Consent Form changes represent a **minor** alteration in risk/benefit ratio. Therefore, sites **must suspend** accrual of new patients to Step 1 Registration until local implementation of the revised consent form. (Patients are considered on study if they have already signed a consent form as of 6/27/16 at 11:59 P.M. Pacific. Such patients may be registered to Step 1 Registration.). The suspension of accrual does not apply to Step 2 Registration (Randomization). Patients currently receiving MK-3475 and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the Model Informed Consent changes in Revision #2. The manner by which the notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented on the patient chart.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

Distribution Date: July 1, 2016
E-mailed Date: June 27, 2016
CTEP Submission Date June 17, 2016

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #2

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
(√) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
(√) Informed Consent changes
  (√) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

REVISION #2

This revision is in response to the June 3, 2016 RRA from Dr. Elad Sharon (sharone@mail.nih.gov). The Action Letter is attached.

1. Title Page, Page 1: The version date of the protocol and model consent form has been updated.

2. Section 3.3c, Pages 22-26: The revised CAEPR (Version 2.2, April 20, 2016) has been inserted and includes the following changes:
   - Added New Risk:
     - Less Likely: Bullous dermatitis; CPK increased; Immune system disorders - Other (pseudoprogression/tumor inflammation); Immune system disorders - Other (immune thrombocytopenic purpura); Infusion related reaction; Joint effusion; Joint range of motion decreased; Lymph node pain; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (tenosynovitis); Skin and subcutaneous tissue disorders - Other (dermatitis); Small intestinal mucositis; Urticaria
     - Rare but Serious: Anaphylaxis; Cytokine release syndrome; Erythema multiforme; Immune system disorders - Other (hemophagocytic lymphohistiocytosis); Myocarditis; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (myasthenic syndrome); Nervous system disorders - Other (neuromyopathy); Nervous system disorders - Other (polyneuropathy); Peripheral motor neuropathy; Serum sickness; Stevens-Johnson syndrome; Vasculitis
     - Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Agitation; Alopecia; Aphonia; Ascites; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Cholesterol high; Depressed level of consciousness; Disseminated intravascular coagulation; Duodenal hemorrhage; Dysphagia; Edema cerebral; Edema face; Eye pain; Facial pain; Fibrinogen decreased; Gait disturbance; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (generalized edema); Heart failure; Hemolysis; Hydrocephalus; Hypercalcemia; Hyperkalemia; Hypertension; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Hypoxia; Laryngeal inflammation; Lethargy; Lymphocyte count decreased; Malaise; Meningismus; Metabolism and nutrition disorders - Other (failure to thrive); Musculoskeletal and connective tissue disorder - Other (groin pain); Myocardial infarction; Nervous system disorders - Other (brainstem herniation); Non-cardiac chest pain; Oral pain; Pelvic pain; Pericardial tamponade; Pneumothorax; Proteinuria; Rectal hemorrhage; Renal and urinary disorders - Other (hydronephrosis); Renal and urinary disorders - Other (nephrotic syndrome); Skin and subcutaneous tissue disorders - Other (drug eruption); Small intestinal perforation; Thromboembolic event; Tremor; Tumor lysis syndrome; Upper gastrointestinal hemorrhage; Urinary tract pain; Ventricular arrhythmia

   - Increase in Risk Attribution:
     - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Adrenal insufficiency; Alkaline phosphatase increased; Arthritis; Avascular necrosis; Blood bilirubin increased; Colitis; Endocrine disorders - Other (hypophysitis, hypopituitarism); Endocrine disorders - Other (thyroiditis); Erythroderma; Hepatobiliary disorders - Other (autoimmune hepatitis); Hyperthyroidism; Myositis; Pancreatitis; Pleuritic pain; Rash acneiform
     - Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: GGT increased; Pericarditis; Serum amylase increased; Paresthesia

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Pruritus; Rash maculo-papular
  - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Abdominal pain; Constipation; Cough; Dyspnea; Edema limbs; Headache; Vomiting; Weight loss

- Provided Further Clarification:
  - Renal and urinary disorders - Other (nephritis autoimmune) (under Rare but Serious) is now reported as Renal and urinary disorders - Other (autoimmune nephritis) (under Rare but Serious).
  - Metabolism and nutrition disorders - Other (insulin resistant diabetes) (under Reported but With Insufficient Evidence for Attribution) is now reported as Hyperglycemia (under Reported but With Insufficient Evidence for Attribution).
  - Footnote 2 is now Footnote 3, and Footnote 3 is now Footnote 2.

- Deleted Risk:
  - Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Amnesia; Depression; Dizziness; Dry eye; Dry mouth; Hot flashes; Hyperhidrosis; Hypothermia; Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine increased); Lower gastrointestinal hemorrhage; Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Peripheral sensory neuropathy; Productive cough; Pulmonary edema; Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (scar pain)

3. Section 5.1s, Page 33: This eligibility criterion has been revised from “Patients must not have evidence of active, non-infectious pneumonitis.” to “Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.”

4. Model Consent Form, Page 12: The risk profile for MK-3475 has been updated with the following changes:
   - Added New Risk:
     - Occasional: Blisters on the skin; Fluid in the joints; Hives; Joint stiffness; Sores in the mouth which may cause difficulty swallowing; Swelling and redness of the skin; The body’s reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet.
     - Rare: Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat; Muscle weakness; Reaction during or following a drug infusion which may cause fever, chills, rash; Severe skin rash with blisters and can involve inside of mouth and other parts of the body; Weakness and paralysis

   - Increase in Risk Attribution:
     - Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Acne; Damage to the bone which may cause loss of motion; Pain and swelling of thyroid
     - Changed to Rare from Reported but With Insufficient Evidence for Attribution: Feeling of "pins and needles" in arms and legs; Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Itching; Rash
  - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Constipation; Cough; Headache; Shortness of breath; Vomiting; Weight loss

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **June 24, 2016**

FROM: Elad Sharon, MD, MPH, Medical Officer, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for MK-3475 (pembrolizumab, NSC 776864)

TO: Investigators for CTEP-supported Studies Involving MK-3475 (pembrolizumab, NSC 776864)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with MK-3475, and to request all trials with MK-3475 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes MK-3475. See the accompanying list of CTEP trials with MK-3475.

In response to the new/modified risk information CTEP is requiring that all trials with MK-3475 be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on July 8, 2016** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Elad Sharon (sharone@mail.nih.gov). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since MK-3475 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice CTEP reviews each CAEPR list on an annual basis. The review includes literature search, CTEP-AERS submission review, and comparison to the latest agent Investigator's Brochure. After review of all the available data, CTEP has identified new and/or modified risk information associated with MK-3475.

In addition, Merck Research Laboratories, who supplies MK-3475, has requested inclusion of updated exclusion criteria on CTEP sponsored protocols (see Attachment 4). CTEP requests that investigators on trials currently enrolling and/or treating patients with MK-3475 amend their protocols to exclude patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis. See "Specific Protocol Revisions to Address Merck's request" below.

Detailed Description of Required Protocol Changes for the Amendment/ Sample Change Memo Template

1) New Protocol Amendment/Version Date Included on the Title/Cover Page per Operations Office Policy:

   Protocol Cover Page: Page Number(s): _____
   Version Date: _____

2) **Specific Protocol Revisions to Address Merck's Request:**

   The following paragraph should be inserted into the Exclusion Criteria of your protocol.

   - **Patient has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.**

3) Revision of the Protocol CAEPR:

   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, April 20, 2016): ___
   Page Number(s): ____

   - Added New Risk:
     - Less Likely: Bullous dermatitis; CPK increased; Immune system disorders - Other (pseudoprogression/tumor inflammation); Immune system disorders - Other (immune thrombocytopenic purpura); Infusion related reaction; Joint effusion; Joint range of motion decreased; Lymph node pain; Mucositis oral; Musculoskeletal and connective tissue disorder - Other (tenosynovitis); Skin and subcutaneous tissue disorders - Other (dermatitis); Small intestinal mucositis; Urticaria
     - Rare but Serious: Anaphylaxis; Cytokine release syndrome; Erythema multiforme; Immune system disorders - Other (hemophagocytic lymphohistiocytosis); Myocarditis; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (myasthenic syndrome); Nervous system disorders - Other (neuromyopathy); Nervous system disorders - Other (polyneuropathy); Peripheral motor neuropathy; Serum sickness; Stevens-Johnson syndrome; Vasculitis

Action Letter

- Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Agitation; Alopecia; Aphonia; Ascites; Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Cholesterol high; Depressed level of consciousness; Disseminated intravascular coagulation; Duodenal hemorrhage; Dysphagia; Edema cerebral; Edema face; Eye pain; Facial pain; Fibrinogen decreased; Gait disturbance; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (generalized edema); Heart failure; Hemolysis; Hydrocephalus; Hypercalcemia; Hyperkalemia; Hypertension; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Hypoxia; Laryngeal inflammation; Lethargy; Lymphocyte count decreased; Malaise; Meningismus; Metabolism and nutrition disorders - Other (failure to thrive); Musculoskeletal and connective tissue disorder - Other (groin pain); Myocardial infarction; Nervous system disorders - Other (brainstem herniation); Non-cardiac chest pain; Oral pain; Pelvic pain; Pericardial tamponade; Pneumothorax; Proteinuria; Rectal hemorrhage; Renal and urinary disorders - Other (hydronephrosis); Renal and urinary disorders - Other (nephrotic syndrome); Skin and subcutaneous tissue disorders - Other (drug eruption); Small intestinal perforation; Thromboembolic event; Tremor; Tumor lysis syndrome; Upper gastrointestinal hemorrhage; Urinary tract pain; Ventricular arrhythmia

- Increase in Risk Attribution:
  - Changed to Less Likely from Reported but With Insufficient Evidence for Attribution: Adrenal insufficiency; Alkaline phosphatase increased; Arthritis; Avascular necrosis; Blood bilirubin increased; Colitis; Endocrine disorders - Other (hypophysitis, hypopituitarism); Endocrine disorders - Other (thyroiditis); Erythroderma; Hepatobiliary disorders - Other (autoimmune hepatitis); Hyperthyroidism; Myositis; Pancreatitis; Pleuritic pain; Rash acneiform
  - Changed to Rare but Serious from Reported but With Insufficient Evidence for Attribution: GGT increased; Pericarditis; Serum amylase increased; Paresthesia

- Decrease in Risk Attribution:
  - Changed to Less Likely from Likely: Pruritus; Rash maculo-papular
  - Changed to Reported but With Insufficient Evidence for Attribution from Less Likely: Abdominal pain; Constipation; Cough; Dyspnea; Edema limbs; Headache; Vomiting; Weight loss

- Provided Further Clarification:
  - Renal and urinary disorders - Other (nephritis autoimmune) (under Rare but Serious) is now reported as Renal and urinary disorders - Other (autoimmune nephritis) (under Rare but Serious).
  - Metabolism and nutrition disorders - Other (insulin resistant diabetes) (under Reported but With Insufficient Evidence for Attribution) is now reported as Hyperglycemia (under Reported but With Insufficient Evidence for Attribution).
  - Footnote 2 is now Footnote 3, and Footnote 3 is now Footnote 2.

- Deleted Risk:
  - Also Reported on MK-3475 Trials But With Insufficient Evidence for Attribution: Amnesia; Depression; Dizziness; Dry eye; Dry mouth; Hot flashes; Hyperhidrosis; Hypothermia; Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine increased); Lower gastrointestinal hemorrhage; Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Peripheral sensory neuropathy; Productive cough; Pulmonary edema; Skin and subcutaneous tissue disorders - Other (hair color changes); Skin and subcutaneous tissue disorders - Other (scar pain)

Action Letter

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2 and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

4) Revision of the ICD as Specified below:

The terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo.

- Added New Risk:
  - Occasional: Blisters on the skin; Fluid in the joints; Hives; Joint stiffness; Sores in the mouth which may cause difficulty swallowing; Swelling and redness of the skin; The body's reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet.
  - Rare: Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat; Muscle weakness; Reaction during or following a drug infusion which may cause fever, chills, rash; Severe skin rash with blisters and can involve inside of mouth and other parts of the body; Weakness and paralysis
- Increase in Risk Attribution:
  - Changed to Occasional from Reported but With Insufficient Evidence for Attribution: Acne; Damage to the bone which may cause loss of motion; Pain and swelling of thyroid
  - Changed to Rare from Reported but With Insufficient Evidence for Attribution: Feeling of "pins and needles" in arms and legs; Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness

- Decrease in Risk Attribution:
  - Changed to Occasional from Common: Itching; Rash
  - Changed to Reported but With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Constipation; Cough; Headache; Shortness of breath; Vomiting; Weight loss

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to MK-3475 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

Action Letter

Attachment 1: Revised MK-3475 CAEPR – Version 2.2, April 20, 2016

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab, NSC 776864).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2, April 20, 2016[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (hypophysitis, hypopituitarism)[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Fever[2]		
	Infusion related reaction		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (immune thrombocytopenic purpura)[2]		
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Nervous system disorders - Other (Guillain-Barre syndrome)[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system disorders - Other (neuromyopathy)[2]	

Action Letter

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 4.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Immune-mediated adverse reactions have been reported in patients receiving MK-3475. Adverse events potentially related to MK-3475 may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475, administration of corticosteroids and supportive care.

[3]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other

(intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); General disorders and administration site conditions - Other (generalized edema); Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Renal and urinary disorders - Other (nephrotic syndrome); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD Section(s) for MK-3475

Please note that the terminology for CTEP's suggested lay terms may change periodically. The condensed risk profile represents CAEPR risks in lay terms in a "patient-friendly" condensed format. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the ICD. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the condensed risk profile in any way, please state, "The condensed risk profile has been modified" in the cover memo. Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 in your ICD.

Risk Profile for MK-3475 (CAEPR Version 2.2, April 20, 2016)

NOTE: The risk list section in the new NCI Consent Form Template (latest version: May 2013) will include the wording below:

"If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The MK-3475 used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you."

Please insert this condensed risk profile as the Table of Possible Side Effects for MK-3475 in your ICD.

HIGHLIGHTED LANGUAGE IS INSTRUCTIONAL TEXT FOR PRINCIPAL INVESTIGATOR-NOT TO BE INCLUDED IN THE INFORMED CONSENT DOCUMENT

PLEASE NOTE THE FOLLOWING IN REVIEWING THESE RISKS:

Action Letter

MK-3475 is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving MK-3475. In clinical trials, most immune-mediated side effects were reversible and managed by stopping MK-3475 temporarily, administration of corticosteroids and supportive care.

COMMON, SOME MAY BE SERIOUS In 100 people receiving MK-3475, more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving MK-3475, from 4 to 20 may have:
• Anemia which may require blood transfusion • Pain • Pain and swelling of thyroid • Diarrhea, nausea • Sores in the mouth which may cause difficulty swallowing • Chills, fever • Swelling of the body which may cause shortness of breath • Infection • Loss of appetite • Damage to the bone which may loss of motion • Fluid in the joints • Joint stiffness • Blisters on the skin, itching, acne, rash, skin changes, hives • Swelling and redness of the skin • The body's reaction to the drug can occur during treatment or weeks to months later: multiple organs may be involved but primarily bowels, liver, skin, nerves and glands that make hormones; symptoms may include diarrhea, rash and numbness/tingling of hands and feet

RARE, AND SERIOUS In 100 people receiving MK-3475, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, cough or tiredness • Swelling and redness of the eye • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Reaction during or following a drug infusion which may cause fever, chills, rash • Weakness and paralysis • Muscle weakness • Feeling of "pins and needles" in arms and legs • Kidney damage which may require dialysis • Severe skin rash with blisters and can involve inside of mouth and other parts of the body

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

1. **Distribute this Action Letter (and any accompanying CTEP-approved amendment) to all participating investigators and IRBs within 2 working days.** For National Clinical Trials Network (NCTN) studies, please follow instructions from your Operations office. For sites participating in the NCI Central-IRB (CIRB) Initiative, CTEP has provided a copy of this Action Letter to the CIRB if the Action Letter affects any studies under CIRB review.

2. Accrual of new patients must be suspended until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter. This amendment can undergo expedited approval at the discretion of the IRB Chair/designee as explained on the first page of the Action Letter.

3. **Patients currently on study may continue on study provided they are informed of the new and/or modified risk information.** This information should be communicated to patients already enrolled on study without waiting for IRB review/approval since this information represents a significant new finding(s) that developed during the course of the research that may relate to a patient's willingness to continue participation and per the Office for Human Research Protections, the regulations do not require IRB review and approval of statements describing such significant new findings before they are provided to already enrolled patients. Documentation of their informed consent should be carried out according to local IRB requirements.

4. **Save a copy of the Action Letter (and any CTEP approval letter for an accompanying amendment) for your records.**

INSTRUCTIONS FOR PREPARATION OF AN AMENDMENT IN RESPONSE TO THIS Action Letter (if a CTEP-Approved amendment for your trial does not already accompany the Action Letter)

General Instructions on Amendment Preparation:

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. **The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.**

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**

- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
- Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

B. Trials with a current status of **"Approved", "Temporarily Closed to Accrual and Treatment", or "Temporarily Closed to Accrual"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter in the next revised protocol draft submitted to CTEP. The protocol amendment must be submitted and approved by CTEP before the trial can be activated or re-opened.
- You may include additional non-Action Letter related changes (any type) in your amendment response.

C. Trials with a current CTEP status of **"In Review"**
- The protocol and ICD must be revised as per the instructions outlined in the Action Letter. These changes must be included in the next revised protocol draft submitted to and approved by CTEP before the trial can be activated.
- You may include additional non-Action Letter related changes (any type) in your revision response. Note the inclusion of non-Action Letter related changes may delay approval of your trial.

D. Trials with a current CTEP status of **"Closed to Accrual"**

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this Action Letter.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.

If your trial is NOT under a CTEP-held IND:
- If Action Letter INCLUDES information that impacts patient care (e.g., new/adjusted dose modifications or special monitoring for patient population at risk) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's amendment request submission policy.
  - **If Action Letter does NOT INCLUDE information that impacts patient care - Amendment is typically NOT required.**

E. Trials with a current CTEP status of **"Closed to Accrual and Treatment"** or **"Complete"**
- Amendment is not required. This information is being sent for informational purposes only. You may follow local IRB or Operations Office procedures and requirements.

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

June 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform sites that there is an error in Section 9.2 of the calendar. Patients on ipilimumab should not receive treatment on Week 13. This will be corrected in an upcoming protocol revision.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

June 1, 2016

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Ipilimumab (BMS-734016)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug ipilimumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung **S1404** Melanoma	Apr. 27, 2016 Mfr Rpt #BMS2016011751 FU

May 03, 2016 Mfr Rpt #BMS2016031561

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza (Bristol Myers Squibb)
May Venturanza – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

June 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Reports for Nivolumab (BMS-936558)

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug nivolumab. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S1400I Lung	Apr. 27, 2016 Mfr Rpt #BMS2016011751 FU
S1404 Melanoma	May 02, 2016 Mfr Rpt #BMS2016031021
	May 03, 2016 Mfr Rpt #BMS2016031561

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in these reports if it is deemed necessary by your institution. Please append this notice and these reports to your copy of the protocol and forward copies to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding these adverse events be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Scott Gettinger, M.D.
Lyudmila Bazhenova, M.D.
Sadia Mirza (Bristol Myers Squibb)
May Venturanza – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

June 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to notify sites that the Master Forms Set for this study has been updated and is available on the protocol abstract page on the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

May 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Kimberly F. Kaberle, Protocol Coordinator (E-mail: kkaberle@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to inform participating institutions that the LabCorp CAP and CLIA licenses are now available on the **S1404** protocol abstract page on the SWOG website (www.swog.org). The Site Manual and Protocol Refreshment Sheet (Imaging) has also been updated on the protocol abstract page.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

April 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S1404 Melanoma	Apr. 1, 2016 AE2416870

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
May Venturanza – Merck

SWOG
Leading cancer research. Together.

October 15, 2017

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

swog.org

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements
(√) Expedited review allowed

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S1404 Melanoma **S1418**/BR006 Breast **S1512** Melanoma **S1607** Melanoma	Sep. 20, 2017 AE-2458073 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistics and Data Management Center

cc: PROTOCOL & INFORMATION OFFICE

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: April 15, 2016
CTEP Submission Date: February 19, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Patricia O'Kane, Protocol Coordinator (E-mail: pokane@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

AMENDMENT #1

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements

(√) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

AMENDMENT #1

The study referenced above has been fully amended to address the recent FDA approval of ipilimumab in this patient population. Because ipilimumab is now a potential choice for standard care in patients who may be eligible for this study, the study team has made the decision to amend the study to allow patients and physicians to choose between either high dose interferon or ipilimumab for patients who are randomized to the standard treatment arm (Arm 1) of this study.

SWOG considers the Protocol and Model Consent Forms changes to represent a major modification to **S1404**. Therefore, accrual of new patients will be suspended to **S1404** as of 5/15/16 (30 days after distribution of this amendment) until the revised Model Consent Forms, in association with this amendment, as approved by the site's IRB of record, **are implemented**, and proof of that IRB approval is received by CTSU. For sites using the CIRB as their IRB of record, the date of CIRB approval was received on 4/7/16.

The changes associated with this amendment are outlined below, but have resulted in a wholesale change to the protocol document. The addition of the ipilimumab option has resulted in minor wording changes throughout the protocol that are not enumerated specifically below.

1. Ipilimumab was added into the study title and as an additional commercial agent on the face page and also in the title on the first page of the Model Informed Consent Form.

2. The new description of standard care options for Arm 1 were added to the study Schema. The timing for MK-3475 (pembrolizumab) was changed from 52 weeks to 18 doses.

3. The new description of standard care options for Arm 1 were added to the study Objectives.

4. The new description of standard care options for Arm 1 were added to the study Background (page 7).

5. A new drug information section for ipilimumab was added (Section 3.2) and the remainder of Section 3.0 was renumbered accordingly.

6. Section 5.1i was amended to exclude patients who have received prior neoadjuvant treatment and also to specifically exclude patients who have received prior ipilimumab.

7. Section 6.0, a new stratification factor (#3) was added to require that the intended control arm regimen be declared prior to randomization for all patients.

8. Section 7.1b.2 was added to provide treatment guidelines for ipilimumab administration.

9. A new Section 8.3 was added to provide dose modification guidelines for ipilimumab. The remainder of Section 8.0 was renumbered accordingly.

10. A new Section 9.2 was added to provide a Study Calendar for ipilimumab administration. The MK-3475 (pembrolizumab) Study Calendar was renumbered as Section 9.3.

11. Wording was added in Section 11.7b to distinguish the statistical characteristics of the toxicity analysis on the investigational arm from that of the two regimens in the control arm.

12. Ipilimumab has been added in Section 16.1g as an additional commercial agent for the purposes of reporting Serious Adverse Events.

13. Reference #21 was added to page 88 to reflect the changes made in the Background section.

14. The new description of standard care options for Arm 1 was added into the Model Informed Consent Form “What are the study groups?” section. Follow up details for patients receiving ipilimumab were added into the Model Informed Consent Form “How long will I be in the study?” section. Side effects for ipilimumab were added into the Model Informed Consent Form “What possible risks can I expect from taking part in this study?” section. The timing of PK/ADA testing and questionnaire completion was updated in the “What extra tests and procedures will I have if I take part in this study?” section.

Additional changes, not associated with the addition of ipilimumab, are outlined below:

1. Hongli Li, M.S. was added as an additional study statistician, the name and acronym for the Canadian Cancer Trials Group (CCTG) was updated (from NCIC-CTG), and Michael Knopp, M.D., Ph.D. was added as the Imaging Co-Chair on the face page.

2. Section 4.0 was updated to correct a typographical error. Stage IIIA includes "N2a" rather than "N2" disease.

3. The first paragraph in Section 5.0 was updated to reference submission of the **S1404** Eligibility Checklist to confirm patient eligibility.

4. Section 5.1e was updated to require that slides cut from an archived block must be submitted within 20 days from cutting the slides. This was also specified in Sections 15.2e.3 and 15.2e.17. Section 5.1l was updated to clarify that the PET-CT must be of diagnostic quality.

5. The cycle length for all regimens was standardized in Section 7.1 to 6 weeks for the first two cycles and 12 weeks for all subsequent cycles. This was also updated in the Study Calendars. Section 7.1a was amended to require the collection and analysis of blood samples for laboratory tests within 3 days prior to dosing.

6. The following wording was added to Section 7.1c: "Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chair. The reason for interruption should be documented in the patient's study record."

7. Section 7.6 was amended to indicate the follow-up period begins at randomization.

8. Section 8.4, the entire dose modification section for MK-3475 was re-written for clarity and simplicity.

9. Sections 9.1 and now 9.3 the requirement for pregnancy testing was changed to allow for frequency according to institutions practice. A new ""s" footnote for Study Calendar 9.1 and "t" footnote for Study Calendar 9.3 was added to require collection of information about menstrual, sexual and contraceptive use history, as a part of taking the patient's history prior to each treatment administration. The timepoint for laboratory testing "within 3 days prior to the start of study treatment" was clarified in footnotes g and o and the related baseline testing was deleted. A requirement for annual brain imaging was added. Albumin, glucose and electrolytes were added to footnote g. The following text was added to footnote k – "The same imaging modality as used at prestudy for disease assessment must be used throughout the trial." AND "For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contraindication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging." Section 9.3 the timing for PK and ADA testing was clarified in footnote q - related to the change in cycle length.

10. Section 14.4a the requirement for submission of the **S1404** Eligibility Checklist was added as was the requirement to submit slides for PD-L1 evaluation. A new Section

11. The timing of cycles per study arm was specified in Section 14.4f.

12. The instruction to upload items as source documentation was added to Sections 14.4g, h and k.

13. The telephone number for the SWOG Data Operations Center was updated in Section 15.1a.

14. Instructions and contact information were updated in Section 15.2.

15. The mention of submission of formalin free tissue was deleted from Section 15.3b.1. Timing for collection of blood specimens was clarified in Sections 15.3b.2, 15.3b3 and 15.4e.

16. Instructions in Section 15.3f.2 and 15.3g (including contact information) were updated. Instructions for PPD Requisition Form was added as a new Appendix 18.7.

17. Timing of questionnaire administration was clarified in Section 15.5d.

18. The following statement was added to Section 15.6: "Any imaging that is used for relapse detection must be submitted; this would include ultrasound imaging if that is used by your institution for nodal basin surveillance. In addition, if imaging done for other reasons detects a relapse (i.e., chest x-ray done for pulmonary symptoms that subsequently detects a metastasis) it must also be submitted."

19. A new version of Appendix 18.4 the **S1404** Local Pathology Review Form was added.

20. The details of "On Site Monitoring" in Appendix 18.6 were revised to indicate that onsite monitoring will be triggered from the time of "randomization" rather than "registration." Additionally the following clarifications were added: "All sites that receive and dispense investigational agents must be monitored on site to allow a visit to the pharmacy with the following exceptions:" and "The need for subsequent onsite visits will be determined on a case by case basis including past audit results, number of patients on the investigational agent, etc."

21. ECG and pregnancy testing were deleted from the "What extra tests and procedures will I have if I take part in this study?" section of the Model Informed Consent form as these tests and their frequency are standard.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

March 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: SWOG Operations Office (E-mail: protocols@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that the Site Manual and Protocol Refreshment Sheet (Imaging) has been added to the protocol abstract page on the SWOG website (www.swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

December 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: IND Safety Report for MK-3475

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug MK-3475. Please access this report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S1404 Melanoma	Nov. 24, 2015 AE #2217298 FU

Protocol amendments are not necessary at this time, but your consent form may be revised to include the information provided in this report if it is deemed necessary by your institution. Please append this notice and this report to your copy of the protocol and forward a copy to your Institutional Review Board (IRB) as required by your local policies and procedures. Should any further information regarding this adverse event be made available, it will be forwarded to you.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
Michael Wu, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza – Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: December 15, 2015
E-mail Date: December 1, 2015
CTEP Submission Date: November 2, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Patricia O'Kane, Protocol Coordinator (E-mail: pokane@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

REVISION #1

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

REVISION #1

This modification to **S1404** is in response to the October 28, 2015, FDA approval of ipilumumab (Yervoy®) for the adjuvant treatment of patients with cutaneous melanoma with pathologic involvement of regional lymph nodes of more than 1 mm who have undergone complete resection, including total lymphadenectomy.

Ipilimumab is a human cytotoxic T-lymphocyte antigen 4 (CTLA-4)-blocking antibody. The approval was based on improvement in recurrence-free survival (RFS) in a randomized (1:1), double-blind, placebo-controlled trial in 951 patients with resected Stage IIIA (lymph node >1 mm), IIIB, and IIIC (with no in-transit metastases) histologically confirmed cutaneous melanoma. The primary efficacy endpoint was RFS determined by an independent review committee. The median RFS was 26 and 17 months in the ipilimumab (n=475) and placebo (N=476) arms, respectively [HR 0.75 (95% CI: 0.64, 0.90), p <0.002, stratified log-rank test].

Investigators must notify their responsible Institutional Review Board (IRB). Patients must be informed of the information outlined below. While this information need not be provided verbatim, the information in the updated Model Informed Consent Form must be provided in a manner recommended by the local IRB. Documentation that this information was provided must be retained in the patient's research record on site and will be subject to verification at the time of a Quality Assurance audit.

The Version Date for both the protocol and Model Informed Consent Form was updated to 11/2/15.

The Model Informed Consent Form has been changed as follows:

"What is the usual approach to high risk melanoma?: This section has been replaced with the following: "You are being asked to take part in this study because you have melanoma, which, although it has been successfully treated with surgery, has a high probability of coming back. There are several treatment options for high risk resected melanoma. These include: 1) high dose interferon alfa-2b, 2) a different version of interferon (called "pegylated" interferon), and 3) ipilimumab which was recently approved by the FDA. However, only some patients benefit from these treatments. Though high dose interferon alfa-2b has been selected as the standard treatment option for this study, please talk with your doctor about the alternative above before finalizing your decision to take part in this study. We hope to find a more effective and long-lasting treatment for your type of cancer."

We ask that local sites implement this consent form update as soon as possible after notification of IRB approval. Patients who are randomized on **S1404** prior to local implementation of the consent form changes must be informed of the new findings regarding approval of ipilimumab by their next scheduled visit and this notification process must be documented in the patient chart. These patients also **must be formally re-consented** within 90 days of distribution of this revision.

Additionally Section 5.1b.b and the "Questionnaires" bullet on page 5 of the Model Informed Consent form were revised to indicate that the patient questionnaires are required for patients who are able to complete them in English, Spanish or French.

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

November 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Patricia O'Kane, Protocol Coordinator (E-mail: pokane@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

MEMORANDUM

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is the inform sites that the following forms have been added to the Master Forms Set located on the protocol abstract page on the SWOG website (www.swog.org).

- **S1404** Baseline Laboratory Values Form
- **S1404** Cover Sheet for Patient-Completed Questionnaires
- **S1404** FACT-BRM (Version 4)
- **S1404** FACT-BRM (4a Versión)
- **S1404** FACT-BRM (4ème Version)
- **S1404** EQ-5D-3L Health Questionnaire
- **S1404** EQ-5D-3L Cuestionario De Salud
- **S1404** EQ-5D-3L Questionnaire Sur La Santé

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza - Merck

SWOG
Leading cancer research. Together.

GROUP CHAIR'S OFFICE
Charles D. Blanke, MD
CHAIR
3181 SW Sam Jackson Pk Rd
MC: L586
Portland, OR 97239
503-494-5586
503-346-8038 FAX

OPERATIONS OFFICE
4201 Medical Dr
Suite 250
San Antonio, TX 78229
210-614-8808
210-614-0006 FAX

STATISTICAL CENTER
1730 Minor Ave
Suite 1900
Seattle, WA 98101
206-652-2267
206-342-1616 FAX

1100 Fairview Ave North
M3-C102
PO Box 19024
Seattle, WA 98109
206-667-4623
206-667-4408 FAX

swog.org

Distribution Date: November 1, 2015
E-mail Date: October 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS

FROM: Patricia O'Kane, Protocol Coordinator (E-mail: pokane@swog.org)

RE: **S1404**, "A Phase III Randomized Trial Comparing High Dose Interferon to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma." Study Chairs: Drs. K.F. Grossmann and S.P. Patel.

STATUS NOTICE

Study Chair: Kenneth F. Grossmann, M.D., Ph.D.
Phone number: 801/587-4735
E-mail: kenneth.grossmann@hci.utah.edu

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

( ) No review required

ACTIVATION

The study referenced above is now open for participation **effective October 15, 2015 at 2:00 p.m. Eastern Time.**

This study has been approved by the NCI's Central Institutional Review Board (CIRB).

Note that because this is a registration trial, participating institutions are required to have at least one person view the **S1404** training module before enrolling patients to the study.

The training is available at:
https://swog.org/Members/Training/S1404/S1404Training.asp.

To obtain credit for completing the training, after viewing the presentation please complete the short form at the bottom of the training page on the website.

The PD-L1 status of the tumor will be assessed before randomization for every patient as it is a key objective to understand this biomarker as it relates to both RFS and OS in the high risk resected melanoma patients enrolled on **S1404**.

Please note that prior to enrolling any patients, you must log onto the SWOG Specimen Tracking System (https://crawb.crab.org/SpecTrack/Logon.aspx) to order your initial specimen kits. When placing this initial order, sites must provide laboratory contact information. The initial order may take up to 15 days to be filled. Once your site's contact information is in the PPD database, subsequent orders can be made via their web site and will be filled within 5 days.

As this test of PD-L1 has been used in many studies, we anticipate that delays in testing will be infrequent events. It is important to send adequate tumor specimens (100 tumor cells per slide), and that the slides are shipped within 7 days of cutting the slides. If the initial slides sent fail to yield results, you will be asked to send more tissue. You will not be notified of the results of the PD-L1 test, only that the testing was successful, and that your patient can be randomized.

As this testing is required for randomization, kit ordering is important as your site activates, and it is the most important early step to initiate in the process of screening patients. Note that you can order kits before you activate the study. An initial order will provide your site with 4 PD-L1 kits and 3 PK/ADA kits.

For further questions regarding tissue submission or eligibility criteria, please contact Jennie Barrett (melanomaquestion@crab.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Megan Othus, Ph.D.
James Moon, M.S.
Jennie Barrett
May Venturanza - Merck

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated October 15, 2015

SWOG

A PHASE III RANDOMIZED TRIAL COMPARING PHYSICIAN/PATIENT CHOICE OF EITHER HIGH DOSE INTERFERON OR IPILIMUMAB TO MK-3475 (PEMBROLIZUMAB) IN PATIENTS WITH HIGH RISK RESECTED MELANOMA.

NCT#02506153

This is an FDA Registration Trial. Additional site requirements include maintenance of a Trial Master File (https://www.swog.org/sites/default/files/docs/2017-10/Guidance%20on%20FDA%20Inspection.pdf) and additional monitoring (see Appendix 18.6).

STUDY CHAIRS:

Kenneth F. Grossmann, M.D., Ph.D. (Medical Oncology)
The Huntsman Institute
Research South Office #2721
2000 Circle of Hope Drive
Salt Lake City, Utah 84112
Phone: 801/213-8435
E-mail: S1404SCquestion@swog.org

Sapna Pradyuman Patel, M.D. (Medical Oncology)
MD Anderson Cancer Center
Melanoma Medical Oncology
1515 Holcombe Blvd., Unit 0430
Houston, TX 77030
Phone: 713/792-2921
FAX: 713/745-1046
E-mail: S1404SCquestion@swog.org

Michael V. Knopp, M.D., Ph.D. (Imaging)
The Ohio State University
395 W 12th Ave, Suite 430
Columbus, OH 43210
Phone: 614/293-9998
E-mail: knopp.16@osu.edu

Vernon K. Sondak, M.D. (Surgery)
H. Lee Moffitt CC
MKC-CutProg
10920 N. McKinley Dr
Tampa, FL 33612
Phone: 813/745-8788
FAX: 813/745-7211
E-mail: vernon.sondak@moffitt.org

AGENTS:

NCI Supplied Investigational Agents (DCTD-sponsored):

MK-3475 (Pembrolizumab) (NSC 776864)
(IND-125133)

Commercially Supplied Agent:

Interferon alfa 2b (NSC 377523)
Ipilimumab (NSC 732442)

CCTG STUDY CHAIR

Teresa Petrella, M.D.
Odette Cancer Centre
Sunnybrook Health Sciences Centre
2075 Bayview Avenue
Toronto, Ontario, Canada M4N 3M5
Phone: 416/480-5248
FAX: 416/480-6002
E-mail: teresa.petrella@sunnybrook.ca

ECOG-ACRIN STUDY CHAIR

Ahmad Tarhini, M.D., Ph.D.
University of Pittsburgh Cancer Institute
UPMC Cancer Pavilion
5150 Centre Avenue, 5th Floor
Pittsburgh, PA 15232
Phone: 412/648-6578
FAX: 412/648-6579
E-mail: tarhiniaa@upmc.edu

BIOSTATISTICIANS:

Megan Othus, Ph.D.
James Moon, M.S.
Hongli Li, M.S.
SWOG Statistical Center
1100 Fairview Ave N, M3-C102
P.O. Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: mothus@fredhutch.org
E-mail: jmoon@fredhutch.org
E-mail: hongli@fredhutch.org

PARTICIPANTS

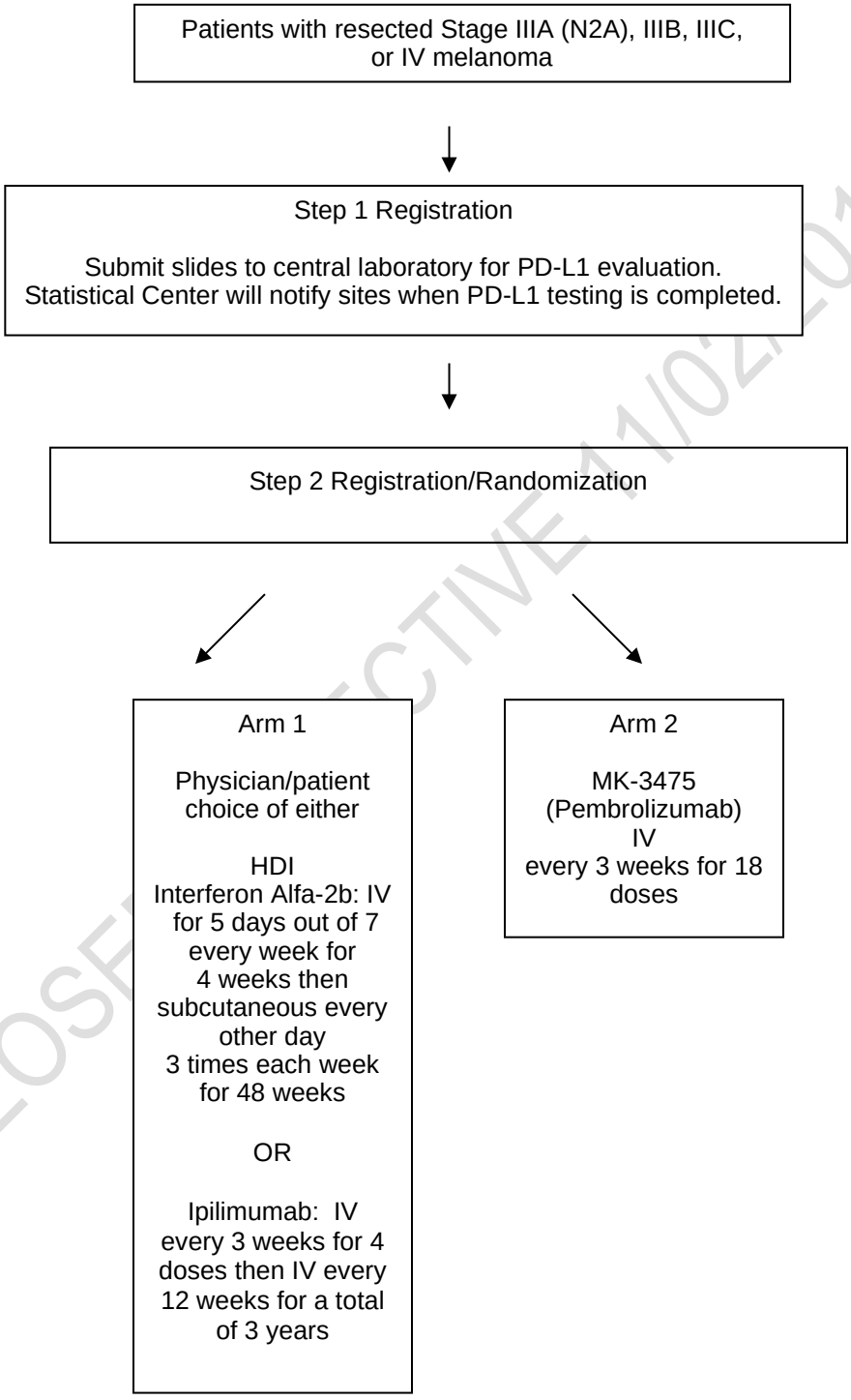
SWOG/SWOG
ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
CCTG/Canadian Cancer Trials Group
NRG/NRG Oncology

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

CONTACT INFORMATION		
For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 to receive further information and support. Contact the CTSU Regulatory Help Desk at 866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS. Note: Non-lead group institutions will order the following supplies from the CTSU Operations Office:		
For patient eligibility or data submission questions contact the SWOG Data Operations Center by phone or email: 206/652-2267 melanomaquestion@crab.org **For treatment or toxicity related questions** contact the Study Chair by phone or email: Kenneth F. Grossmann, M.D., Ph.D. Phone: 801/587-4735 E-mail: S1404SCquestion@swog.org		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Website is located at https://www.ctsu.org.		

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objectives

a. To compare overall survival (OS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab)

b. Among patients who are PD-L1 positive, to compare OS of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab versus MK-3475 (pembrolizumab).

c. To compare relapse-free survival (RFS) of patients with resected Stage III and IV melanoma treated with physician/patient choice of either high dose interferon alfa-2b or ipilimumab to MK-3475 (pembrolizumab).

1.2 Secondary Objectives

a. To estimate OS and RFS for patients who are PD-L1 negative or PD-L1 indeterminate in this population.

b. To compare OS and RFS of patients between the two arms within PD-L1 positive and negative subgroups and to look at the interaction between PD-L1 (positive versus negative) and treatment arm.

c. To assess the safety and tolerability of the regimens.

1.3 Additional Objectives

a. To bank tissue and whole blood in anticipation of future correlative studies in this patient population.

b. To evaluate PD-L1 expression through immunohistochemistry assay.

c. To evaluate the effect of treatment-related side effects that may have an impact on the health-related domains of quality of life (QOL) using the FACT-BRM, EQ-5D-3L, and FACIT-D between patients treated with physician/patient choice of either high-dose interferon alfa-2b or ipilimumab and MK-3475 (pembrolizumab).

d. Pharmacokinetic (PK) and anti-drug antibody (ADA) testing will be performed on all patients receiving MK-3475 (pembrolizumab). These analyses will evaluate exposure-response analyses for activity and efficacy, potential pharmacodynamic biomarkers, and the safety of MK-3475 (pembrolizumab).

1.4 Other Objectives

a. Translation Medicine Objective Related to T-Cell Receptor Beta Chain Sequencing

1. To evaluate the association between TCRβ variable gene (TRBV) haplotype and Grade 3-4 immune-related adverse events (irAEs) among Stage III melanoma patients treated with adjuvant Ipilimumab or Pembrolizumab.

2. To describe the TRBV haplotype distribution among this cohort of patients studied.

b. Translational Medicine Objective Related to Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients

c. To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms.

d. To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms.

e. To evaluate associations between pretreatment ctDNA and relapse within 2 years of randomization in a case-control analysis within each treatment arm (after treatment arm data are unblinded to investigators).

f. To evaluate associations between "early-on treatment" ctDNA levels and relapse within 2 years of randomization.

g. To describe ctDNA levels at end of therapy and time of relapse.

2.0 BACKGROUND

Although the long term RFS for most patients with low risk Stage I and II melanoma is excellent following surgery, patients who have high risk features such as tumor-involved lymph nodes (Stage III) have poorer outcomes with an average 5-year OS of Stage III patients approximating 50%. *(1)* Although modern therapy has significantly improved outcomes for patients with Stage IV melanoma such that 20% of patients achieve survival beyond 4 years, this still reflects a minority of patients. *(2)* Furthermore, relapses in this disease can be severely detrimental to quality of life with distant relapses accounting for greater than 50% of the relapse events in Stage III patients. *(3)* Adjuvant therapy is currently considered for patients with Stage III melanoma and selected patients with resected Stage IV melanoma.

Adjuvant treatment for Stage III melanoma – Rationale for Physician/Patient Choice of either High Dose Interferon alfa-2b or Ipilimumab as the Control Arm (Arm 1):

Multiple studies have investigated adjuvant immunotherapy alone or in combination with other treatments for high-risk melanoma. The first trial to demonstrate an OS advantage compared high dose interferon-alfa-2b (HDI) to observation. *(4)* This study established HDI as the standard of care for the adjuvant treatment of melanoma, and HDI remains the most widely used adjuvant treatment option in the US today. Subsequent studies involving differing doses, schedules, and preparations of interferon have been extensively reviewed and taken together have shown consistent relapse-free survival (RFS) and OS benefit in large meta-analyses. *(5,6,7)* Pegylated interferon has also been studied by the EORTC in a single large Phase III trial in Stage III melanoma that showed a RFS advantage compared to observation, but no OS advantage was demonstrated. *(8)* Based upon the RFS advantage of this EORTC study, the FDA granted approval for pegylated interferon for the adjuvant treatment of Stage III melanoma. Biochemotherapy consisting of interferon, interleukin-2, dacarbazine, vinblastine, and cisplatin has also been studied in the adjuvant setting (**S0008**) and results show a RFS advantage compared to HDI but no OS difference. *(9)*

Unfortunately, the toxicity of this regimen limits the use of biochemotherapy to institutions with sufficient expertise in its administration, and the lack of an OS advantage compared to HDI argues against this becoming a community-based standard for the adjuvant treatment of melanoma.

Ipilimumab, administered intravenously, was originally approved in 2011 to treat late-stage melanoma that cannot be removed by surgery. Ipilimumab is a monoclonal antibody that blocks a molecule known as CTLA-4 (cytotoxic T-lymphocyte antigen). CTLA-4 may play a role in slowing down or turning off the body's immune system, and affects its ability to fight off cancerous cells. Ipilimumab may work by allowing the body's immune system to recognize, target and attack cells in melanoma tumors.

In October 2015, based on preliminary results from **EORTC 18071**, the U.S. Food and Drug Administration expanded the approved use of ipilimumab to include a new use as adjuvant therapy for patients with stage III melanoma, to lower the risk that the melanoma will return following surgery. The safety and effectiveness of ipilimumab for this new use were studied in 951 patients who received ipilimumab or a placebo as adjuvant therapy following complete surgical removal of melanoma. The study measured recurrence-free survival and overall survival. Forty-nine percent of participants taking ipilimumab had their cancer return after an average of 26 months, compared to 62 percent of those receiving a placebo, whose cancer returned after an average of 17 months. The analysis of overall survival data has not yet occurred. *(10)*

The most common side effects of ipilimumab in this study were rash, diarrhea, fatigue, itching, headache, weight loss and nausea. Ipilimumab can also cause autoimmune disease in the digestive system, liver, skin, nervous system (which would each require treatment with corticosteroids), as well as in the hormone-producing glands (which requires life-long hormone replacement therapy). Women who are pregnant should not take ipilimumab because it may cause harm to a developing fetus. *(11)* In addition, the relative adjuvant therapeutic impact of ipilimumab as compared to HDI is currently unknown. Similarly, given the toxicity profile of ipilimumab at 10 mg/kg, there is a need to better assess the risk-benefit ratio relative to the standard 3 mg/kg dose currently approved for inoperable metastatic melanoma.

The benefits described above for HDI, though statistically significant, remain modest with the most recently published meta-analysis showing an OS advantage with a hazard ratio of 0.91 (95% CI 0.85 to 0.97; P value = 0.003). *(12)* Additionally, the toxicity of HDI can be significant and prolonged over the course of one year of administration.

The current landscape of other studies ongoing in high-risk melanoma:

Ongoing adjuvant clinical trials in patients with melanoma include a study investigating ipilimumab at either 10 mg/kg or 3 mg/kg compared to HDI (U.S. Intergroup **E1609**). The co-primary endpoints of this study are RFS and OS. **E1609** completed accrual of adult patients August 15, 2014 (remains open for pediatric/adolescent patients). Results of **E1609** are not expected until after completion of accrual to the present trial, and until that time there is insufficient evidence to consider ipilimumab at either dose as a standard form of adjuvant therapy for high risk melanoma patients.

Two additional ongoing adjuvant studies are industry-sponsored BRAF inhibitor-based studies, investigating vemurafenib or dabrafenib/trametinib compared to observation. Results of these studies are not expected until after completion of accrual to the present trial, and until that time there is insufficient evidence to consider BRAF inhibitors alone or in combination with MEK inhibitors as a form of adjuvant therapy for high-risk melanoma patients.

Clinical Rationale for PD-1 blockade for the adjuvant treatment of high-risk melanoma:

Novel therapies have been developed recently targeting the programmed cell death – 1 (PD-1) inhibitory co-receptor on T-cells. *(13)* Monoclonal antibodies directed at the PD-1 co-receptor, or the cognate PD-L1 receptor on tumor cells, have robust activity in advanced melanoma. *(14,15)*

The drug MK-3475 (pembrolizumab) is a member of this class of medications and targets the PD-1 receptor. A recently reported Phase I study in 411 patients defined safe and effective dosing regimens (10 mg/kg IV q 2 weeks, 2 mg/kg IV q 3 weeks, 10 mg/kg IV q 3 weeks) and showed the highest confirmed response rate yet observed for any single agent immunotherapy in Stage IV melanoma (41% objective responses across all cohorts). *(16)* Furthermore, the safety and tolerability of pembrolizumab (12% Grade 3/4 toxicities) appears superior to both HDI (64% Grade 3/4 toxicities in **S0008**) and ipilimumab (43% Grade 3/4 toxicities in **EORTC 18071**), making it ideally suited for evaluation as adjuvant therapy. *(17)* Ongoing studies, including Phase III studies for Stage IV patients, are confirming the high response rate and the favorable toxicity profile of pembrolizumab such that an adjuvant Phase III study is warranted.

PK data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to Investigator Brochure). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (> 21 days). This early PK and pharmacodynamic data provided a scientific rationale for evaluating the Q3W dosing schedule.

The choice of the 200 mg Q3W as an appropriate dose for fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that is well-tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Rationale for one year of dosing with pembrolizumab

Adjuvant therapy for melanoma with HDI or pembrolizumab is aimed at inducing an immune response that eradicates micrometastatic tumor deposits that may lead to a future melanoma relapse. Based on the experience with HDI it is postulated that one year of adjuvant therapy would be able to induce the desired antitumor effects and eradicate small metastatic lesions.

Biological rationale for the study population based on the anticipated mechanism of action of pembrolizumab:

PD-L1 is known to be expressed by cells in the tumor microenvironment and engages PD-1 on T cells to subsequently trigger inhibitory signaling downstream of the T-cell receptor (TCR), blocking effect or functions and reducing T-cell killing capacity. PD-L1 can be constitutively expressed on the surface of melanoma cells through poorly characterized oncogenic signaling pathways or alternatively, expressed in response to the presence of T cells producing immune-stimulating cytokines such as interferons. *(18,19,20)* This process has been termed “adaptive immune resistance” and represents a mechanism by which cancer cells attempt to protect themselves from immune-cell mediated cell killing. Based on this conceptual framework, pre-existing tumor-infiltrating CD8+ T-cells with associated PD-1/PD-L1 engagement within tumors represented a key factor in determining clinical response to PD-1 blocking therapy. Emerging evidence from the analysis of samples from 46 patients with metastatic melanoma obtained before and during anti-PD-1 therapy with pembrolizumab (24 responders and 22 non-responders) using quantitative immunohistochemistry, quantitative multiplex immunofluorescence, and next generation sequencing for T-cell receptors (TCR), supports the concept that the pre-requisite for responses to pembrolizumab is the presence of clonal CD8 T cells expressing PD-1 and closely interacting with PD-L1 expressed by melanoma cells. *(21)* These data indicate the requirement for the presence of

CD8 cells interacting with adaptive immune resistance-mediated PD-L1 expression by melanoma cells to lead to responses to PD-1 blockade.

Rationale for PD-L1 status blinding

Although patients will be stratified based on PD-L1 status, they and the investigator will be blinded to this result at randomization. Presently there is no indication that PD-L1 status predicts response to PD-L1 antibody treatment in the adjuvant setting so this will not impact patient care during treatment on the study. PD-L1 expression is dynamic and PD-L1 expression of primary or lymph node tissue is not necessarily indicative of PD-L1 status in other sites. Thus, at relapse we recommend that patients have the biopsy confirming relapse tested for PD-L1 expression with a CLIA certified test. We recommend against using the **S1404** baseline PD-L1 expression for subsequent treatment decisions. Only in the event that tissue is limited in the relapsed setting and that there is no other reasonable alternative to attain PD-L1 expression for the patient, should the **S1404** baseline PD-L1 expression be used. **S1404** baseline PD-L1 expression will be provided to patients on study at report of relapse.

FDA approval of MK-3475 (pembrolizumab) for Stage IV and unresectable Stage III melanoma

MK-3475 (pembrolizumab) has recently received accelerated approval by the FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if B-RAF V600 mutation positive, a B-RAF inhibitor. This approval is based on the high response rate and durability of response seen in the clinical studies conducted so far with MK-3475 as described above. We anticipate extensive use of MK-3475 among the patients who relapse on HDI, and also anticipate the use of other PD-1, and PD-L1 targeted antibodies in both groups. Data regarding post-relapse therapy will be collected as part of this study.

Rationale for collecting quality of life (QOL) data and the potential impact of the trial on QOL

An important issue in the adjuvant treatment of patients with high-risk melanoma is the how patients weigh the benefits of overall survival and QOL. Adjuvant HDI has been demonstrated to provide relapse-free survival and overall survival benefits for this patient population but it is also known to be associated with major Grade 3-4 toxicities. *(22)* Patients treated with MK-3475 (pembrolizumab) can also experience Grade 3-4 drug-related toxicities and immune-related adverse events (irAEs). The Functional Assessment of Chronic Illness Therapy Diarrhea (FACIT-D) utilizes the four primary domains of the FACT-BRM (Physical Well-Being, Social Well-Being, Emotional Well-Being, and Functional Well-Being). *(23)* The additional measure of the FACIT-D instrument includes 11 questions tailored to bowel symptoms. It is appropriate for patients with any form of cancer, and content was determined and validated by experts with patient input. We therefore plan to collect QOL data utilizing the FACT-BRM, FACIT-D and EQ-5D-3L health questionnaires to evaluate health-related quality-of-life outcomes between the two arms.

Pharmacokinetic/Pharmacodynamic Evaluations

To further evaluate pembrolizumab immunogenicity and pembrolizumab exposure in this indication, and also to evaluate exposure of the proposed dosing regimen, samples will be collected for analysis of anti-drug antibodies (ADA) and pharmacokinetics (PK).

Based on PK data obtained in this study as well as PK data obtained from other studies, a population PK analysis will be performed to characterize pharmacokinetic parameters (Clearance (CL), Volume of distribution (V)) as endpoints and evaluate the effect of extrinsic and intrinsic factors to support the proposed dosing regimen. Pharmacokinetic samples will also be used to explore the exposure-response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately from the primary results of this trial.

Inclusion of Women and Minorities

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. To date, studies of MK-3475 (pembrolizumab) and similar agents have not shown evidence of significant gender or race-based differences in efficacy. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	6	0	0	6
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	4	0	0	4
Black or African American	10	3	0	0	13
White	359	840	4	10	1213
More Than One Race	0	0	0	0	0
Total	369	855	4	10	1238

INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	1	0	0	1
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	0	0	0	0
White	41	96	0	0	137
More Than One Race	0	0	0	0	0
Total	41	99	0	0	140

3.0 DRUG INFORMATION

Investigator's Brochures

For information regarding Investigator Brochures, please refer to SWOG Policy 15.

For this study, MK-3475 (pembrolizumab) is investigational and is being provided under an IND held by the National Cancer Institute. The current version of the Investigator Brochure (IB) will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed via email to IBcoordinator@mail.nih.gov or by phone (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET). Interferon alfa-2b and ipilimumab are commercially available drugs.

3.1 Interferon alfa-2b (Intron® A)

a. PHARMACOLOGY

Mechanism of Action: Interferons exert their cellular activities by binding to specific membrane receptors on the cell surface. Once bound to the cell membrane, interferons initiate a complex sequence of intracellular events. In vitro studies demonstrated that these include the induction of certain enzymes, suppression of cell proliferation, immunomodulating activities such as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells, and inhibition of virus replication in virus-infected cells.

b. PHARMACOKINETICS

1. *Absorption: Time to peak, serum: IM, SubQ: ~3-12 hours; IV: by the end of a 30-minute infusion*

2. Distribution: Volume of distribution = 31 L, but has been noted to be much greater, (370-720 L) in leukemia patients receiving continuous infusion. Interferon alfa-2b does not penetrate the CSF.

3. Metabolism: Primarily renal

4. Elimination: Half-life IV: ~2 hours; IM, SubQ: ~2-3 hours

c. ADVERSE EFFECTS

1. Possible Side Effects of Interferon alfa-2b

Common (>20%): infection, diarrhea, nausea, vomiting, flu-like symptoms including fever, chills body aches, and muscle pain, fatigue, loss of appetite, disorder of taste, headache, confusion, depression, suicidal thoughts, alopecia, rash, and/or pain.

Less common (4 to ≤ 20%): cardiomyopathy, cirrhosis of liver, hepatotoxicity, thrombocytopenia, organ damage and/or failure, edema, injection site extravasation, erythema of injection site, generalized exfoliative dermatitis, Stevens-Johnson Syndrome, toxic epidermal necrolysis, transient ischemic attack (TIA), cerebral infarction, cerebrovascular accident, and/or ischemic stroke.

Rare (≤ 3%), and serious: anemia, arrhythmias, ischemic heart disease, myocardial infarction, NSTEMI, hypersensitivity reaction, anaphylaxis.

Refer to the current FDA-approved package insert for the most comprehensive and up to date information on adverse effects.

2. Pregnancy and Lactation: Pregnancy category C. There are no adequate and well-controlled studies in pregnant women. Breastfeeding is not recommended

3. Drug Interactions: Interferon alfa-2b drug interactions have not been fully evaluated. Caution should be exercised when combining with other potentially myelosuppressive agents such as: aldesleukin, clozapine, dipyrone, methadone, ribavirin, telbivudine, theophylline derivatives, and zidovudine. Due to potential drug interactions, a complete patient medication list, including interferon alfa-2b, should be screened prior to initiation of and during treatment with interferon alfa-2b. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. DRUG SUPPLY:

Interferon alfa-2b is commercially available and will not be supplied. Refer to the current FDA-approved package insert for the most comprehensive and up to date information.

f. DOSAGE FORMS:

Interferon alfa-2b is available in vials as powder for reconstitution and in vials containing solution for injection.

NOTE: Intron® A (interferon alfa-2b) formulation must be consistent with the approved product labeling for the intended route of administration.

1. Interferon alfa-2b powder for injection

a) Interferon alfa-2b powder for injection appears white to cream-colored. The powder for injection must be reconstituted prior to injection using the diluent (sterile water for injection USP) provided with the vial. Refer to the package insert for current reconstitution and infusion solution preparation.

b) Available vial strengths include 10 million units, 18 million units or 50 million units per vial. Refer to the package insert for current available formulations.

c) Interferon alfa-2b powder for injection vials do NOT include a preservative. Reconstituted vials must be discarded immediately after the appropriate dose is withdrawn from the vial.

d) All powder for injection vials may be used for intravenous, intramuscular or subcutaneous injection.

Vials containing 10 million units may be used for intralesional injection.

e) Ingredients in the formulation include purified sterile recombinant interferon product, glycine, sodium phosphate dibasic, sodium phosphate monobasic, and human albumin.

2. Interferon alfa-2b solution for injection

a) Interferon alfa-2b solution for injection appears clear or colorless and is available in 18 million units per vial or 25 million units per vial. Please refer to the package insert for current available formulations.

b) Solution for injection vials containing 18 million units or 25 million units may be used for subcutaneous or intramuscular injection. Solution for injection vials containing 25 million units may be used for intralesional injection.

The Intron® A (interferon alfa-2b) formulation must be consistent with the approved product labeling for the intended route of administration.

c) Ingredients in the formulation include purified sterile recombinant interferon product, sodium chloride, sodium phosphate dibasic, sodium phosphate monobasic, edetate disodium, polysorbate 80, and cresol as a preservative.

g. STORAGE AND STABILITY

1. Interferon alfa-2b powder for injection

a) Vials should be stored in a refrigerator at 2°C - 8°C (36°F- 46°F) until the expiration date indicated on the vial or packaging has been reached or until immediately prior to use. Vials should be allowed to come to room temperature prior to use.

b) Reconstituted vials may be stored refrigerated at 2°C - 8°C (36°F - 46°F) for no longer than 24 hours. However, the reconstituted vial must be discarded after one dose has been withdrawn from the vial.

c) Interferon alfa-2b powder for injection vials do not contain a preservative. Reconstituted vials containing leftover medication should not be re-used, as the sterility is not guaranteed. Bacterial contamination may occur in reconstituted vials used for more than a single dose.

2. Interferon alfa-2b solution for injection

a) Vials should be stored in a refrigerator at 2°C - 8°C (36°F - 46°F) until the expiration date indicated on the vial or packaging has been reached.

Multidose solution for injection vials contain preservatives and can be stored refrigerated for up to one month. Unused doses remaining in the vial must be discarded after one month.

b) Vials should not be frozen or exposed to excessive heat.

3.2 Ipilimumab (BMS-734016, MDX-010, YERVOY®) (NSC 732442)

a. PHARMACOLOGY

Mechanism of Action: Cytotoxic T-lymphocyte antigen-4 CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a full human monoclonal immunoglobin (lg) antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response.

b. PHARMACOKINETICS

1. Absorption: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes.

2. Distribution: Ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined ipilimumab is confined mainly to the extracellular fluid. Peak concentration (Cmax), trough concentration (Cmin), and area under the plasma concentration versus time curve (AUC) of ipilimumab increased dose proportionally within the dose range examined. Based on population pharmacokinetic analysis, the mean volume of distribution (% coefficient of variation) at steady state was 7.47 liters (10%).

3. Metabolism: Not applicable. Monoclonal antibodies are usually degraded into amino acids and small peptides, independently from CYP450 or other drug-metabolizing enzymes.

4. Elimination: Clearance increased with body weight, but no dose adjustment is required with dosing on a mg/kg basis. Upon repeated dosing every 3 weeks, the clearance (CL) of ipilimumab was found to be time-invariant, and systemic accumulation was 1.5-fold or less. The mean value (% coefficient of variation) generated through population pharmacokinetic analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for CL was 16.8 mL/h (38%).

c. ADVERSE EFFECTS

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.10, March 29, 2019[1]

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
		Blood and lymphatic system disorders - Other (acquired hemophilia)	
CARDIAC DISORDERS			
	Atrial fibrillation		
		Myocarditis[2]	
		Pericardial effusion	
EAR AND LABYRINTH DISORDERS			
	Hearing impaired		
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Hyperthyroidism[2]		
	Hypophysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
	Testosterone deficiency[2]		
EYE DISORDERS			
	Eye disorders - Other (episcleritis)[2]		
	Uveitis[2]		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		***Colitis[2] (Gr 3)***
		Colonic perforation[3]	
	Constipation		
Diarrhea			***Diarrhea (Gr 3)***
	Enterocolitis		
	Esophagitis		
		Ileus	
Nausea			***Nausea (Gr 3)***
	Pancreatitis[2]		
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Chills		
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
		General disorders and administration site conditions - Other (systemic inflammatory response syndrome [SIRS])	
		Multi-organ failure	
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
	Autoimmune disorder[2]		
		Immune system disorders - Other (GVHD in the setting of allotransplant)[4]	
INFECTIONS AND INFESTATIONS			
		Infections and infestations - Other (aseptic meningitis)[2]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
		Lymphocyte count decreased	
	Neutrophil count decreased		
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Dehydration		
	Hyperglycemia		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Arthritis		
		Generalized muscle weakness	
	Musculoskeletal and connective tissue disorder - Other (polymyositis)[2]		
NERVOUS SYSTEM DISORDERS			
		Ataxia	
	Facial nerve disorder[2]		
	Guillain-Barre syndrome[2]		
	Headache		
	Myasthenia gravis[2]		
		Nervous system disorders – Other (immune-mediated encephalitis) [2]	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
	Trigeminal nerve disorder		
PSYCHIATRIC DISORDERS			
		Psychiatric disorders - Other (mental status changes)	
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
	Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis)		

Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pneumonitis		
		Respiratory failure	
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
		Respiratory, thoracic and mediastinal disorders - Other (lung infiltration)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 3)***
Rash maculo-papular			***Rash maculo-papular (Gr 3)***
	Skin and subcutaneous disorders - Other (Sweet's syndrome)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
	Urticaria		
VASCULAR DISORDERS			
	Hypotension		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis,

conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3] Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4] Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5] In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[7] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that ipilimumab (MDX-010) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[2]; Febrile neutropenia
CARDIAC DISORDERS - Conduction disorder; Restrictive cardiomyopathy
EYE DISORDERS - Extraocular muscle paresis[5]; Eye disorders - Other (retinal pigment changes)
GASTROINTESTINAL DISORDERS - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[6]; Proctitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Flu like symptoms; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure[2]
IMMUNE SYSTEM DISORDERS - Allergic reaction
INFECTIONS AND INFESTATIONS - Infection[7]
INVESTIGATIONS - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
PSYCHIATRIC DISORDERS - Anxiety; Confusion; Depression; Insomnia
RENAL AND URINARY DISORDERS - Proteinuria
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Cough; Dyspnea; Laryngospasm

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
VASCULAR DISORDERS - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

Note: Ipilimumab (MDX-010) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. Pregnancy and Lactation: There are no adequate and well-controlled studies of Ipilimumab in pregnant women. Use of Ipilimumab during pregnancy only if the potential benefit justifies the potential risk to the fetus. Human IgG1 is known to cross the placental barrier and ipilimumab is an IgG1; therefore, ipilimumab has the potential to be transmitted from the mother to the developing fetus.

   It is not known whether ipilimumab is secreted in human milk. Because many drugs are secreted in human milk and because of the potential for serious adverse reactions in nursing infants from ipilimumab, a decision should be made whether to discontinue nursing or to discontinue ipilimumab, taking into account the importance of ipilimumab to the mother.

2. Drug Interactions: No formal pharmacokinetic drug interaction studies have been conducted with ipilimumab. Ipilimumab is not expected to have pharmacokinetic drug-drug interactions, since it is not metabolized by CYP450 or other drug metabolizing enzymes

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan.

Ipilimumab injection is to be administered as an infusion with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not administer as IV push or bolus injection.

e. HOW SUPPLIED

Ipilimumab is a sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow solution for intravenous infusion, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. It is supplied in single-use vials of 50 mg/10 mL and 200 mg/40 mL (5 mg/mL). Each milliliter contains 5 mg of ipilimumab and the following inactive ingredients: diethylene triamine pentaacetic acid (DTPA) (0.04 mg), mannitol (10 mg), polysorbate 80 (vegetable origin) (0.1 mg), sodium chloride (5.85 mg), tris hydrochloride (3.15 mg), and Water for Injection, USP at a pH of 7.

Ipilimumab is commercially available and will not be supplied. Refer to the current FDA-approved package insert.

f. STORAGE, PREPARATION & STABILITY

1. Store intact vials of ipilimumab refrigerated at (2° to 8°C), protected from light. Do not freeze.

2. Dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare a diluted solution with a final concentration ranging from 1 mg/mL to 2 mg/mL. Mix diluted solution by gentle inversion. Refer to package insert for complete preparation and dispensing instructions

3. The product may be infused using a volumetric pump at the protocol-specific dose(s) and rate(s) through a PVC IV solution infusion set with an in-line, sterile, nonpyrogenic, low-protein-binding filter (pore size of 0.2 micrometer to 1.2 micrometer).

4. Do not administer ipilimumab as an IV push or bolus injection.

5. Stability of prepared IV ipilimumab solution is stable up to 24 hours refrigerated at (2° to 8°C) or at room temperature/ room light.

6. Partially used vials or empty vials of ipilimumab injection should be discarded at the site according to appropriate drug disposal procedures.

3.3 MK-3475 (Pembrolizumab) (NSC-776864, IND #125133)

a. PHARMACOLOGY

MK-3475 (Pembrolizumab) is a humanized MAb of the IgG4/kappa isotype. The programmed cell death 1 (PD-1) receptor is an inhibitory receptor expressed by T cells. When bound to either of its ligands, PD-L1 or PD-L2, activated PD-1 negatively regulates T-cell activation and effector function. The pathway may be engaged by tumor cells expressing PD-1 ligands to suppress immune control. MK-3475 blocks the negative immune regulatory signaling by binding to the PD-1 receptor, inhibiting the interaction between PD-1 and its ligands and thereby promoting the host immune system to recognize tumor cells as foreign bodies to be eliminated.

b. PHARMACOKINETICS

The pharmacokinetic profile of MK-3475, with low clearance and limited volume of distribution, is typical for therapeutic antibodies. Elimination half-life after IV administration was approximately 14 to 21.6 days. Steady state concentration levels were achieved within 16 weeks of treatment when tested at 3 and 10mg/kg dosing as administered at 2 week intervals. During repeated dosing of 2 or 10mg/kg Q3W, steady state in trough concentrations appeared to have been achieved after approximately three months. Furthermore, MK-3475 has a low potential of eliciting the formation of anti-drug antibodies.

c. ADVERSE EFFECTS

Comprehensive Adverse Events and Potential Risks list (CAEPR) for MK-3475 (pembrolizumab, NSC 776864) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3793 patients.* Below is the CAEPR for MK-3475 (pembrolizumab).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, December 27, 2019[1]

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia[2]		
	Lymph node pain[2]		
	Thrombotic thrombocytopenic purpura[2]		
CARDIAC DISORDERS			
		Myocarditis[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[2]		
	Endocrine disorders - Other (thyroiditis)[2]		
	Hyperthyroidism[2]		
	Hypohysitis[2]		
	Hypopituitarism[2]		
	Hypothyroidism[2]		
EYE DISORDERS			
		Uveitis[2]	
		Eye disorders - Other (Vogt-Koyanagi-Harada syndrome)	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Colitis[2]		
	Diarrhea[2]		***Diarrhea[2] (Gr 2)***
	Mucositis oral[2]		
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[2]		
	Small intestinal mucositis[2]		
GENERAL DISORDERS AND ADMINISTRATION SITE			

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
CONDITIONS			
	Chills[2]		
Fatigue			***Fatigue (Gr 2)***
	Fever[2]		
HEPATOBILIARY DISORDERS			
	Hepatobiliary disorders - Other (autoimmune hepatitis)[2]		
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis[2]	
		Cytokine release syndrome[2]	
		Immune system disorders - Other (acute graft-versus-host-disease)[2,3]	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis)[2]	
	Immune system disorders - Other (pseudoprogression/tumor inflammation)[2]		
	Immune system disorders - Other (sarcoidosis)[2]		
		Serum sickness[2]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
		Infusion related reaction	
INVESTIGATIONS			
	Alanine aminotransferase increased[2]		
	Alkaline phosphatase increased		
	Aspartate		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	aminotransferase increased[2]		
	Blood bilirubin increased		
	CPK increased		
		GGT increased	
		Serum amylase increased	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
	Hyponatremia		
		Metabolism and nutrition disorders - Other (diabetic ketoacidosis)[2]	
		Metabolism and nutrition disorders - Other (type 1 diabetes mellitus)[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		***Arthralgia[2] (Gr 2)***
	Arthritis[2]		
	Avascular necrosis[2]		
	Back pain		
	Joint effusion[2]		
	Joint range of motion decreased		
	Musculoskeletal and connective tissue disorder - Other (tenosynovitis)[2]		
	Myalgia[2]		
	Myositis[2]		
NERVOUS SYSTEM DISORDERS			
		Guillain-Barre syndrome[2]	
		Nervous system disorders - Other (myasthenic syndrome)[2]	
		Nervous system	

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		disorders - Other (neuromyopathy)[2]	
		Nervous system disorders - Other (non-infectious encephalitis)[2]	
		Nervous system disorders - Other (non-infectious meningitis)[2]	
		Nervous system disorders - Other (non-infectious myelitis)	
		Nervous system disorders - Other (polyneuropathy)[2]	
		Paresthesia	
		Peripheral motor neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (autoimmune nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Pleuritic pain[2]		
	Pneumonitis[2]		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Bullous dermatitis[2]		
		Erythema multiforme[2]	
	Erythroderma		
		Palmar-plantar erythrodysesthesia syndrome	
	Pruritus[2]		***Pruritus[2] (Gr 2)***
	Rash acneiform[2]		
	Rash maculo-papular[2]		***Rash maculo-papular[2] (Gr 2)***
	Skin and subcutaneous		

Adverse Events with Possible Relationship to MK-3475 (pembrolizumab) (CTCAE 5.0 Term) [n= 3793]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	tissue disorders - Other (dermatitis)[2]		
	Skin hypopigmentation[2]		
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis	
	Urticaria[2]		
VASCULAR DISORDERS			
		Vasculitis[2]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Immune-mediated adverse reactions have been reported in patients receiving MK-3475 (pembrolizumab). Adverse events potentially related to MK-3475 (pembrolizumab) may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of MK-3475 (pembrolizumab), administration of corticosteroids and supportive care.

[3] Acute graft-versus-host disease has been observed in patients treated with MK-3475 (pembrolizumab) who received hematopoeitic stem cell transplants.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on MK-3475 (pembrolizumab) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MK-3475 (pembrolizumab) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Hemolysis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocardial infarction; Pericardial effusion; Pericardial tamponade; Ventricular arrhythmia
EYE DISORDERS - Eye pain
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Constipation; Duodenal hemorrhage; Dysphagia; Gastritis; Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (intestinal obstruction); Gastrointestinal disorders - Other (intussusception); Oral pain; Rectal hemorrhage; Small intestinal perforation; Upper gastrointestinal hemorrhage; Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Edema limbs; Facial pain; Gait disturbance; General disorders and administration site conditions - Other (general physical health deterioration); Generalized edema; Malaise; Non-cardiac chest pain; Pain
INVESTIGATIONS - Cholesterol high; Creatinine increased; Fibrinogen decreased; Lymphocyte count decreased; Neutrophil count decreased; Platelet count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hypertriglyceridemia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Pain in extremity
NERVOUS SYSTEM DISORDERS - Aphonia; Depressed level of consciousness; Dysarthria; Edema cerebral; Encephalopathy; Headache; Hydrocephalus; Lethargy; Meningismus; Nervous system disorders - Other (brainstem herniation); Seizure; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion
RENAL AND URINARY DISORDERS - Acute kidney injury; Nephrotic syndrome; Proteinuria; Renal and urinary disorders - Other (hydronephrosis); Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Pelvic pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia; Laryngeal inflammation; Pleural effusion; Pneumothorax; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Skin and subcutaneous tissue disorders - Other (drug eruption)
VASCULAR DISORDERS - Hypertension; Peripheral ischemia; Thromboembolic event

Note: MK-3475 (pembrolizumab) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

1. Pregnancy and Lactation: MK-3475 may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-3475 has transient adverse effects on the composition of sperm. Patients are excluded from this study if pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

   Men and non-pregnant, non-breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 2 years will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be barrier method or a barrier method plus a hormonal method to prevent pregnancy. Patients should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy. The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any

registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Patients should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period. If there is any question that a patient will not reliably comply with the requirements for contraception, that patient should not be entered into the study.

Pregnancy: If a patient inadvertently becomes pregnant while on treatment with MK-3475, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported without delay and within 24 hours if the outcome is a serious adverse experience (*e.g.*, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn.

It is unknown whether MK-3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, patients who are breast-feeding are not eligible for enrollment.

2. Drug Interactions: No studies on pharmacodynamic drug interactions have been performed. Due to potential drug interactions, a complete patient medication list, including MK-3475, should be screened prior to initiation of and during treatment with MK-3475. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

d. DOSING & ADMINISTRATION

See Section 7.0 Treatment Plan

e. HOW SUPPLIED

MK-3475 is supplied by Merck & Co., Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL). Proteinaceous particles may be present. MK-3475 solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

f. PREPARATION

MK-3475 solution for infusion must be diluted prior to administration. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of MK-3475 to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the

bag 10-15 times to mix the solution. The final concentration must be between **1 mg/mL to 10 mg/mL**.

Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

g. STORAGE

Store intact vials between 2°C - 8°C (36°F - 46°F). Do not freeze. Protect from light by storing in the original box. If a storage temperature excursion is identified, promptly return MK-3475 to between 2-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

h. STABILITY

Stability testing of the intact vials is on-going.

Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 20 hours. MK-3475 solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

i. ROUTE OF ADMINISTRATION

IV infusion only. Do not administer as an IV push or bolus injection.

j. METHOD OF ADMINISTRATION

Infuse over approximately 30 minutes (range: 25 - 40 minutes) using an infusion set containing a low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Compatible infusion set materials: PVC plasticized with DEHP or DEHT, PVC and tri-(2-ethylhexyl) trimellitate, polyethylene lined PVC, polyurethane, or polybutadiene

k. PATIENT CARE IMPLICATIONS

Refer to Section 8.3a for information on evaluation and management of potential immune-related adverse events.

l. DRUG ORDERING AND ACCOUNTABILITY

1. Drug Ordering

Study specific supplies will be provided to sites once a patient has been randomized. Starter supplies will not be provided. NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management

Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP assigned protocol number (**S1404**) must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 and a CV. If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application at https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

2. Drug Handling and Accountability (NCI logs or other)

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Electronic logs are allowed as long as a print version of the log process has the exact same appearance as the current NCI DARF.

3. Drug return and/or disposition instruction

b. Drug Disposition: All undispensed drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g., sealed bottles remaining when PMB sends a stock recovery letter), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

c. *Drug Expiration: Stability testing is ongoing. PMB will send a stock recovery letter when notified that the agent is no longer suitable for use.*

4. Contact Information

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 240/276-6575 Monday through Friday between 8:30 am and 4:30 pm Eastern Time or email at PMBAfterHours@mail.nih.gov.

4.0 STAGING CRITERIA (AJCC 7TH Edition, 2010)

Pathologic Staging included in this trial:

Stage IIIA	T1-T4a	N2a	M0
Stage IIIB	T1-4a	N1-N2b	M0
	T1b (ulcerated)	N1-N2a	M0
	T2b-4b	N1-N2a	MO
	T1-4a.b	N2c	M0
Stage IIIC	T1-4b	N1-N2b	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

See Section 18.5 for TNM Definitions for Pathologic Staging.

5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the **S1404** Eligibility Checklist to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at melanomaquestion@crab.org prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28, 42 or 90 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 STEP 1 REGISTRATION

Disease Related Criteria

a. Patients must have completely resected melanoma of cutaneous origin or of unknown primary in order to be eligible for this study. Patients must be classified as Stage IIIA (N2a), IIIB, IIIC, or Stage IV melanoma. Patients with non-ulcerated T1b N1a disease are not eligible. Patients with melanoma of mucosal or other non-cutaneous origin are eligible. Patients with melanoma of ocular origin are not eligible. Patients with a history of brain metastases are ineligible.

b. Patients are eligible for this trial either at initial presentation of their melanoma or at the time of the first detected nodal, satellite/in-transit, distant metastases, or recurrent disease in prior lymphadenectomy basin or distant site. Nodal, satellite/in-transit metastasis, distant metastases or disease in a prior complete lymphadenectomy basin must have been confirmed histologically by H & E stained slides.

c. Patients with multiple regional nodal basin involvement are eligible. Gross or microscopic extracapsular nodal extension is permitted.

d. Patients at initial presentation of melanoma must undergo an adequate wide excision of the primary lesion, if present. (See Section 18.1 for guidelines on surgical management.) Patients with previously diagnosed melanoma must have had all current disease resected with pathologically negative margins and must have no evidence of disease at the primary site or must undergo re-resection of the primary site. A full lymphadenectomy meeting the criteria outlined in Section

18.1 is required for all node-positive patients including those with positive sentinel nodes. Patients with recurrent disease who have had a prior complete lymphadenectomy fulfill this requirement as long as all recurrent disease has been resected. For all patients, all disease must have been resected with negative pathological margins and no clinical, radiologic, or pathological evidence of any incompletely resected melanoma. **Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.**

Specimen Submission Criteria

e. Patients must have available and be willing to submit a minimum of five unstained slides from primary, lymph node, or metastatic site to determine PD-L1 expression as described in Section 15.2. The tumor tissue must be adequate for PD-L1 testing (defined as ≥ 100 tumor cells as confirmed by the treating institution's local pathologist). This must be documented by having a pathologist sign the **S1404** Local Pathology Review form (see Section 18.4) prior to Step 1 registration. The specimens may come from an archived block but must be submitted within 20 days from cutting the slides.

f. Patients must be offered the opportunity to participate in specimen banking as outlined in Section 15.3.

g. Patients must be willing to have blood draws for PK/ADA analysis as outlined in Section 15.4, should the patient be randomized to the MK-3475 arm.

Prior/Concurrent Therapy Criteria

h. Patients may have received prior radiation therapy, including after the surgical resection. All adverse events associated with prior surgery and radiation therapy must have resolved to ≤ Grade 1 prior to registration.

i. Patients must not have received neoadjuvant treatment for their melanoma. Patients must not have had prior immunotherapy including, but not limited to ipilimumab, interferon alfa-2b, high dose IL-2, PEG-IFN, anti-PD-1, anti-PD-L1 intra-tumoral or vaccine therapies. Patients must not be planning to receive any of the prohibited therapies listed in Section 7.2 during the screening or treatment phases of the study.

j. Patients must not be planning to receive concomitant other biologic therapy, radiation therapy, hormonal therapy, other chemotherapy, surgery or other therapy after Step 2 registration.

Clinical/Laboratory Criteria

k. Patients must be ≥ 18 years of age.

l. All patients must have disease-free status documented by a complete physical examination and imaging studies within 42 days prior to registration. Imaging studies must include a total body PET-CT scan that is of diagnostic quality (with or without brain) or a CT of the chest, abdomen and pelvis. For patients with melanoma arising from the head and neck, dedicated neck imaging (CT with IV contrast or PET-CT through the region) is required. If the patient has had unknown primary with disease in the axilla, neck imaging is required to assure region is clear of cancer. CT imaging should be done with intravenous contrast if there are no contraindications for it. Any other clinically-indicated imaging studies if performed (e.g. bone scan) must show no evidence of disease.

m. All patients must have a CT or MRI of the brain within 90 days prior to registration. The brain CT or MRI should be performed with intravenous contrast (unless contraindicated).

n. Patients must have adequate bone marrow function as evidenced by all of the following: ANC ≥ 1,500 microliter (mcL); platelets ≥ 100,000/mcL; Hemoglobin ≥ 10 g/dL. These results must be obtained within 42 days prior to registration.

o. Patients must have adequate hepatic function as evidenced by the following: total bilirubin ≤ 1.5 x institutional upper limit of normal (IULN) (except Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL), and SGOT (AST) and SGPT (ALT) and alkaline phosphatase ≤ 2 x IULN. These results must be obtained within 42 days prior to registration.

p. Patients must have adequate renal function as evidenced by ONE of the following: serum creatinine ≤ IULN OR measured or calculated creatinine clearance ≥ 60 mL/min. This result must have been obtained within 42 days prior to registration.

Calculated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$

q. Patients must have LDH performed within 42 days prior to registration.

r. Patients must have Zubrod Performance Status ≤ 1 (see Section 10.4).

s. Patients must have a baseline ECG performed within 42 days of registration that is normal or considered not clinically significant by the site investigator.

t. Patients must not have a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

u. Patients must not have an active infection requiring systemic therapy.

v. Patients must not have active autoimmune disease that has required systemic treatment in past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

w. Patients must not have received live vaccines within 42 days prior to registration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.

x. Patients known to be HIV positive are eligible if they meet the following criteria within 30 days prior to registration: stable and adequate CD4 counts (≥ 350 mm^3), and serum HIV viral load of < 25,000 IU/ml. Patients may be on or off anti-viral therapy so long as they meet the CD4 count criteria.

y. Patients must not have known active Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV) infection prior to registration.

z. Patients must not have a history or current evidence of any condition, therapy or laboratory abnormality that might confound the trial results, interfere with the patient's participation for the full duration of the trial, or indicate that participation

in the trial is not in the patient's best interests, in the opinion of the treating investigator.

aa. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, lobular carcinoma of the breast in situ, atypical melanocytic hyperplasia or melanoma in situ, adequately treated Stage I or II cancer (including multiple primary melanomas) from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for three years.

bb. Women of childbearing potential must have a negative urine or serum pregnancy test within 28 days prior to registration. Women/men of reproductive potential must have agreed to use an effective contraceptive method for the course of the study through 120 days after the last dose of study medication. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy, or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures. Patients must not be pregnant or nursing due to unknown teratogenic side effects.

cc. Patients who are able to complete questionnaires in English, Spanish or French must participate in the quality of life assessments. (Those patients who cannot complete the quality of life questionnaires in English, Spanish or French can be registered to **S1404** without contributing to the quality of life studies.)

Regulatory Criteria

dd. Patients must be informed of the investigational nature of this study and must sign and give written informed consent for this protocol in accordance with institutional and federal guidelines.

ee. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

5.2 STEP 2 REGISTRATION (Randomization)

An e-mail notification from the SWOG Statistical Center should be received within 10 business days of submitting tissue as described in Section 15.2.

The following additional criteria must be met in order for a patient to be considered eligible for registration to the randomized trial. Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at melanomaquestion@crab.org prior to registration.

a. Patients must not be registered until receiving confirmation from the SWOG Statistical Center that the patient's tissue specimen was adequate for PD-L1 testing. Patients must be registered within 7 working days of receiving the e-mail notification.

b. Women of childbearing potential must plan to have a urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a negative serum pregnancy test will be required.

c. No tests or exams are required to be repeated for Step 2 registration (Randomization). However, patients who are known to have a change in eligibility status after Step 1 registration are not eligible for Step 2 registration. For example, ANC is not required to be repeated between Step 1 and Step 2 registration, but the most recent ANC performed before Step 2 registration is required to be ≥ 1,500 mcL.

6.0 STRATIFICATION FACTORS

Patients will be randomized between Arm 1 – physician/patient choice of either high dose interferon or ipilimumab and Arm 2 – MK-3475 (pembrolizumab) in a 1:1 fashion, using a randomized block design. Stratification is based on:

1) surgically resected AJCC stage:

IIIA (N2a) versus IIIB versus IIIC versus IV

2) PD-L1 status (see Section 15.2): positive versus negative versus indeterminate

(NOTE: Institutions will be blinded to the patient's PD-L1 status.)

3) Planned control arm regimen *: high dose interferon versus ipilimumab.

* NOTE: The intended control arm regimen must be declared prior to randomization for all patients.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Grossmann at 801/587-4735 (or S1404SCquestion@swog.org) or Dr. Sapna Patel at 713/792-2921. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Procedures" under the "About" menu and choose Policy 38).

7.1 Treatment

a. Pretreatment Labs:

Blood samples collected for pretreatment laboratory tests must be collected and analyzed no more than 3 days prior to dosing. Albumin, glucose, and electrolytes (Na, K, HC03 or CO2) are required within 3 days prior to dosing to obtain baseline data for future toxicity assessments.

b. Arm 1: **Physician/Patient Choice of Either High Dose Interferon or Ipilimumab**

1. High Dose Interferon

Induction Therapy

Agent	Dose	Route	Days	Schedule
Interferon Alfa-2b	20 MU/m^2/d*	IV over 20 min	1-5 5 days a week	Weeks 1 - 4

* Dose rounding ± 10% is allowable per institutional standards.

For the purpose of data reporting, 1 cycle = 6 weeks (4 weeks of HDIFN plus first 2 weeks of IFN maintenance.).

If possible, on the days when patients are required to come in for a clinic visit, Interferon treatment should be administered after all questionnaires, procedures and assessment have been completed.

Interferon doses must be rounded to the nearest 1 million unit. Interferon is given over a 20 minute infusion. Day 1 of each week of induction therapy should be administered at the registering institution. Days 2 – 5 of interferon administration for Weeks 1 - 4 may be administered at an institution other than the registering institution provided that during treatment to-date, the patient has not encountered any life-threatening or unusual toxicities and that the registering physician still retains primary responsibility for the patient's treatment. Documentation concerning all drugs administered, side effects, and tests performed must be forwarded to the registering institution. Home Health Agencies (HHA) may be used to treat patients. The registering institution must document any care given at an outside institution.

Maintenance Therapy

Agent	Dose	Route	Days	Schedule
Interferon Alfa-2b	10 MU/m^2/d*	SC	1, 3, 5 M,W,F	Weeks 5 - 52

For the purpose of data reporting, Cycle 2 (Weeks 7-12) is 6 weeks, and all subsequent cycles are 12 weeks.

Self-Administration of Subcutaneous Doses

Interferon doses must be rounded to the nearest 1 million unit. Patients who are deemed competent to self-administer the subcutaneous maintenance doses of Interferon alfa-2b may do so following the first 4 weeks of treatment. Patients must complete compliance documentation (Section 7.3) for self-administered doses. If patient cannot self-administer, a nurse, or qualified HHA staff may administer the injections. The registering institution must document any care given at an outside institution.
* Dose rounding ± 10% is allowable per institutional standards.

2. Ipilimumab

Induction Therapy

Agent	Dose	Route	Days	Schedule
Ipilimumab	10 mg/kg*	IV infusion over 90 minutes	1	Weeks 1-10; Q 3 weeks for a total of four doses

For the purpose of data reporting, 1 cycle = 6 weeks.
* Dose rounding ± 10% is allowable per institutional standards.

If possible, on the days when patients are required to come in for a clinic visit, treatment should be administered after all questionnaires, procedures and assessment have been completed.

The final concentration must be between 1-2 mg/mL.

Maintenance Therapy

Agent	Dose	Route	Days	Schedule
Ipilimumab	10 mg/kg*	IV infusion over 90 minutes	1	Weeks 25-145; Q 12 weeks for 11 doses ending at 3 years)

For the purpose of data reporting, 1 cycle = 12 weeks.
* Dose rounding ± 10% is allowable per institutional standards.

If possible, on the days when patients are required to come in for a clinic visit, treatment should be administered after all questionnaires, procedures and assessment have been completed.

The final concentration must be between 1-2 mg/mL.

c. Arm 2: **MK-3475 (Pembrolizumab)**

Agent	Dose	Route	Schedule
MK-3475 (Pembrolizumab)	200 mg	IV over 30 minutes	Day 1, Q 3 weeks for 52 weeks

For the purpose of data reporting, Cycle 1 and Cycle 2 are 6 weeks and all subsequent cycles are 12 weeks.

MK-3475 (pembrolizumab) treatment should be administered after all questionnaires, procedures and assessments have been completed. MK-3475 (pembrolizumab) treatment may be administered up to 3 days before or after the protocol-specified Q 3 weeks due to administrative reasons.

MK-3475 (pembrolizumab) treatment will be administered on an outpatient basis.

MK-3475 (pembrolizumab) will be administered as a 30 minute IV infusion. Infusion timing should be as close to 30 minutes as possible; however, a window of -5 minutes and +10 minutes is permitted (*i.e.*, infusion time is 25-40 minutes).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chairs. The reason for interruption should be documented in the patient's study record.

All planned doses must be administered. Missed doses must be made up.

7.2 Prohibited and Cautionary Medications

Radiation therapy must be completed at least 1 day prior to starting ipilimumab or MK-3475 and must be completed at least 7 days prior to starting interferon.

Patients are prohibited from receiving the following therapies after registration to Step 1 and through completion of protocol therapy:

- Anti-cancer systemic chemotherapy or biological therapy.
- Immunotherapy not specified in this protocol.
- Any non-study anti-cancer agent (investigational or non-investigational).
- Investigational agents other than MK-3475.
- Live vaccines: Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, shingles, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and **are allowed**; however, intranasal influenza vaccines (*e.g.* Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic doses of

corticosteroids (defined as 10 mg prednisone) are acceptable, however site investigators should consult with the Study Chair for any dose higher than 10 mg prednisone.

Patients who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from protocol treatment. Patients may receive other medications that the investigator deems to be medically necessary.

7.3 Drug Compliance Documentation

Patients who self-administer interferon alfa-2b, may complete the **S1404** Patient Interferon Diary which can be found in Section 18.3. Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. The completed patient diary should be kept in the patient's clinic chart. Note that the diary is provided only as a tool for tracking patient compliance. Do not submit patient diaries to the SWOG Data Operations Office. Sites may utilize institutional diaries or other source documentation in place of the **S1404** Patient Interferon Diary at the discretion of the treating physician. The completed Interferon Diary, institutional diary, or other source documentation in place of the **S1404** Interferon Diary must be available for upload if requested as part of the risk based monitoring.

7.4 Criteria for Removal from Protocol Treatment

a. Recurrence of disease (as defined in Section 10.0).

b. Unacceptable toxicity.

c. The patient may withdraw from the study at any time for any reason.

d. The investigator may discontinue treatment if they determine that the patient's continued treatment on the study is detrimental to their long-term health, or due to poor compliance with the study's required visits and treatments.

e. Positive pregnancy test.

f. Completion of protocol treatment.

g. Patients will be removed from protocol treatment if there is a treatment delay > 84 consecutive days for any reason.

7.5 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.6 Follow-Up Period, End of Study

Randomized patients will be followed until death or 10 years after randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

8.2 Dose Modification Considerations for Patients Receiving Interferon (Arm 1)

a. General

Induction therapy by the IV route in Weeks 1-4 shall be evaluated separately from Maintenance therapy in Weeks 5-52. A patient requiring dose modification(s) in the first 4 weeks will therefore commence Week 5 at full dose. **Doses missed during treatment due to toxicity, patient compliance, holiday, etc. should not be made up.**

b. Arm 1 – IFN Dose Modification Table

	Full Dose	Dose mod 1	Dose mod 2	Dose mod 3
Induction (Weeks 1-4)	20 MU/m^2	13.3 MU/m^2	6.6 MU/m^2	Remove from protocol treatment
Maintenance (Weeks 5-52)	10MU/m^2	6.6 MU/m^2	3.3 MU/m^2	Remove from protocol treatment

PLEASE NOTE: If a patient experiences any of the toxicities listed below, the patient must have a dose modification as follows: treatment must be held until the toxicity returns to institution's normal limits, patient's baseline, or normal limits per CTCAE or as listed in the table under Section 8.2c, then reduced per above.

EXCEPTIONS: For Grade 3 proteinuria without creatinine or BUN elevation, dose should be held until return to Grade 2 toxicity. For Grade 2 weight loss observed over a period of one month, dose should be held until weight gain or stabilization.

Dose modifications outside of the guidelines prescribed below are allowed at the discretion of the treating physician if:

- The modification is being performed due to toxicity related to HDI therapy; and,
- After consideration of the patient's safety and overall clinical status, the treating physician feels that the modification is in the patient's best interest.

Any modifications outside of the prescribed guidelines must be documented in the comment section of the **S1404** Treatment Form.

c. ARM 1 (IFN) TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS *(24)*

TOXICITY	GRADE 2	GRADE 3	GRADE 4
<u>Blood/Bone Marrow</u> Thrombocytopenia	Full Dose	Hold therapy*; Reduce one dose level	Remove from protocol treatment
Anemia	Hold therapy* until return to Grade 1 or baseline; reduce one dose level	Hold therapy* until return to Grade 1 or baseline; reduce one dose level	Remove from protocol treatment
Neutropenia	Full Dose	Full Dose	Reduce one dose level
<u>Cardiovascular</u> Arrhythmia Cardiac-Other	Hold therapy until return to normal*; reduce one dose level after formal cardiologic evaluation and clearance	Removal from protocol treatment	Removal from protocol treatment
<u>Gastrointestinal</u> Nausea, vomiting and/or diarrhea	Administer supportive care; if persistent for more than 2 weeks, reduce one dose level	Hold therapy*; reduce one dose level	Removal from protocol treatment
Weight loss	Hold therapy for weight loss observed over a 1 month period until weight gain or stabilization*		
<u>Hepatic</u> ALK PHOS. Bilirubin or SGOT(AST)/SGPT (ALT)	Full Dose	Hold therapy until return to ≤ Grade 1*; reduce one dose level	Removal from protocol treatment
<u>Neurology</u> Cognitive disturbance Mood alteration Neuropathy – motor	Full Dose	Hold therapy *; reduce one dose level (evaluation by specialist)	Removal from protocol treatment

TOXICITY	GRADE 2	GRADE 3	GRADE 4
Neuropathy - sensory			
<u>Renal/Genitourinary</u> Proteinuria Creatinine	Full Dose Hold therapy*; reduce one dose level	Hold therapy until return to ≤ Grade 2*; reduce one dose level Removal from protocol treatment	Removal from protocol treatment Removal from protocol treatment

***PLEASE NOTE:** If a patient experiences any of the toxicities listed in the above table, the patient must have a dose modification as indicated (unless otherwise specified). Treatment must be held until the toxicity returns to institution's normal limits, patient's baseline, or normal limits per the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov, then reduce as indicated above. Dose re-escalation will not be attempted following resolution of toxicity that required dose interruption or attenuation.

8.3 Dose Modification Considerations for Patients Receiving Ipilimumab (Arm 1)

a. Dose and schedule modifications for ipilimumab

There will be no dose reductions for ipilimumab. The dose of ipilimumab will either be given or delayed/discontinued. Patients may develop study drug-related toxicities that may require skipping doses or dose discontinuation. Some of these adverse events may be consistent with potentially drug-related immune-mediated phenomena; termed IRAEs. Details of how to dose study medication in the presence of adverse drug reactions that may or may not be IRAEs are addressed below.

Patients will delay or discontinue treatment with ipilimumab if they experience at least one adverse event, specified below, considered by the investigator to be **definitely**, **probably**, or **possibly** related to ipilimumab treatment unless otherwise specified. The following criteria will be used to determine dosing delay, restarting doses, or discontinuing ipilimumab. For an adverse event, review the following criteria in a stepwise manner: First, assess the dose delay criteria and decide whether a scheduled dose should be delayed. Second, determine whether the permanent discontinuation criteria apply to the adverse event in question as well.

NOTE: Due to the possible effect of treatment with ipilimumab on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) 1 week before or after any dose of ipilimumab.

b. Criteria to delay/skip one dose of ipilimumab

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Delay ipilimumab dosing for any of the following definitely, probably, or possibly treatment related adverse events, unless otherwise specified:

- Grade ≥ 1 diarrhea and/or colitis **regardless of attribution**. Grade ≥ 2 diarrhea and/or colitis, definitely, probably, or possibly related to ipilimumab, requires permanent discontinuation.
- Any other ≥ Grade 2 non-skin related adverse event (including IRAEs) except for laboratory abnormalities.
- Grade ≥ 2 laboratory abnormalities that are secondary to an immune-related adverse event or autoimmune phenomenon (e.g., Grade ≥ 2 TSH associated with a CTCAE v.4 grade 2 thyroid dysfunction induced by ipilimumab, anemia, neutropenia, amylase, lipase, CPK, hyperglycemia, or elevated LFTs) should also lead to an ipilimumab dosing delay/skipping.
- Any other ≥ Grade 3 laboratory abnormality.
- Any ≥ Grade 3 skin-related adverse event (including IRAEs) **regardless of attribution**.

c. Criteria to resume ipilimumab treatment

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Ipilimumab **may not** be restarted while the patient is being treated with oral or intravenous corticosteroids for the management of immune related adverse events except for patients on stable doses of hormone replacement therapy for adrenal insufficiency such as hydrocortisone. In addition, patients must be off and have no requirement for oral/I.V. corticosteroids for at least 1 week and meet the other criteria for retreatment as outlined below.

Restart ipilimumab dosing if/when the adverse event(s) resolve(s) to ≤ Grade 1 severity or returns to baseline within 3 weeks of last dose administration:

- If the adverse event has resolved (to ≤ Grade 1 severity or returns to baseline), restart ipilimumab dosing at the next scheduled time point per protocol.
- If the adverse event has not resolved in the protocol-specified dosing window, the next scheduled dose will be omitted.
- Patients with Grade 1 diarrhea and/or colitis who require steroid therapy must have resolution to Grade 0 (or baseline) before resuming dosing with ipilimumab. Patients with Grade ≥ 2 related diarrhea and/or colitis must have ipilimumab permanently discontinued.

d. Criteria for permanent discontinuation of ipilimumab for Related Adverse Events

**NOTE: See also: Section 8.3e: Dose Modification and Management for Cardiomyophathy Myocarditis

Ipilimumab administration must be permanently discontinued for any of the following definitely, probably, or possibly treatment related adverse events, unless otherwise specified:

- Any ≥ Grade 2 eye pain or reduction of visual acuity that does not respond to topical therapy and does not improve to ≤ Grade 1 severity within 2 weeks of starting therapy, OR, requires systemic treatment.
- Any ≥ Grade 2 diarrhea and/or colitis related to ipilimumab. Any ≥ Grade 2 diarrhea/colitis should be considered RELATED unless immune related colitis is definitely ruled out (including by endoscopy and biopsy.)
- Any ≥ Grade 2 hypophysitis, pneumonitis, nephritis, and/or sarcoid-like lesions.
- Any new motor or sensory neurologic toxicity ≥ Grade 2 regardless of attribution (including Guillain-Barré syndrome and myasthenia gravis).
- Any ≥ Grade 3 bronchospasm or other hypersensitivity reaction.
- Any other ≥ Grade 3 non-skin adverse event with the exception of events listed under “Exceptions to Permanent Discontinuation”
- AST or ALT > 5 x ULN.
- Total Bilirubin > 3 x ULN.
- Any other ≥ Grade 4 laboratory abnormalities except for specified exceptions
- Any other ≥ Grade 4 adverse event.
- Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration or necrotic, bullous, or hemorrhagic manifestations.
- Any adverse event, laboratory abnormality or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the patient with continued dosing.
- Patients who require high dose steroids, other immune suppressants or anti-TNF drug therapy for the management of immune related adverse events as described in the Toxicity Management Guidelines/Algorithms should have ipilimumab permanently discontinued.

e. Dose Modification and Management for Cardiomyopathy Myocarditis

- Drug will be held for Grade 2 cardiac dysfunction pending evaluation
- Drug will be permanently discontinued for Grade 3 or 4 cardiac dysfunction and Grade 2 events that do not recover to baseline or that reoccur
- Treatment with steroids as clinically indicated

Cardiac *	**Management/Next Dose for BMS-936558 (Nivolumab) + Ipilimumab Cardiac Toxicities**
≤ Grade 1	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

f. Exceptions to permanent discontinuation of ipilimumab

Ipilimumab administration may be resumed in the following cases:

- Potentially reversible inflammation (< Grade 4), attributable to a local anti-tumor reaction and a potential therapeutic response. This includes inflammatory reactions at sites of tumor resections or in draining lymph nodes, or at sites suspicious for, but not diagnostic of metastasis.
- Laboratory abnormalities that are rapidly reversible, not life threatening, do not reflect underlying organ system dysfunction, and are not related to the study treatment, such as transient elevations of uric acid, hypocalcaemia, hypophosphatemia.
- Hospitalization for ≤ Grade 2 adverse events (not including Grade 2 events that require permanent discontinuation) where the primary reason for hospitalization is to expedite the clinical work-up.
- Patients with the following conditions where in the investigator's opinion continuing study drug administration is justified:
  - Ocular toxicity that has responded to topical therapy and has improved to ≤ Grade 1 severity within 2 weeks of starting therapy.
  - Patients without a diagnosis of hypophysitis who have Grade 2 hypothyroidism, Grade 2 low testosterone or Grade 2 adrenal insufficiency where clinical symptoms are controlled with appropriate hormone replacement therapy.

8.4 Dose Modification Considerations for Patients Receiving MK-3475 (pembrolizumab) (Arm 2)

a. General MK-3475 Dose Modifications

Missed doses of MK-3475 must be made up.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 1 below. See Section 8.4b for supportive care guidelines, including use of corticosteroids.

NOTE: Due to the possible effect of treatment with MK-3475 on the immunologic response to infectious disease vaccines, patients must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) within 1 week before or after any dose of MK-3475.

Dose Modification

Dose modification and toxicity management for immune-related AEs associated with pembrolizumab

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 1.

Table 1 Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last pembrolizumab treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab has been withheld, pembrolizumab may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity grade (CTCAE V5.0)	Action with pembrolizumab	Corticosteroid and/or other therapies	Monitoring and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Recurrent Grade 2, Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

				• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion
AST or ALT elevation or Increased Bilirubin	Grade 2 [a]	Withhold	• Administer corticosteroids (initial dose of 0.5 - 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 [b] or 4 [c]	Permanently discontinue	• Administer corticosteroids (initial dose of 1 - 2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [d]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [d]		
Hyperthyroi-dism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or permanently discontinue [d]		

Hypothyroi-dism	Grade 2, 3, 4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1 – 2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue based on the event [e]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

[a] AST/ALT: >3.0 - 5.0 x ULN if baseline normal; >3.0 - 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 - 3.0 x ULN if baseline normal; >1.5 - 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 - 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 - 10.0 x ULN if baseline normal; >3.0 - 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include but are not limited to: Guillain-Barre Syndrome, encephalitis, Stevens-Johnson Syndrome and toxic epidermal necrolysis.

Other allowed dose interruption for pembrolizumab

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

Dose modification and toxicity management of infusion-reactions related to pembrolizumab

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table Y.

Dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Patients should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Study Chair. The reason for interruption should be documented in the patient's study record.

b. Management of Infusion Reactions

- Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion

Table 2 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-3475 (pembrolizumab).

Table 2 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) at http://ctep.cancer.gov		

8.5 Use of Transfusion and/or EPO

Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications on the S1404 Concomitant Medication Form. Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

8.6 Use of G-CSF

Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

8.7 Anti-infectives

Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice. Document on the **S1404** Concomitant Medication Form.

8.8 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Grossmann at 801/585-0255 or S1404SCquestion@swog.org or if Dr. Grossmann is not available, contact Dr. Sapna Patel at 713/792-2921. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Procedures" under the "About" menu and choose Policy 38).

8.9 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDARS

9.1 Arm 1: Interferon alfa-2b

REQUIRED STUDIES	Pre-study screening	Ran-domiza-tion	Induction Phase[a] Days 1-5 (M-F) of Weeks 1-4				Maintenance Phase[a] Days 1, 3, 5 (M, W, F) of Weeks 5-52										End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse	Relapse /Recu-rrence	F/U post relapse[d]
			Cycle 1						C2	C3		C4		C5		C6				
			W 1	W 2	W 3	W 4	W 5	W 6	W7-12	W 13	W 19	W 25	W 31	W 37	W 43	W 49				
PHYSICAL	Reg Step 1	Reg Step 2																		
History & Physical (w/BSA, BP, Height & Weight) [s]	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
PS & Tox Notation	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																				
Cover Sheet for Patient-Completed Questionnaires			X			X				X		X		X		X		X[p]	X[q]	
FACT-BRM, EQ-5D-3L and FACIT-D Questionnaire			X			X				X		X		X		X		X[p]	X[q]	
LABORATORY[e]																				
ANC, platelets, Hgb	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
LDH [f]	X																		X[f]	
AST and ALT, Alkaline Phosphatase	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Alb, Glu, Na, K, HCO3 (or CO_2) [a]			X[a]	X	X	X	X		X	X	X	X	X	X	X	X	X	X		
Triglycerides [g]	X											X[g]					X[g]			
Free T_3, TSH, Free T_4 [r]	X									X[r]		X[r]		X[r]			X[r]			
Pregnancy Test [i]	X		X[i]						X[i]	X[i]		X[i]		X[i]		X[i]				

Calendar continued on next page. Click here for footnotes.

9.1 Arm 1: Interferon alfa-2b (contd.

REQUIRED STUDIES	Pre-study screening	Ran-domiza-tion	Induction Phase[a] Days 1-5 (M-F) of Weeks 1-4						Maintenance Phase[a] Days 1, 3, 5 (M, W, F) of Weeks 5-52								End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse [c]	Relapse /Recu-rrence	F/U post relapse[d]
			Cycle 1						C2	C3		C4		C5		C6				
			W 1	W 2	W 3	W 4	W 5	W 6	W7 -12	W 13	W 19	W 25	W 31	W 37	W 43	W 49				
X-RAYS AND SCANS	Reg Step 1	Reg Step 2																		
Whole Body PET/CT or CT neck [j], chest abdomen & pelvis [k]	X									X		X		X		X		X [j k]		
Brain MRI or CT with Contrast [k]	X															X[k]		X[k]		
EKG [h]	X																			
Image Submission [o]		X								X		X		X		X		X		
SPECIMEN SUBMISSION																				
Slides for PD-L1 Expression [l]	X																			
E-mail confirmation tissue was adequate for PD-L1 analysis [l]		X																		
Tissue[m] for banking		X																	X	
Serum[m] for banking		X[n]								X		X					X		X	
Plasma & Buffy Coat[m] for RNA/DNA for banking		X[n]								X		X					X		X	
TREATMENT																				
Interferon alfa-2b			X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.
Footnotes for Study Calendar 9.1: Arm 1 (Interferon alfa-2b)

a. The following exams and labs are done weekly during induction (Weeks 1-4 of Cycle 1), the first week of maintenance (Week 5 of Cycle 1), then every first and seventh week of each subsequent cycle until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at Week 53 or whenever patient comes off treatment.
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: If a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of IFN treatment and at the end of IFN treatment.
h. To be performed at baseline, then as clinically indicated throughout treatment.
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months(± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized on Step 2 until e-mail confirmation has been received indicating that the specimen was adequate for determining PD-L1 status.
m. If patient consents, submit specimens for banking as specified in Section 15.0.
n. Blood needs to be drawn prior to treatment.
o. Submit scans as outlined in Sections 14.0 and 15.0.
p. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks(± 2 weeks) after the date of last treatment.

q. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.

r Thyroid function tests need to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post-treatment follow-up. Additional testing to be done as clinically indicated.

s History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.

9.2 Arm 1: Ipilimumab

REQUIRED STUDIES	Pre-screen-ing	Rand-dom-ization	ON TREATMENT [a]															End of treat [b]	Post treat F/U pre-re-lapse[c]	Re-lapse /Rec ur-rence	F/U post re-lapse[d]
PHYSICAL	Reg Step 1	Reg Step 2	Induction				C 3	C 4	C 5	C6	C 7	C 8	C 9	C 10	C 11	C 12	C 13	C 14				
			Cy 1		C 2																	
*			W 1	W 4	W 7	W 10	W 13	W 25	W 37	W 49	W 61	W 73	W 85	W 97	W 109	W 121	W 133	W 145				
History & Physical (w/ BSA, BP, Height & Weight) [t]	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PS & Toxicity Notation	X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																						
Cover Sheet for Patient-Completed Questionnaires			X	X			X	X	X	X										X[r]	X[s]	
FACT-BRM, EQ-5D-3L and FACIT-D Questionnaire			X	X			X	X	X	X										X[r]	X[s]	
LABORATORY[e]																						
ANC, platelets, Hgb	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
LDH [f]	X																				X[f]	
AST and ALT, Alkaline Phosphatase	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Albumin, Glucose, Na, K, HCO3 (or CO_2) [a]			X[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Triglycerides[g]	X							X[g]											X[g]			
Free T_3, TSH, Free T_4 [o]		X					X[o]	X[o]	X[o]											X		
Cardiac Function [u]			X		X		X	X	X	X	X	X	X	X	X	X	X	X				
Pregnancy Test[i]	X		X[i]				X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]	X[i]			

Study Calendar 9.2 continued on next page. Click here for footnotes.

9.2 Arm 1: Ipilimumab (contd.)

	Pre-StudyScreening	Randomization	ON TREATMENT [a]															End of treat [b]	Post treat F/U pre-relapse [c]	Relapse/Recurrence	F/U post relapse [d]
	Reg Step 1	Reg Step 2	Induction				C 3	C 4	C 5	C6	C 7	C 8	C 9	C 10	C 11	C 12	C 13	C 14				
			Cy 1		Cy 2																	
*			W 1	W 4	W 7	W 10	W 13	W 25	W 37	W 49	W 61	W 73	W 85	W 97	W 109	W 121	W 133	W 145				
X-RAYS AND SCANS																						
Whole body PET/CT or CT neck [j], chest, abdomen & pelvis [k]	X						X	X	X	X	X	X	X	X	X	X	X	X		X [j k]		
Brain MRI or CT with contrast [k]	X									X[k]					X[k]					X [k]		
EKG[h]	X																					
Image Submission [p]		X					X	X	X	X	X	X	X	X	X	X	X	X		X		
SPECIMEN SUBMISSION																						
Slides for PD-L1 expression [l]	X																					
E-mail confirmation tissue was adequate for PD-L1 analysis		X																				
Tissue [m] for banking		X																			X	
Serum [m] for banking		X [n]					X	X											X		X	
Plasma & Buffy Coat [m] for RNA/DNA for banking		X [n]					X	X											X		X	
TREATMENT																						
Ipilimumab			X	X	X	X		X	X	X	X	X	X	X	X	X	X	X				

Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form submission guidelines are found in Section 14.0.

NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Study Calendar 9.2: Arm 1 Ipilimumab

a. The following exams and labs are performed prior to receiving first dose and at the start of every cycle until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at the 15th infusion or whenever patient comes off treatment (treatment stops at the end of Year 3, even if the patient has not received all 15 infusions).
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first 2 follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse event assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation date, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: if ipilimumab was delayed per the dose delay/scheduling criteria or if a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of treatment and the end of treatment.
h. To be performed prior to Registration Step 1, then as clinically indicated. Also see footnote “u”.
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease. Patients may still be on treatment until 3 years from randomization.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized to Step 2 until e-mail notification has been received indicating that the specimen was adequate for determining PD-L1 status.

m. If patient consents, submit specimens for banking as specified in Section 15.0.
n. Blood needs to be drawn prior to treatment.
o. Thyroid function tests to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post treatment follow-up. Additional testing to be done as clinically indicated.
p. Submit scans as outlined in Sections 14.0 and 15.0.
r. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks (± 2 weeks) after the date of last treatment.
s. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.
t History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.
u Patients with history of CHF or who are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs should have an ECHO prior to treatment and an ECHO and EKG at the start of each cycle, as clinically indicated. Patients who have evidence at baseline (or subsequently) of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, ECHO cardiogram, as clinically indicated.
* These are the corresponding weeks if there are no dose delays.

9.3 Arm 2: MK-3475 (Pembrolizumab)

REQUIRED STUDIES	Pre-study Screen	Random-ization	ON TREATMENT [a] The first two cycles consist of 2 infusions, subsequent cycles consist of 4 infusions. Infusions to be given q 3 weeks for 18 total infusions (5.5 cycles).											End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse[c]	Re-lapse/ Recur-rence	F/U post relapse[d]
PHYSICAL	Reg Step 1	Reg Step 2	Cycle 1		Cycle 2		C3		C4		C5		C6				
			*W 1	*W 4	*W 7	*W 10	*W 13	*W 19	*W 25	*W 31	*W 37	*W 43	*W 49				
History & Physical (w/ BSA, BP, Height & Weight) [t]	X		X		X		X	X	X	X	X	X	X	X	X		
PS & Toxicity Notation	X		X		X		X	X	X	X	X	X	X	X	X		
FORMS FOR QOL STUDIES																	
Cover Sheet for Patient-Completed Questionnaires			X	X			X		X		X		X		X[r]	X[s]	
FACT-BRM, EQ-5D-3L, and FACIT-D Questionnaire			X	X			X		X		X		X		X[r]	X[s]	
LABORATORY[e]																	
ANC, platelets, Hgb	X		X		X		X	X	X	X	X	X	X	X	X		
Total bilirubin	X		X		X		X	X	X	X	X	X	X	X	X		
LDH [f]	X															X[f]	
AST and ALT, Alkaline Phosphatase	X		X		X		X	X	X	X	X	X	X	X	X		
Serum Creatinine or CrCl	X		X		X		X	X	X	X	X	X	X	X	X		
Albumin, Glucose, Na, K, HCO3 (or CO_2) [a]			X[a]		X		X	X	X	X	X	X	X	X	X		
Triglycerides [g]	X								X[g]					X[g]			
Free T_3, TSH, Free T_4 [o]	X						X[o]		X[o]		X[o]			X[o]	X		
Pregnancy Test[i]	X		X[i]		X[i]		X[i]		X[i]		X[i]		X[i]				
Cardiac Functiont[v]			X		X		X		X		X		X				

Study Calendar 9.3 continued on next page. Click here for footnotes.

9.3 Arm 2: MK-3475 (Pembrolizumab) (contd.)

	Pre-study Screen	Random-ization	ON TREATMENT [a] The first two cycles consist of 2 infusions, subsequent cycles consist of 4 infusions. Infusions to be given q 3 weeks for 18 total infusions (5.5 cycles).											End of treat-ment assess-ment[b]	Post treat-ment F/U prior to relapse[c]	Re-lapse/Recur-rence	F/U post relapse[d]
	Reg Step 1	Reg Step 2	Cycle 1		Cycle 2		C3		C4		C5		C6				
			*W 1	*W 4	*W 7	*W 10	*W 13	*W 19	*W 25	*W 31	*W 37	*W 43	*W 49				
X-RAYS AND SCANS																	
Whole body PET/CT or CT neck [j], chest, abdomen & pelvis [k]	X						X		X		X		X		X [j k]		
Brain MRI or CT with contrast [k]	X												X [k]		X [k]		
EKG[h]	X																
Image Submission [p]		X					X		X		X		X		X		
SPECIMEN SUBMISSION																	
Slides for PD-L1 expression [l]	X																
Serum for PK/ADA [q]			X	X		X		X	X				X		X [q]		
E-mail confirmation tissue was adequate for PD-L1 analysis		X															
Tissue [m] for banking		X														X	
Serum [m] for banking		X [n]					X		X					X		X	
Plasma & Buffy Coat [m] for RNA/DNA for banking		X [n]					X		X					X		X	
TREATMENT																	
MK-3475 (Pembrolizumab)			X	X	X	X	X	X	X	X	X	X	X				

Study Calendar 9.3 continued. Click here for footnotes.

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Form submission guidelines are found in Section 14.0.
NOTE: Unless indicated otherwise in the protocol, scheduled procedures and assessments (treatment administration, toxicity assessment for continuous treatment, disease assessment, specimen collection and follow-up activities) must follow the established SWOG guidelines as outlined in https://www.swog.org/sites/default/files/docs/2017-10/Best%20Practices%20upddate.pdf.

Footnotes for Study Calendar 9.3: Arm 2 MK-3475 (Pembrolizumab)

a. Following exams & labs are performed prior to receiving first dose & prior to every other infusion until end of protocol treatment: physical (w BSA, BP & WT), PS, toxicity notation, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated.
b. End of treatment assessment occurs at the 18th infusion or whenever patient comes off treatment.
c. Post-treatment follow-up (prior to relapse): Patients should be seen at 6 weeks (-/+ 1 week) after the last dose, then 12 weeks (-/+ 1 week) after the last dose, then every 3 months (+/- 2 weeks) if patient is < 2 years from study entry, every 6 months (+/- 4 weeks) if patient is 2-5 years from study entry, and every 12 months (+/- 4 weeks) if patient is > 5 years from study entry for up to 10 years. The first two follow-up visits may be scheduled to allow follow-up visits and scans to occur on the same date for on-going follow-up. The following exams and labs should be performed: physical (w BSA, BP & wt), PS, ANC, platelets, Hgb, total bilirubin, AST and ALT, alk phos, serum creatinine or CrCl, albumin, glucose, Na, K, HCO_3 (or CO_2). Adverse Event Assessments on the study will continue for all patients until 30 days after the last study drug administration. However, patients with ongoing toxicities should be seen more often as clinically indicated. For post-treatment follow-up regarding scans, see footnote k.
d. Follow-up post relapse: Patients who develop recurrent melanoma will be followed for survival (vital status). Adverse Events Assessment on the study will continue for all patients until 30 days after the last study drug administration. Patients should be followed every 6 months for up to 2 years from the date of treatment discontinuation, then annually thereafter until 10 years from date of randomization. However, patients with ongoing toxicities should be seen more often as clinically indicated.
e. While on study, blood samples collected for pretreatment laboratory tests may be collected and analyzed no more than 3 days prior to dosing. NOTE: if MK-3475 was delayed per the dose delay/scheduling criteria or if a visit had to be delayed due to major circumstances (such as a health emergency, family/personal emergency, transportation difficulties, scheduling difficulties; a visit date falls on a holiday), the study assessments scheduled for these dates will be delayed.
f. LDH to be done at baseline and at relapse.
g. Triglycerides to be done at screening, after 6 months of treatment and at the end of treatment.
h. To be performed prior to Registration Step 1, then as clinically indicated. Also see footnote "v".
i. Women of child bearing potential must have a negative serum or urine pregnancy test at screening within 28 days prior to registration. Following randomization, serum or urine pregnancy tests are required within 72 hours prior to the first dose of study treatment, then according to institutional practice during therapy, tests should coincide with clinic visits for blood work and ending with the discontinuation of study treatment. At discontinuation, a negative pregnancy test within the preceding 6 weeks is sufficient. A pregnancy test should be done at any time there are clinical concerns for possible pregnancy.
j. Patients with primary melanoma of the head and neck or unknown primary with disease in the axilla will also require a neck CT.
k. Disease assessments by PET-CT or CT chest/abdomen/pelvis (or MRI if CT cannot be done), and neck CT as needed will be performed every 12 weeks (-/+ 2 weeks) until 2 years from randomization, then every 6 months (± 4 weeks) until 5 years from randomization, then follow for survival. The same imaging modality as used at prestudy for disease assessment should be used throughout the trial. During treatment and follow-up, brain MRI/CT or other imaging studies must be repeated annually (± 4 weeks). For PET-CT imaging, iodinated contrast is recommended in addition to FDG for optimal relapse detection. If there is a contra-indication to iodine, non-contrast chest CT and MRI of abdomen/pelvis with gadolinium are acceptable body imaging alternatives. If there is a gadolinium allergy, or MRI brain intolerable for the patient, CT with iodinated IV contrast is adequate brain imaging. MRI of the brain is required for patients with progressive disease.
l. Slides must be submitted as described in Section 15.2. Patients cannot be randomized to Step 2 until e-mail notification has been received indicating that the specimen was adequate for determining PD-L1 status.
m. If patient consents, submit specimens for banking as specified in Section 15.0.

Footnotes for Study Calendar 9.3: Arm 2 MK-3475 (Pembrolizumab) (contd. on next page)

n. Blood needs to be drawn prior to treatment.
o. Thyroid function tests to be done at screening, within 3 days prior to the start of study treatment on Week 13, Week 25 and Week 37 and at initial post treatment follow-up. Additional testing to be done as clinically indicated.
p. Submit scans as outlined in Sections 14.0 and 15.0.
q. Serum for PK and anti-MK-3475 antibody testing must be submitted for all patients randomized to the MK-3475 arm as described in Section 15.4. Pre-dose trough PK and anti-MK-3475 samples will be collected before the first infusion Cycle 1 (Week 1), before second infusion Cycle 1 (Week 4), before second infusion Cycle 2 (Week 10), before third infusion Cycle 3 (Week 19), before first infusion Cycle 4 (Week 25), before infusion Cycle 6 (Week 49) and 30 days after discontinuation of study drug (or until patient starts new anti-cancer therapy). **All pre-dose trough samples should be drawn within 24 hours before infusion of MK-3475. (AS OF 12/11/2017 PK/ADA SAMPLING HAS BEEN DISCONTINUED. SPECIMENS ALREADY COLLECTED MUST STILL BE SHIPPED.)**
r. Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed 24 weeks (± 2 weeks) and 48 weeks (± 2 weeks) after the date of last treatment.
s. If relapse occurs before 48 weeks after date of last treatment, Cover Sheet, FACT-BRM, EQ-5D-3L and FACIT-D should be completed at the time of relapse.
t History prior to each treatment initiation to include a menstrual, sexual and contraceptive use history, including date of last menstrual period (for women of childbearing potential) which will help determine the need for pregnancy testing. Similar questions regarding contraceptive use to be asked of men who are sexually active with women of childbearing potential. Height is only required at baseline.
* These are the corresponding weeks if there are no dose delays.
v Patients with history of CHF or who are deemed at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs should have an ECHO prior to treatment and an ECHO and EKG at the start of each cycle, as clinically indicated. Patients who have evidence at baseline (or subsequently) of CHF, MI, cardiomyopathy, or myositis cardiac evaluation (NYHA I/II) should have additional consult by a cardiologist, including review of EKG, CPK, troponin, ECHO cardiogram, as clinically indicated.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

Measurement of Effect

10.1 Progression/Relapse

Appearance of any new lesion/site. Death due to disease without prior documentation of progression.

- Appearance of a new melanoma in-situ or Stage I melanoma which can be treated curatively by wide excision does not constitute recurrence. If this does occur, upload pathology and operative reports via the Source Documentation: Follow-Up Form in Rave.
- In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), either symptoms persist beyond 4 weeks or there must be additional evidence of progression.
- For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
- Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.

2) No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, X-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

10.2 Relapse-Free Survival

Measured from date of randomization to date of first documentation of relapse or death due to any cause. Patients last known to be alive and relapse-free are censored at date of last contact.

10.3 Overall Survival

Measured from date of randomization to date of death due to any cause. Patients known to be alive are censored at date of last contact.

10.4 Performance Status

Patients will be graded according to the Zubrod Performance Status Scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual goals

Based on **E1609**, an intergroup accrual rate of at least 45 patients per month is assumed.

It is assumed that up to 10% of patients will be ineligible. It is expected that 1378 registered patients will be required to accrue 1,240 eligible patents (see below for sample size calculations). Including time to ramp up accrual, it is anticipated that it will take less than 2.5 years to complete accrual for this trial.

11.2 Overall survival (OS) and relapse-free survival (RFS) objectives

There are three primary objectives of this study: 1) to test whether OS is improved with pembrolizumab compared to a control arm of physician/patient choice of high-dose interferon (HDI) or ipilimumab in this patient population, 2) to test whether among patients who are PD-L1 positive OS is improved with pembrolizumab compared to this control arm in this patient population, 3) to test whether RFS is improved with pembrolizumab compared to this control arm in this patient population.

11.3 Overall survival (OS) and relapse-free survival (RFS) design assumptions

OS and RFS estimates from **S0008** indicate that a proportion of patients may be long-term survivors in the sense that they will not be observed to relapse or die during the follow-up period planned for the study. It is further assumed that there are no differences in OS or RFS between the treatment regimens in the control arm.

An exponential cure rate model fit to OS on the HDI arm of **S0008** indicated that 40% of patients were long-term survivors and that median OS for patients who were not long-term survivors was 3.01 years (null hypothesis). The null OS model is written that the OS at year t is equal to 0.40+0.60*exp(-0.23t). For sample size calculations, it is assumed that OS with pembrolizumab will also follow an exponential cure rate model, but with 45% of patients long-term survivors and a median OS for non-long term survivors of 3.96 years (alternative hypothesis). The alternative OS model is written that the OS at year t is equal

to 0.45+0.55*exp(-0.175t). This corresponds to an average hazard ratio (HR, average of 10,000 simulated hazard ratios from the Cox model) of 0.73 from a Cox proportional hazards model at 100% OS events (374 events at Study Year 5).

An exponential cure rate model fit to RFS on the HDI arm of **S0008** indicated that 35% of patients were long-term survivors and that median RFS for patients who were not long-term survivors was 1.03 years (null hypothesis). The null RFS model is written that the RFS at year t is equal to 0.35+0.65*exp(-0.67t). For sample size calculations, it is assumed that RFS with pembrolizumab will also follow an exponential cure rate model, but with 41% of patients long-term survivors and a median RFS for non-long term survivors of 1.44 years (alternative hypothesis). The alternative RFS model is written that RFS at year t is equal to 0.41+0.59*exp(-0.48t). This corresponds to an average hazard ratio (HR) of 0.70 from a Cox proportional hazards model at 100% RFS information.

We assume a total two-sided alpha of 5% (one-sided alpha of 2.5%) allocated between the four co-primary objectives as detailed below. We assume 1:1 randomization, 2.5 years of accrual, 2.5 years of follow-up after accrual completes. We assume 48.2% of patients will be PD-L1 positive, (based on the lower limit of the 95% confidence interval of the prevalence from ClinicalTrials.gov trial NCT 01704287), 46.8% will be PD-L1 negative, and 5% will be PD-L1 indeterminate. All testing will be stratified by the randomization stratification. Tests of the null hypothesis will be done using the log-rank test. Futility analysis testing will be performed using a modified log-rank test modified for testing non-null hypotheses (a score test of the alternative hazard ratio).

11.4 Alpha allocation between Overall survival (OS) and Relapse-free survival (RFS)

Using a Bonferroni split, 4.6% (two-sided) of the alpha will be allocated to the OS endpoint (overall population and PD-L1+ subgroup) and 0.4% (two-sided) of the alpha will be allocated to the RFS endpoint (overall population). For OS, 80% of the alpha will be allocated to the overall population and the remaining alpha will be allocated to the PD-L1 positive subgroup using the method described in the next paragraph.

Under the null hypothesis, the test statistics for the overall population and the PD-L1 positive subgroups are multivariable normal with correlation equal to the proportion of events the PD-L1 positive subgroup relative to the whole population. *(25)* The residual alpha for the PD-L1 population can be calculated using this relationship. For clarity in the exposition of the design we will assume the PD-L1 positive subgroup has 48.2% of the total OS events of the study (based on the lower limit of the 95% confidence interval of the prevalence from ClinicalTrials.gov trial NCT 01704287). For the final analyses involving the PD-L1 positive subgroups, the actual alpha level will be calculated using the multivariate normal relationship based on the PD-L1 positive proportion observed in the trial

Under these assumptions, the alpha allocation is expected to be as follows: the OS overall population with 3.7% (two-sided) and the PD-L1 + subgroup OS with 1.52% (two-sided). Accounting for the correlation between the subgroup and overall group, the overall alpha is 4.6% (two-sided) for OS and 0.4% (two-sided) for RFS.

- OS overall population 3.7%
- OS PD-L1 + subgroup 1.52%
- RFS overall population 0.4%

11.5 Interim and final analysis plans

The primary analysis will be intent-to-treat population.

All testing will be stratified by the randomization stratification factors. Tests of the null hypothesis will be done using the log-rank test. Futility analysis testing will be performed using a modified log-rank test modified for testing non-null hypotheses (a score of the alternative hazard ratio).

100% of expected RFS is 536 events. One formal interim analysis of the overall population RFS endpoint is scheduled at approximately 75% of RFS events (402 RFS events calculated across both arms under the alternative). At the interim analysis, an efficacy test will be done (test of null hypothesis HR=1) with a one-sided alpha=0.09%. At the interim analysis a futility test will evaluate if the HR from a Cox regression model stratified by the randomization factors favors the control arm (HR>1). If an efficacy or futility boundary is crossed at the interim analysis, the DSMC will consider early release of the RFS results. The final analysis of the overall population RFS will test of the null hypothesis (HR=1) at the two-sided 0.32% level (one-sided 0.16% level) in order to account for the interim analysis.

Up to two formal interim analyses of the overall population OS will be completed at approximately 55% and 80% events (206 and 399 events, respectively, events calculated across both arms under the alternative). At both interim analyses, an efficacy test will be done (test of null hypothesis HR=1) with a one-sided alpha=0.125%. At the first interim analysis a futility test will evaluate if the HR from a Cox regression model stratified by the randomization factors favors the control arm (HR>1). At the second interim analysis a futility test will be done testing the alternative hazard ratio (HR=0.73) with a one-sided alpha of 2.5%. If a boundary for futility is crossed at an interim analysis, the DSMC will consider the toxicities on each arm. Considering the magnitude of the survival difference between the two arms along with the relative toxicities, the DSMC can choose not to recommend reporting results early if additional data on the potential non-inferiority of pembrolizumab is warranted. The final analysis of the overall population OS will test of the null hypothesis (HR=1) at the two-sided 3.6% level (one-sided 1.8% level) in order to account for interim analyses. At the final analysis for the overall population OS, a two-sided test of the null hypothesis of OS in the PD-L1 positive subgroup will be performed at the two-sided alpha=1.52% level[2] (one-sided 0.76% level).

The final OS superiority test will be performed in a stepwise fashion following an OS non-inferiority test using a margin of 1.045. An upper limit of a one-sided 98.15% confidence interval less than 1.045 will be considered evidence of non-inferiority of pembrolizumab compared to the control arm.

At the final analysis for OS, results for RFS with updated follow-up will be presented. We note that because of the expected survival patterns with this population, the average hazard ratio is expected to become more null (closer to 1) over time. Under the alternative hypothesis, at 3.5 years since the first patient is randomized the hazard ratio is 0.70, while at 5 years since the first patient is randomized the hazard ratio is 0.73.

There will be no formal interim testing of RFS (overall or PD-L1 positive subgroup) or of OS in the PD-L1 positive subgroup.

If 100% RFS or OS events has not been reached by 3.5 years after the last eligible patient is randomized, the final RFS and OS analyses will be performed at this time.

[1] Alpha to be calculated based on observed proportion of total OS events in the PD-L1 positive group.

The sample size of this trial was determined to ensure appropriate power to detect meaningful OS differences. As such, the trial is overpowered for RFS, and may therefore detect small RFS differences of uncertain clinical benefit. Hence, regardless of the statistical significance of the RFS results, the clinical benefit of pembrolizumab will be assessed by the magnitude of the relative and absolute RFS improvement of the pembrolizumab arm over the control arm, and by the comparisons of overall survival and toxicity between the treatment arms.

Under this design and assuming PD-L1 positive patients have the same OS on the control arm as the whole population, the alternative OS survival model for 80% power is model is written that OS at year t is equal to 0.44+0.56*exp(-0.13t) [44% long-term survivors and median OS of 5.3 years for non-long-term survivors]. This corresponds to an average HR of 0.58 from a Cox proportional hazards model at 100% OS events. The alternative OS survival model for 90% power is model is written that OS at year t is equal to 0.45+0.55*exp(-0.13t) [45% long-term survivors and median OS of 5.3 years for non-long-term survivors]. This corresponds to an average HR of 0.56 from a Cox proportional hazards model at 100% OS events.

Design properties were determined via simulation with 100,000 replications. Properties of the design are summarized in the tables below.

Table 1 Overall population OS Interim and final analysis summary. Events calculated across both arms. Actual analysis timing may vary.

Percent OS events	Study Year	N events	Tests done
55%	3	206	Efficacy and futility
80%	4	299	Efficacy and futility
100%	5	374	Efficacy

Table 2 Characteristics of interim and final overall population OS analyses

OS Scenario	Probability under alternative	Probability under null
Probability stop for futility at 1st interim analysis	1%	50%
Probability stop for efficacy at 1st interim analysis	28%	<1%
Probability stop for futility at 2nd interim analysis	1%	17%
Probability stop for efficacy at 2nd interim analysis	19%	<1%
Probability stop early for futility	2%	67%
Probability stop early for efficacy	48%	1%
Probability of positive result	86%	2.1%[a]

[a] Ignoring futility monitoring two-sided, alpha level=3.7%

Table 3 Overall population RFS Interim and final analysis summary. Events calculated across both arms. Actual analysis timing may vary.

Percent RFS events	Expected time	N events	Tests done
75%	Mid-2018	402	Efficacy and futility
100%	Late 2018	536	Efficacy

Table 4 Characteristics of interim and final overall population RFS analyses

RFS Scenario	Probability under alternative	Probability under null
Probability stop for futility at interim analysis	<1%	50%
Probability stop for efficacy at interim analysis	69%	<1%
Probability of positive result	90%	0.22%[a]

[a] Ignoring futility monitoring two-sided, alpha level=0.4%

Table 5 Additional characteristics of overall population OS analyses. Events calculated across both arms. Actual analysis timing may vary.

Analysis	Alpha level	HR threshold	OS Events
Year 3 interim efficacy	0.125% (one-sided)	0.67	206
Year 3 interim futility	NA	1	206
Year 4 interim efficacy	0.125% (one-sided)	0.70	299
Year 4 interim futility	2.5%	0.92	299
Year 5 final efficacy	3.6% (two-sided)	0.81	374

HR threshold = HR that will correspond to a significant p-value based on alpha level. For efficacy analyses HRs less than the threshold will be significant, for futility analyses HRs larger than the threshold will warrant early closure of the study.

Table 6 Characteristics of overall population RFS analyses. Actual analysis timing may vary.

Analysis	Alpha level	HR threshold	RFS Events
interim efficacy	0.09% (one-sided)	0.66	402
Interim futility	NA	1	402
Final efficacy	0.32% (two-sided)	0.78	536
Year 5 follow-up	NA	NA	668

HR threshold = HR that will correspond to a significant p-value based on alpha level. For efficacy analyses HRs less than the threshold will be significant.

Table 7 PD-L1 positive subgroup analysis details, N = 596 (48.2% prevalence)*

Endpoint	Time point	Alpha-level (two sided)*	HR threshold	Design HR	Power
OS	Year 5	1.52%	0.66	0.57	80%
OS	Year 5	1.52%	0.68	0.56	90%

* These calculations assume a 48.2% event fraction in the PD-L1 positive subgroup. For the final analysis, calculations will be based on the observed fraction of events in the trial. HR threshold = HR that will correspond to a significant p-value based on alpha level. Design HR = HR that provides stated level of power.

How to interpret the first line of Table 7: If 48.2% of patients are PDL1-positive (and making all the assumptions about survival in the protocol), at Year 5 we will have 80% power to detect a true hazard ratio of 0.57 for OS. In other words, if the true hazard ratio between the arms is 0.57 and we ran the trial many times, 80% of the trials would have an observed hazard ratio of 0.62 or less or a two-sided p-value less than 0. 0152.

11.6 Anticipated stage distribution.

Eligibility for SWOG trial **S0008** included Stages IIIA(n2), IIIB, and IIIC. Eligibility for ECOG trial **E1609** included Stages IIIB, IIIC, M1a, and M1b. Eligibility for this trial **S1404** includes Stages IIIA(n2), IIIB, IIIC, M1a, M1b, and M1c. Null (historical) survival estimates for **S1404** are based on **S0008** data. We note that compared to **S0008**, **S1404** will also include M1a, M1b, and M1c patients. In **E1609** 6% of patients were Stage M1a and 2% were M1b. We expect approximately 1% of randomized patients to be Stage M1c. We expect less than 10% of randomized patients in **S1404** to be Stage M1, and because of modest differences in expected survival we have used **S0008** survival patterns as a historical reference for this trial.

11.7 Analyses of other objectives

a. **Estimation of OS and RFS in PD-L1 negative subgroup:** Cox regression models will be used to estimate hazard ratios and calculate confidence intervals to compare treatment arms in the PD-L1 negative subgroup. In addition Cox regression models for OS and RFS will be used to estimate interaction terms between PD-L1 status and treatment arm.

b. **Analysis of toxicity:** On the MK-3475 (pembrolizumab) arm, six hundred and twenty eligible patients will be sufficient to estimate toxicity rates within ± 4% (95% confidence interval). Any toxicity occurring with at least a 0.8% probability is likely to be observed at least once (99% probability). Assuming that on the Control Arm 310 patients receive HD-IFN and 310 patients receive ipilimumab, this will be sufficient to estimate toxicity rates for these regimens to within ± 6% (95% confidence interval). Under this assumption any toxicity occurring on a particular control arm regimen with at least a 1% probability is likely to be observed at least once (96% probability).

c. **Analysis of post-relapse therapy:** Data on therapy after relapse will be collected for three years after relapse (or until 10 years after registration maximum). Therapies will be categorized into one of two categories: systemic or local. Specific therapies after relapse will be tabulated and summarized. Therapy after relapse will be analyzed as a time-dependent variable in Cox regression analyses for the endpoint of OS after relapse.

d. **Analysis of BRAF mutation data:** Prestudy BRAF mutation status on patients will be collected. BRAF mutation status will be analyzed as a covariate in Cox regression analyses and exponential-logistic cure regression models. *(26)* In addition, the interaction between BRAF mutation status and treatment arm will be analyzed in Cox regression models and in exponential-logistic cure regression model.

e. **Analysis of long-term survivors/cured patients:** Exponential-logistic cure regression models will be used to examine the association between known prognostic factors (including stage) and long-term survivor/cure status, and survival for patients who are not long-term survivors/cured. *(27)*

f. **Other analyses of OS and RFS:** A restricted mean survival time analysis will be done as a supportive analysis.

g. **T-cell Receptor Beta Chain sequencing:** The statistical plan for the T-cell receptor beta chain sequencing objectives is included in Appendix 18.8

11.8 Quality of life (QOL data)

This pre-specified statistical analysis plan (SAP) is intended to describe the strategy, rationale, and statistical techniques that will be used to assess the patient-reported outcomes (PROs) data gathered in the **S1404** trial.

a. **Objectives:** The key objective of the PRO analysis is to evaluate overall health-related quality of life (QOL) for patients with melanoma treated with physician/patient choice of either high-dose interferon alfa-2b or ipilimumab and MK-3475 (pembrolizumab).

b. **Instruments:** The FACT-BRM measures quality of life domains important to patients treated with biological response modifiers (BRMs). The domains are represented by six sets of response items, four of which comprise the FACT-General (FACT-G) subscales including Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being; and two additional subscales specific to the FACT-BRM instrument, the BRM Physical Subscale, and the BRM Cognitive/Emotional subscale. Each subscale is derived from 6-7 items on the questionnaire, with responses given on a five-point Likert-type scale ranging from 0 to 4 (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, and 4 = very much). The six subscales are also combined to form a single FACT-BRM total score. In addition, the FACT-BRM Trial Outcome Index (TOI) is derived from a subset of four of the subscales (Physical Well-Being, Functional Well-Being, BRM Physical, and BRM Cognitive/Emotional). Each FACT BRM subscale, the FACT BRM total score, and the FACT BRM TOI will all be analyzed. Scoring of the scales will follow the standard published metrics. For the FACT BRM, the higher the score, the better the quality of life.

The FACIT-D comprises the FACT-G and a symptom-specific subscale that measures quality of life specific to diarrhea. Like the FACT-BRM, the FACIT-D subscales is scored on a 5-point Likert-type scale ranging from 0 to 4, with higher scores indicating better quality of life. The FACIT-D subscales (distinct from the FACT-BRM subscales) and FACT-D total score will all be analyzed.

The EQ-5D-3L has two systems. The descriptive system measures three functional domains (mobility, self-care, usual activities) and two symptom domains (pain/discomfort and anxiety/depression). Each domain has three levels (no

problems, some problems, extreme problems). A visual analog system (VAS) records self-rated global health between “best imaginable health state” and “worst imaginable health state” and can be used as a quantitative measure of health outcome as judged by individual patients. The three functional and two symptom domains can be summarized categorically, and the VAS global health rating can be summarized quantitatively. The measures can then be combined into a single summary index. Utility scoring will follow the US and European algorithms.

c. **Endpoints**: PRO endpoints are measured by the FACT-BRM, FACIT-D, and EQ-5D-3L. These endpoints are affected by both disease progression and treatment tolerability.

The Trial Outcome Index (TOI) from FACT-BRM is the primary PRO endpoint for this study. The TOI combines four subscales: Physical Well-Being, Functional Well-Being, the BRM Physical Subscale, and the BRM Cognitive/Emotional Subscale. The primary TOI endpoint will be the TOI score at Cycle 3.

Secondary PRO endpoints from the FACT-BRM are the six individual FACT-BRM subscales and the FACT-BRM total score. Secondary PRO endpoints from the FACIT-D are symptom-specific subscale and specific items and the FACIT-D total score. Secondary PRO endpoints from the EQ-5D-3L include the summary index as well as each of the six individual EQ-5D-3L domains.

For PRO endpoints, the baseline score will be accounted for as a covariate in multivariable regression models. The change between the baseline and Cycle 3 scores will also be examined as a sensitivity analysis. In addition, the changes over all time points in the TOI endpoint as well as all of the secondary PRO endpoints will be analyzed using longitudinal data analytic approaches described below.

d. Schedule for PRO data collection:

Table 11.8.1 PRO Data Collection Schedule

Treatment Cycle	Baseline	Cycle 1	Cycle 3	Cycle 5	Cycle 7	Cycle 9	Follow-up	Recurrence
Study Time*	Before first day of treatment	4 weeks	13 weeks	25 weeks	37 weeks	49 weeks	24 and 48 weeks after protocol treatment discon-tinuation	See below (a, b)

* assuming no treatment delays
a) Once patient has disease recurrence, no subsequent PRO data will be collected.
b) If recurrence occurs more than 48 weeks after protocol discontinuation, then PRO data collection at the time of recurrence is not required.

With the exception of the recurrence time point, at each time point the FACT-BRM, FACIT-D, and EQ-5D-3L will be administered prior to all other study procedures. At the time of recurrence, the FACT-BRM, FACIT-D, and EQ-5D-3L will be administered after the patient sees the treating investigator. At each time point, if

a patient does not complete one or both PRO instruments, the site staff will record the reason on the PRO Coversheet from predefined choices.

e. **Analysis Populations:** The primary analysis population will be based on an intent-to-treat (ITT) approach, incorporating data from all eligible randomized patients. To be evaluable, patients must have completed both the baseline and the Cycle 3 assessments.

f. PRO instrument completion and compliance:

The completion rate for the primary endpoint is defined as the number of patients who complete a sufficient number of items to score the FACT-BRM TOI according to the missing data rules for the instrument, divided by the number of eligible randomized patients at each time point. The completion rate is expected to decrease over time because some patients will not complete all protocol therapy and some patients will have disease recurrence or die.

The compliance rate for the primary endpoint is defined as the number of patients who complete a sufficient number of items to score the FACT BRM TOI according to the missing data rules for the instrument, divided by the number of patients who were expected to complete the PRO instrument. The denominator of the compliance rate will not include patients who have died, recurred, or went off protocol therapy prior to that time point, or could not complete an instrument due to language translation not being available.

The completion and compliance rates of the other subscales and total scores will be defined in a similar fashion. Completion and compliance rates by instrument, visit, and treatment arm will be described.

For any subscales, trial outcome indexes, or total scores, we also define the minimum completion rate as the number of patients who complete at least one item included in the subscale, TOI, or total score, respectively, in order to assess the extent to which sites successfully administer a form to patients, even if only minimal information on the form is collected and the form cannot be scored according to the missing data rules for the instrument.

The primary reason for not completing any of the PRO assessments for any assessment time point will be collected on the PRO Coversheet, to be filled out by the personnel administering PROs at each site. The reasons will be summarized in table format.

g. **PRO analyses:** Consistent with the design and to aid in clinical interpretation, the analysis of the primary endpoint of the Cycle 3 FACT BRM TOI will be conducted using multivariable linear regression analysis, adjusting for randomization stratification factors and the baseline FACT BRM TOI score as covariates. A window of +/- 2 weeks around the completion of cycle 3 will be allowed for inclusion of the FACT-BRM TOI in the final analysis. We will also conduct longitudinal modeling of the outcome measures over time, to assess whether the longitudinal results are consistent with the primary analysis. Power for the longitudinal analysis will be greater since the addition of all available FACT BRM TOI scores over time will provide more information. For longitudinal modeling, linear mixed models will be used, with random effects for intercepts and slopes and using both compound symmetric and unstructured correlation models. Covariates for longitudinal modeling will include treatment arm, assessment time, their interaction, the baseline score, as well as the randomization stratification variables and the baseline FACT BRM TOI score. Additionally, a treatment by time-squared interaction will be evaluated. These models are nested and so log-likelihood

values will be compared using a Chi-squared tests with appropriate degrees of freedom to assess which model provides a best fit to the data. When summarizing results from models with the best fit, coefficients for the intercept, treatment arm, time point, and baseline score will be tabulated, along with 95% confidence intervals and nominal p-values. We will also plot scale and subscale means for groups of patients based on the number of time points that instruments were completed.

The potential for differential dropout by arm will be mitigated by reminder notifications to site investigators to encourage proper assessment and submission of forms at every required time point for all patients. Dropout patterns will be monitored on an ongoing basis. Nonetheless the potential for non-random dropout exists. The linear mixed models described above assume that data is missing at random (MAR). The MAR assumption implies that the probability of missingness depends only on the observed data, which can be accounted for through covariate adjustment in the models. However the potential exists that missing data are a function of other, unobserved variables. For instance, in this study missingness may also depend on ill health, death, and disease recurrence, in a fashion that cannot be predicted by baseline factors. If the alternative hypothesis is correct and patients on the standard treatment arm are more likely to have worse PRO outcomes, they are also more likely not to report PRO outcomes due to worsening health or death. In this setting, differential dropout by arm will bias the results towards the null hypothesis of no difference between arms, in which case the observed result by arm is likely to be conservative, such that difference between the arms in favor of the experimental arm would, in truth, be even more favorable that what is observed. However such a pattern cannot be assumed.

Additional analyses will be performed to assess the MAR assumption. To evaluate potential cohort biases, baseline characteristics will be compared between evaluable (that is, those who complete both their baseline and cycle 3 FACT BRM TOI) and inevaluable patients. Also, cohort plots will be prepared to examine the extent to which missing data are informative (i.e., scores are higher (worse) for patients just before their data are missing for the subsequent assessment). If there is evidence of non-random dropout, pattern-mixture models will be utilized as a sensitivity analysis. *(28,29,30)* Pattern mixture models estimate PRO trajectories for different patterns of attrition. The pattern groups are defined by the last PRO assessment time points for patients. In this study a total of six patterns will be identified: 1) complete all PRO assessments; 2) die before end of PRO assessments; 3) disease recurrence before end of PRO assessments; 4) alive without disease recurrence before end of PRO assessments but do not complete 9 cycles of protocol therapy; 5) alive, recurrence-free, and complete 9 cycles of protocol therapy but stopped completing PRO assessments before Cycle 3; 6) alive, recurrence-free, and complete 9 cycles of protocol therapy but stopped completing PRO assessments after Cycle 3. If some patterns have small numbers of patients, patterns may be collapsed for analysis.

The pattern mixture models will be fit by estimating a linear mixed model within the six pattern groups defined above, estimating the proportion of patients in each pattern group, and then averaging out the pattern-specific PRO endpoint trajectories using weights equal to the proportions. The variance will be calculated using the delta-method.

Observed mean scores for the quantitative endpoints will be plotted across assessment time points with fitted results from the linear mixed model analysis overlaid.

Descriptive statistics, multivariable linear regression analyses, and longitudinal modeling analyses will also be conducted for the FACIT-D and EQ-5D instruments and all subscale scores as secondary analyses. As additional secondary analyses, the same analyses will be done in the subgroups of patients identified by choice of control arm before randomization (used a randomization stratification factor, choice between high-dose interferon alfa-2b or ipilimumab).

Interpretation of Longitudinal Model Results: For models in which the simple linear model (no interaction) provides the best fit, the fitted models will have parallel trajectories for the treatment arms, representing a treatment effect that is constant over time. Significant non-zero treatment arm coefficients will indicate that one arm having higher endpoint values over time compared to the other arm. Significant non-zero time coefficients will indicate upward or downward endpoint changes over time (depending on the sign of the coefficient).

Models with an interaction will indicate a differential treatment effect on PRO endpoints over time, so the trajectories will not be parallel. If a square interaction is significant, the differential treatment effect will be modeled as quadratic (i.e., non-linear or curved). With significant interactions, the main effect coefficients for treatment arm and time cannot be interpreted independently but must be considered in combination with the coefficients for the interaction terms.

h. **Power and sample size calculations:** The primary hypothesis for sample size calculation is that pembrolizumab is superior to IFN with respect to the cycle 3 TOI score. PRO will be collected and data analyzed on all patients on the trial, not a subset of patients.

We do not have preliminary PRO data on the FACT-BRM TOI with pembrolizumab or IFN in this particular patient population (the trial has wider eligibility than prior trials). The follow-up standard deviation for the FACT-BRM TOI was 20 in a set of nearly 200 patients receiving IFN for renal cell carcinoma. *(31)* This is consistent with data from Trask et al. (2004) in a small series of patients receiving IFN for high risk melanoma. *(32)* Thus we assume a cycle 3 standard deviation of the FACT BRM TOI of 20, common between both arms. Using Yost (2005), the estimated minimally important difference for the FACT BRM TOI is 5-8 points. If the standard deviation is 20 points, this difference is consistent with clinically meaningful effect sizes of 0.25-0.33, using distribution-based methods and anchor-based methods, respectively, identified by Yost et al. *(33)* Given the sample size is large, power is based on identifying a small effect size of 0.25. It is assumed, conservatively, that with a median OS for non-long term survivors of 3.96 and a median RFS for non-long term survivors of 1.44 years, then by cycle 3, 5% of patients will drop out due to death, 12% due to worsening disease, and 3% for other reasons, producing an overall dropout rate of 20% at cycle 3. Further, an additional 10% patients are assumed to be non-adherent. Patients who drop out or are non-adherent are considered inevaluable. Note that in power calculations, the 10% non-adherence rate reduces the nominal effect size by 10% (to 0.225), while the 20% dropout rate inflates the estimated sample size by a factor of 1/(1-0.2) or 25%. Using a 2-sided alpha=0.05 test and a two-arm normal design, and accounting for dropout and non-adherence as specified, there will be 94% power to detect the effect size difference of 0.25 between the two arms.

Power will be worse with a smaller sample size. For instance, a sample size of 260 patients (130 per arm) will provide 83% power for a notably higher standardized difference (difference between means / standard deviation) of 0.4, using the same parameters as specified above. This effect size corresponds to a minimally important difference of 8 points in the FACT BRM TOI at cycle 3 if the standard deviation is 20%, the upper limit of the range of the minimally important difference as indicated in Yost et al.

11.9 Data and Safety Monitoring

A Data and Safety Monitoring Committee will oversee the conduct of this study. The Committee consists of four members from outside of the SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

In addition to the above DSMC review, toxicity and accrual monitoring are done routinely by the Study Chair, study Statistician, and the Disease Committee Chair. Endpoint monitoring is done by the study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer, and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

a. STEP 1 Registration - Screening

Patients must meet the eligibility criteria in the Step 1 Registration criteria in Section 5.0. Patients must be registered within 7 business days prior to submission of specimens for PD-L1 testing. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

b. STEP 2 Registration – Randomization

Patients who meet the eligibility criteria as stated in the Step 2 Registration criteria in Section 5.0 will be registered to STEP 2 – Randomization. Patients must register within 7 working days after receiving the e-mail notification confirming that their tissue sample was adequate for PD-L1 testing.

Patients must be randomized prior to the initiation of treatment (no more than 5 working days prior to the planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an “active” investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at http://ctep.cancer.gov/investigatorResources/investigator_registration.htm
For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at pmbregpend@ctep.nci.nih.gov

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at http://ctep.cancer.gov/branches/pmb/associate_registration.htm
For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at ctepreghelp@ctep.nci.nih.gov

c. CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including

but not limited to: an active Federal Wide Assurance (FWA) number, an active roster affiliation with the Lead Network or a participating organization, a valid IRB approval, and compliance with all protocol specific requirements.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Downloading Site Registration Documents:

Site registration forms may be downloaded from the **S1404** protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU RSS.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the SWOG link to expand, then select trial protocol **S1404**
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements for S1404 Site Registration:

- CTSU Transmittal Sheet (optional)
- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

  NOTE: Per NCI policy all institutions that participate on protocols with a radiation therapy component must participate in the Image and Radiation Oncology Core (IROC) monitoring program. If this form has been previously submitted to CTSU it does not need to be resubmitted unless updates have occurred at the RT facility

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Text for Patient Enrollment
Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

d. **Text for Data Submission / Data Reporting**

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):
- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org, from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
- The study site is listed as "approved" in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (User ID and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. Questions should be directed to the CTEP Associate Registration Help Desk by e-mail at ctepreghelp@ctep.nci.nih.gov.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

  1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

  2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible

Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM

account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

- If prompted, select the 'CTEP-IAM IdP' link.
- Enter your valid and active CTEP-IAM User ID and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (https://swog.org) and logon using your CTEP ID and password. After you have logged on, click on the "Member Resources" tab, and then from this page click on "CRA Workbench", to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For non-SWOG members, please visit https://crawb.crab.org/TXWB/Logon.aspx.

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION TO STEP 1:

Submit the following:

S1404 Eligibility Checklist, confirmed a patient's eligibility (NOTE: This must be uploaded into Rave® via Source Documentation Baseline Form)

S1404 Onstudy Form

S1404 Medical History Form

Submit slides for PD-L1 evaluation as specified in Section 15.2.

*__S1404__ Local Pathology Review Form (Section 18.4)

*Radiology reports from all scans performed to assess disease at baseline

*Pathology reports documenting histologic confirmation and complete resection of all disease.

*NOTE: Upload reports via the Source Documentation: Baseline form in Rave®.

b. IF PATIENT WILL NOT BE REGISTERED TO STEP 2 (RANDOMIZATION), SUBMIT WITHIN 7 DAYS OF DECISION NOT TO RANDOMIZE PATIENT:

S1404 Pre-Randomization Off Study Form

NOTE: For patients who do not register to Step 2 (Randomization), no additional follow-up is required other than the items listed in Sections 14.4a and 14.4b.

c. WITHIN 28 DAYS OF REGISTRATION TO STEP 2 (RANDOMIZATION):

If patient consents to banking, submit specimens as specified in Section 15.3.

d. WITHIN 14 DAYS OF REGISTRATION TO STEP 2 (RANDOMIZATION):

Submit **S1404** Baseline Laboratory Values Form

Submit to IROC via TRIAD for Image Banking. Images from scans performed to assess disease as specified in Section 15.6.

e. PATIENTS RANDOMIZED TO ARM 2, MK-3475 (PEMBROLIZUMAB), THEREBY PARTICPATING IN PHARMACOKINETIC (PK) AND ANTI-DRUG ANTIBODY (ADA) TESTING:

Submit specimens as specified in Section 15.4.

f. WITHIN 14 DAYS AFTER EACH CYCLE OF TREATMENT (CYCLE 1 AND CYCLE 2 = 6 WEEKS EACH; ALL SUBSEQUENT CYCLES = 12 WEEKS):

Submit the following:

S1404 Treatment Form

S1404 Adverse Event Form

S1404 Laboratory Values Form

S1404 Concomitant Medications Form

g. AFTER RANDOMIZATION, WITHIN 14 DAYS AFTER EACH DISEASE ASSESSMENT, INCLUDING ANNUAL BRAIN IMAGING (SEE STUDY CALENDAR FOR SCHEDULE) UNTIL RECURRENCE (AS DEFINED IN SECTION 10.0) OR 5 YEARS AFTER RANDOMIZATION (WHICHEVER OCCURS FIRST):

Submit the following:

S1404 Disease Assessment Form

Radiology reports from all scans performed to assess disease (uploaded via the Source Documentation: Follow-Up Form in Rave®)

Submit to IROC via TRIAD for image banking. Images from scans performed to assess disease as specified in Section 15.6.

If patient is no longer on protocol treatment, also submit the Adjuvant Melanoma Follow-up Form

h. AFTER RANDOMIZATION, WITHIN 14 DAYS AFTER EVERY QOL ASSESSMENT (SEE STUDY CALENDAR FOR SCHEDULE):

Submit the following:

S1404 Cover Sheet for Patient-Completed Questionnaires

S1404 FACT-BRM - FACIT-D

S1404 EQ-5D-3L

For the first two patients enrolled at each site, in addition, upload copies of the patient completed paper forms via Source Documentation: Other form in Rave®. NOTE: Some sites, identified by Risk-Based Monitoring, may be required to submit for additional patients.

i. WITHIN 7 DAYS OF DISCONTINUATION OF PROTOCOL TREATMENT:

Submit the following:

Off Treatment Notice documenting reasons for off treatment

S1404 Treatment Form

S1404 Adverse Event Form

S1404 Laboratory Values Form

S1404 Concomitant Medications Form

j. ONCE OFF ALL PROTOCOL TREATMENT, SUBMIT EVERY 6 MONTHS FOR THE FIRST 2 YEARS, THEN YEARLY THROUGH YEAR 10:

Adjuvant Melanoma Follow-Up Form

Late Effects Form (if prior to treatment for progression or relapse or a second primary, and prior to non-protocol treatment, the patient experiences any severe [Grade ≥ 3] long term toxicity that has not been previously reported).

k. WITHIN 14 DAYS OF PROGRESSION OR RELAPSE:

Submit the following:

S1404 Disease assessment form

S1404 Cover Sheet for Patient-Completed Questionnaires

S1404 FACT-BRM-FACIT-D

S1404 EQ-5D-3L

Site(s) of progression/relapse Form

Radiology reports from all scans performed to assess disease (uploaded via the Source Documentation: Follow-Up Form in Rave®).

Submit to IROC via TRIAD for image banking. Images from scans performed to assess disease as specified in Section 15.6.

If patient is no longer on protocol treatment, also submit the Adjuvant Melanoma Follow-Up Form.

l. WITHIN 28 DAYS OF KNOWLEDGE OF DEATH:

Notice of Death and **all of the items listed in** Section 14.4e **or** 14.4f (if the patient was still on protocol treatment) or the Adjuvant Melanoma Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 SWOG Specimen Tracking System (STS)

a. All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on the online system via the CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (https://swog.org) and logon using your CTEP ID and password. After you have logged on, click on the "Member Resources" tab, and then from this page click on "CRA Workbench". . Non- SWOG users may log into SpecTrack using their CTSU User ID and password on the SpecTrack login page located at https://crawb.crab.org/SpecTrack/Logon.aspx (select the option "SWOG – SWOG – CTSU"). SpecTrack start-up instructions (both written and demo) are available after signing in to SpecTrack. For non-SWOG members, please visit https://crawb.crab.org/TXWB/Logon.aspx.

A copy of the Shipment Packing List produced by the online Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (http://dnet.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

In the online specimen tracking system, the appropriate SWOG laboratory for submission of tissue and blood samples for SWOG Biospecimen Bank Submission is identified as follows:

Lab #201:	SWOG Specimen Biospecimen Bank Solid Tissue, Myeloma, and Lymphoma Division
Phone:	614-722-2865
FAX:	614-722-2897
E-mail:	bpcbank@nationwidechildrens.org

b. Federal guidelines for the shipment of blood products:

1. The tube must be wrapped in an absorbent material.

2. The tube must then be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and tube in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. Mark the box "Biohazard".

15.2 Submission of slides for PD-L1 Evaluation

At time of tissue selection, quality control measures of tumor tissue should be performed to ensure sufficient viable tumor tissue, which should contain ≥ 100 viable tumor cells. Tumor material must be reviewed by a local pathologist to ensure sufficient tumor cells are present in the sample. This must be documented by having the pathologist sign the **S1404** Local Pathology Review form (see Section 18.4). If slides do not contain a sufficient number of cells for analysis the site will be asked to resubmit and/or the patient may be deemed ineligible.

Specimens for PD-L1 evaluation (submitted to the designated central laboratory, Lab #218) (**required** for patient):

a. Five unstained slides from the primary, lymph node, or metastatic site, and the Pathology Report must be submitted at the following times:

- Within 7 days after Registration to Step 1.

b. Specimen submissions must be entered and tracked using the SWOG **Online Specimen Tracking System (SpecTrack). See Section 15.1 for instructions.**

The following will be provided to sites by the Central Laboratory:

- Plastic slide holders (each can hold up to 5 slides)
- Positively charged microscope slides
  - Please use only positively charged slides provided by CENTRAL LAB which are standard sized positively charged microscope slides (75 mm x 25 mm x 1 mm).
- Bubble wrap pouch
- CENTRAL LAB Labels (NOTE: Labels may use an alternate study ID number: "MK3475-053". This is how the lab is identifying **S1404**).
- Amber Bag
- Biohazard Bag (also labeled as Specimen Transport Bag)
- Shipping container
- Gel packs

NOTE: Expiry dates will be clearly marked on the label that is placed on the outside of the collection kit box. The expiry date is always reflective of the tube that expires the earliest. The expiry date displayed on the label is good to the last day of the month displayed unless otherwise noted.

c. Kit Ordering

1. To order initial specimen kits log onto the SWOG Specimen Tracking System (https://crawb.crab.org/SpecTrack/Logon.aspx) and click on the link "Specimen kits for S1404" at the bottom of the page. When placing this initial order, sites must provide laboratory contact information. For SWOG institutions the fields will be pre-populated based on the current data in the SWOG roster. Please note, the initial order will contain four PD-L1 kits and three PK/ADA kits and may take up to 15 days to be filled by PPD. Once PPD CL receives site information, a site username will be assigned and faxed to the site on the fax verification form. This username will be used for sites to access http://preclaruslabdata.ppdi.com to reorder supplies.

If your site does not receive the fax verification form within 3 days of registration, please call SWOG Data Operations at 206/652-2267.

2. For subsequent orders only, sites may reorder supplies at http://preclaruslabdata.ppdi.com. After reordering, a confirmation email will be sent automatically to the site email address.

d. Sample Preparation and Collection Procedures

1. A fine needle aspirate, frozen sample, plastic embedded sample, cell block, bone, bone marrow, clot, or cytologic specimen will **not** be acceptable for IHC analysis.

2. Obtain a plastic slide holder container from kit. Each slide holder can hold a maximum of 5 slides (placing additional slides in the holder above 5 will result in slide breakage during shipping).

3. Prepare freshly cut serial sections at 4 micron thickness onto the provided positively charged microscope slides (4-5 micron thickness is acceptable) as close to the day of shipping as possible (no more than 20 days). Other non-standard sized slides cannot be accepted for testing.

4. Standard sized positively charged slides are required for samples; slide measurements are 75 mm x 25 mm x 1 mm. Other sized slides cannot be accommodated.

5. DO NOT BAKE SLIDES – only air dry at room temperature12-24 hours prior to shipment.

6. Five slides are required to be submitted.

7. **Label each slide with SWOG Patient ID Number and serially in the order they were sectioned with indelible ink**.

8. Place slides in slots of the plastic slide holder in order of sectioning, with a maximum of 5 slides per plastic slide holder. Place the provided label on one side of the plastic slide holder to allow the barcode to be scanned. Do not wrap the label.

9. Once plastic slide holder is closed, tape shut with some standard masking or general purpose tape prior to shipment.

10. Place sample within amber bag to ensure sample will be in the dark.

11. Store in the dark at 2-8 ºC until ready to ship.

12. Bubble wrap the slide holders to help prevent breakage.

13. Place bubble wrapped slide holders in the biohazard bag (Specimen Transport Bag).

14. If needed, secure the slide box in the shipping container with packing paper.

15. **Using the appropriate provided shipper from kits, ship cold (2-8ºC) by using the frozen gel packs/wraps.**

16. In the shipping container along with the Specimen Transport Bag and frozen gel packs/wraps, place copies of 1) the Pathology Report, and 2) the SWOG Specimen Tracking System Packing List.

17. **A minimum of 5 slides need to be shipped for PD-L1 testing and slides need to be shipped within 20 days of cutting the slides**.

18. PD-L1 testing may need to be repeated if first set of slides were not adequate for testing. A minimum of 5 slides would need to be shipped for PD-L1 re-testing.

e. Shipping instructions

When submitting tissue to LabCorp for PD-L1 testing, be prepared to provide answers to the following questions in the SWOG specimen Tracking System:

- Tissue collection method (surgical resection, biopsy)
- Anatomic location of tumor tissue collection (Liver, Lung, Lymph node, Oral, Skin/subcutaneous tissue, Other)
- Month and year of patient's birth
- Date unstained slides were cut
- Method used to prepare paraffin embedded tissue (unknown, 10% neutral buffered formalin, Other)
- Time from tissue excision to immersion in fixative (unknown, >= 60 min, >30 - < 60 min, <= 30 min)

Shipping:

- Airway bills will be provided by PPD for shipping directly to **LabCorp**
- Shipments to LabCorp should be on **Mondays through Thursdays.**
- Forms to be included in shipping:
  - A copy of SWOG Specimen Tracking System Packing List
  - A copy of the pathology report
- FFPE sectioned slides should be shipped refrigerated (2ºC-8ºC) and in the dark (amber bag to be used). GEL packs used must be FROZEN.

- Ship the container overnight Monday through Thursday, along with a copy of SWOG Specimen Tracking System Packing List, the same day to the address below:

  Lab #218: LabCorp Clinical Trials

  Note: LabCorp identifies **S1404** using an alternate study ID number: "MK3475-053".

- Refer to PPD Laboratory Manual for additional shipping instructions.

f. Within 10 business days after specimen submission, institutions will be notified via e-mail whether or not the tissue specimen was adequate for PD-L1 testing. If the result comes back as "adequate", register the patient to Step 2 "Randomization" with 7 working days of receiving the email. If the result comes back as "inadequate", a second tissue specimen may be submitted if sufficient tissue remains. NOTE: The email will not include the patient's PD-L1 status.

If there are any questions, please contact the SWOG Data Operations Center at 206/652-2267.

15.3 Specimens for Banking

Specimens for banking (submitted to the SWOG Specimen Biospecimen Bank – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) (**optional** for patient):

a. Specimen collection kits are not being provided for this submission; sites will use institutional supplies. Please do not use tubes provided by PPD. **Do NOT submit specimens for banking to LabCorp.**

b. With patient's consent, the following specimens must be submitted at the following times:

1. Entire block of paraffin embedded tissue (from primary, lymph node, and metastasis if present) or 10 unstained slides may be submitted if the institution cannot release a pathology paraffin embedded block, **and one H&E (Hematoxylin and Eosin) stained slide** at the following times:
   - Baseline
   - Relapse

   Submit tissue according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect three tubes of whole blood in 10 mL red/black marble top (SST) vacutainer tubes with no anticoagulant. Process whole blood to **serum** according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect at the following times:
   - Baseline (prior to the start of study treatment)
   - Start of Cycle 3 (Week 13, if there are no dose delays)
   - Start of Cycle 4 (Week 25 if there are no dose delays)
   - When patient is removed from protocol therapy for any reason
   - Relapse

   Collect three tubes of whole blood in 10 mL pink/lavender top vacutainer tubes with EDTA. Process whole blood to **plasma and buffy coat** according to guidelines provided by SWOG Biospecimen Bank: https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures.

   Collect at the following times:
   - Baseline (prior to the start of study treatment)
   - Start of Cycle 3 (Week 13 if there are no dose delays)
   - Start of Cycle 4 (Week 25 if there are no dose delays)
   - When patient is removed from protocol therapy for any reason
   - Relapse

c. If a patient has a treatment delay or interruption due to an adverse event, the blood sample for banking should be drawn even if the patient did not receive study treatment. The goal is to collect the sample as close to the week designated by the protocol.

d. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://www.swog.org/clinical-trials/biospecimen-resources/biospecimen-processing-and-submission-procedures).

15.4 Pharmacokinetic (PK) and Anti Drug Antibody (ADA) testing

NOTE: AS OF 12/11/2017 PK/ADA SAMPLING HAS BEEN DISCONTINUED.

a. Requirements

All patients randomized to the MK-3475 (pembrolizumab arm) will have blood draws for PK and ADA analysis.

b. PK/ADA Sampling for the trial

PK/ADA sampling may be discontinued upon confirmation that results are consistent with the current PK/ADA profile of MK-3475 (pembrolizumab) as determined by the Merck Pharmacokinetics and Pharmacodynamics Drug Metabolism Quantitative Pharmacology and Pharmacometrics group.

c. Specimen Tracking

Specimen submissions must be entered and tracked using the SWOG Online Specimen Tracking System (SpecTrack). See Section 15.1 for instructions.

d. Kit ordering

1. To order initial specimen kits log onto the SWOG Specimen Tracking System (https://crawb.crab.org/SpecTrack/Logon.aspx) and click on the link "Specimen kits for **S1404**" at the bottom of the page. When placing this initial order, sites must provide laboratory contact information. For SWOG institutions the fields will be pre-populated based on the current data in the SWOG roster. Please note, the initial order will contain three (3) PK/ADA kits and four (4) PD-L1 kits and may take up to 15 days to be filled by PPD. Once PPD receives site information, a site username will be assigned and faxed to the site on the fax verification form. This username will be used for sites to access the PPD portal to reorder supplies: http://preclaruslabdata.ppdi.com.

   If your site does not receive the fax verification form within 3 days or registration, please call SWOG Data Operations at 206/652-2267.

2. For subsequent orders only, sites may reorder supplies at http://preclaruslabdata.ppdi.com. After placing the order, a confirmation email will be sent automatically to the site email address.

e. Frequency

PK and ADA samples will be collected before first infusion Cycle 1 (Week 1), before second infusion Cycle 1 (Week 4), before second infusion Cycle 2 (Week 10), before third infusion Cycle 3 (Week 19), before first infusion Cycle 4 (Week 25), before infusion Cycle 6 (Week 49) and 30 days after discontinuation of study drug (as long as patient has not started new anti-cancer therapy). Samples should be drawn within 24 hours before infusion of MK-3475 (pembrolizumab).

f. Sample collection and preparation procedures

1. SST and corning tubes will be pre-labeled with study/protocol number. Note that the study number on the pre-printed labels appear as MK3475-053 instead of **S1404**. That is how the lab is identifying the study. Site should write the 6-digit SWOG Patient ID and collection date/time on the label and the PPD Requisition Form. Please ensure to mark the corresponding visit name on the PPD Requisition Form.

   Each pre-labeled tube is linked to a pre-labeled Requisition Form in each kit.

2. At each time point, collect 3 mL whole blood PK sample in one properly labeled 3.5 mL SST tube and collect 6 mL whole blood ADA sample into one properly labeled 8.5 mL SST tube.

   Record the time and cycle number (or week since off protocol therapy) each sample is collected as you will need to enter these data into the SWOG Specimen Tracking System. Record the date and time of administration of MK-3475 (pembrolizumab) as you will need to enter these data on the **S1404** Treatment Form (see Section 14.4d) and on audit the times will need to confirm that the PK/ADA samples were drawn before infusion of MK-3475 (pembrolizumab). NOTE: If a sample needs to be drawn post-dose in error, the sample collection must be from the opposite arm to that used for study drug infusion. If drug was administered via a central venous catheter, the sample collection should be from a different site.

3. Invert each tube 5 times and let stand for 30 minutes (but no longer than 60 minutes). The blood samples should remain at room temperature prior to centrifugation.

4. Centrifuge each sample 1100-1300 g for 15 minutes (speed/time may vary according to make and model of centrifuge).

5. Immediately transfer the PK serum evenly to two labeled 2mL Corning cryovials (PK Aliquot 1 and 2). Transfer the ADA serum evenly to three labeled 2 mL Corning cryovials (ADA Aliquot 1, 2, and 3) (each containing approximately 1 mL of serum). Serum samples must be frozen within 30 min of separation after the centrifuge at -20ºC for storage up to 1 month) and maintained in the frozen state until assayed.

g. Shipping instructions

1. Batch ship monthly to PPD Central Lab
   - Place PK Aliquot 1 and ADA Aliquot 1 in one box.
   - Place PK Aliquot 2 and ADA Aliquot 2, 3 in a separate box.

   NOTE: Samples from multiple patients may be sent in the same box.

2. Complete the PPD Requisition Form (2-part form) that is included in each kit. Include the original form (white form) in the sample shipment box and keep the copy (yellow form) on site for your records. The visit and patient information on the Requisition form is critical to accession of samples. Incomplete or missing requisition forms will delay testing and put the site lab report on hold. Refer to PPD Laboratory Manual for additional shipping

instructions and PPD requisition forms. Instructions for filling out the PPD Requisition Form are also provided in Appendix 18.7.

3. All shipments should be made in freezer boxes containing at least 20 kg DRY ICE, and labeled as HUMAN SAMPLES: NONINFECTIOUS. Samples should not be shipped on a holiday. It is recommended to send batched dry ice shipments monthly on Monday through Wednesday to ensure arrival before the weekend. PK and ADA samples should be shipped frozen on dry ice (-20°C):

   Lab #219: PPD Central Lab for PK and Anti-pembrolizumab Antibodies

15.5 Quality of life assessments: Instructions for administration

a. Administration of questionnaires

1. All questionnaires should be completed prior to the visit with the physician. The time the questionnaire is completed and the time of the physician visit should be documented.

2. The first time the patient completes the questionnaires: Please read to the patient the instructions attached to each patient questionnaire. Explain the specific administration times for this protocol. Patients should be directed to report all symptoms and limitations whether or not they are related to the cancer or its treatment.

3. It is permissible to assist patients with completing the questionnaires being careful not to influence the patient's response. Note on the **S1404** Cover Sheet for Patient-Completed Questionnaires what assistance was required and indicate reason (e.g., elderly, too sick, etc.). Discourage family members from: 1) being present while the patient completes the questionnaire and/or 2) influencing patient responses to the questions.

4. It is very important to review the questionnaires after the patient has completed them to be sure all of the questions have been answered and that only one answer is marked. If the patient has marked more than one answer per question, ask the patient which answer reflects how she is feeling. If the patient has skipped a question, tell the patient that a question was not answered and ask if she would like to answer the question. Always give the patient the option to refuse. Indicate on the form by the question that the patient did not want to answer this question.

5. If a patient refuses or cannot complete the questionnaire for some reason, this must be documented on the **S1404** Cover Sheet for Patient Completed Questionnaires and submitted (see Section 14.4h).

6. Questionnaires must be completed by the patient at disease recurrence. On-treatment questionnaires may be submitted in place of recurrence questionnaires if:
   - The patient has already completed the on-treatment questionnaires, AND
   - The patient was aware of recurrence prior to completing the on-treatment questionnaires, AND
   - The patient did not receive any treatment after completing the on-treatment questionnaires.

Otherwise, separate recurrence questionnaires must be completed by the patient and submitted by the study site.

b. Additional quality control procedures:

When a patient is registered on **S1404**, a calendar should be made with dates of upcoming patient-completed questionnaires noted. A copy of this calendar can be given to the patient with the notation that the questionnaires should be completed. You may wish to photocopy the Study Calendar, Section 9.0, and include the patient's name and specific dates. A copy of this should be kept in the patient file.

If a patient refuses or cannot complete the patient questionnaires at one time **point, he or she should be asked to do so at the next scheduled assessment** time. Submit the **S1404** Cover Sheet for Patient-Completed Questionnaires documenting the reason why the questionnaires were not done.

Anyone involved in the collection of quality of life data in SWOG trials should review the training program available on the SWOG website accessible from three locations. On the SWOG Home Page (prior to member login), in the QUICKLINKS section on the bottom right corner of the page, there is a link to the Patient Reported Outcomes Training. The other two locations that the training is available are after SWOG member login on the CRA Workbench. The Training section and the New CRAs! section both contain access to the Patient Reported Outcomes (PROs) training module. The training program is a narrated set of slides designed to standardize the way quality of life data is collected from patients. Questions regarding the quality of life assessments can be addressed to the SWOG Data Operations Office (206/652-2267).

c. **S1404** Cover Sheet for Patient-Completed Questionnaires

For each time point that the FACT-BRM, EQ-5D-3L, and FACIT-D are administered, the nurse or CRA completes the **S1404** Cover Sheet for Patient-Completed Questionnaires. The Cover Sheet is submitted with the set of patient-completed forms at each scheduled assessment. The Cover Sheet is very important for tracking how and when the patient forms were completed. When a patient-completed form is not administered at a scheduled time point, it is important to know why the assessment did not occur; the form includes potential reasons for a patient not completing a form. See Section 14.4g for data submission guidelines.

d. QOL Questionnaire Administration Schedule

The FACT-BRM, EQ-5D-3L, and FACIT-D are scheduled to be administered at the following time points:

- Prior to Cycle 1
- Week 4 of the first cycle of treatment
- Prior to Cycles 3, 4, 5 and 6
- Week 24 after the date of last treatment
- Week 48 after the date of last treatment
- Relapse

Patients who relapse before 48 weeks after date of last treatment will complete a questionnaire at relapse. Patients do not need to complete any further questionnaires after relapse. Patients who go off protocol therapy before Week 49 (Cycle 6) without recurrence will complete the two post-treatment questionnaires (at 24 and 48 weeks from the date of last treatment).

15.6 Submission of Images for Banking (Required)

All participants will undergo PET-CT, CT or MRI imaging at baseline/pre-treatment and every 12 weeks until 2 years from randomization, then every 6 months until 5 years from randomization. Imaging exams must then be submitted to the Imaging and Radiation Oncology Core (IROC) at Ohio via TRIAD Imaging Submission procedures for quality control and image banking. Any imaging that is used for relapse detection must be submitted; this would include ultrasound imaging if that is used by your institution for nodal basin surveillance. In addition, if imaging done for other reasons detects a relapse (i.e., chest-x-ray done for pulmonary symptoms that subsequently detects a metastasis) it must also be submitted.

a. TRIAD Digital Image Submission

TRIAD is the secure electronic image upload application utilized for IROC Services of this trial. TRIAD de-identifies and validates the images as they are transferred.

TRIAD Access Requirements:

TRIAD will be the sole means of image transfer to the IROC Ohio. TRIAD should be installed prior to study participant enrollment to ensure prompt secure, electronic submission of imaging.

- Site staff who submit images through TRIAD will need to be registered with the Cancer Therapy Evaluation Program (CTEP) and have a valid and active CTEP-IAM account (see Section 13.2).
- To submit images, the site user must be on the site's affiliate rosters and be assigned the 'TRIAD site user' role on the CTSU roster. Users should contact the site's CTSU Administrator or Data Administrator to request assignment of the TRIAD site user role.

TRIAD Installations:

After a user receives a CTEP-IAM account with the proper user role, he/she will need to have the TRIAD application installed on his/her workstation to be able to submit images. TRIAD installation documentation can be found by following this link https://triadinstall.acr.org/triadclient/

Questions regarding image submissions, including TRIAD, should be directed to SWOG1404@irocohio.org or call IROC Ohio at 614-293-2929.

15.7 Mandatory Site Training

Prior to registering patients, at least one person involved with the study at each institution is required to view the **S1404** training module. To obtain credit for completing the training, after viewing the presentation sites must complete the short form at the bottom of the training page. The form is automatically forwarded to CTSU Regulatory Support System for processing and may take up to 3 days to be included in the system.

The training is available at:
https://www.swog.org/member-resources/training-forms/required-s1404-training

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between Merck (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines in addition to the provisions in the "Intellectual Property Option to Collaborator"
(http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award apply to the use of the Agent in this study:

a. Agent(s) may not be used outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

    1. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    2. NCI will provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

3. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

4. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

b. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

c. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

d. Any data provided to the Collaborator(s) for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

e. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

E-mail: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31. This study will have abbreviated CDUS monitoring.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol.

b. Reporting method

This study requires that expedited adverse events be reported using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1.

In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 301/897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agents as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in this study is MK-3475 (pembrolizumab). If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1:
Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] MK-3475 (Pembrolizumab).

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR or [Section 16.1f.]

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP IND**:

1. **Group-specific instructions**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the Operations Offices in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210-614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used this study are interferon alfa 2b and ipilimumab. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2. Expedited reporting requirements for adverse events experienced by patients on interferon alfa-2b or ipilimumab who have received the commercial drug(s) listed in Section 16.1g within 30 days of the last administration of the commercial agent(s).

ATTRIBUTION	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. *Reporting Secondary Malignancy, including AML/ALL/MDS*

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.
   For more information see:
   http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

2. Any supporting documentation should be submitted to CTEP per NCI guidelines for AE reporting located at:
   http://ctep.cancer.gov/protocoldevelopment/electronic_applications/aeguidelines.pdf.

   A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days by fax to 210-614-0006 or mail to the address below:

   - a copy of the pathology report confirming the AML/ALL /MDS diagnosis
   - (if available) a copy of the cytogenetics report

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. ***Reporting Pregnancy, Fetal Death, and Death Neonatal***

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

2. *Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.*

3. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

4. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder **characterized by cessation of life occurring during the first 28 days of life"** that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the* CTEP-AERS *interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

17.0 BIBLIOGRAPHY

1 Balch CM, Gershenwald JE, Soong SJ, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 27 (36): 6199-206, 2009.

2 Balch CM, Gershenwald JE, Soong SJ, et al. Final Version of 2009 AJCC Melanoma Staging and Classification. J Clin Oncol 27 (36): 6199-206, 2009.

3 Romano E, et al. Site and timing of first relapse in stage III melanoma patients: implications for follow-up guidelines. J Clin Oncol, 28(18): p. 3042-7, 2010.

4 Kirkwood JM, Strawderman MH, Ernstoff MS, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: The Eastern Cooperative Oncology Group Trial EST 1684. J Clin Oncol 14(1):p. 7–17, 1996.

5 Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev. Jun 18;6:CD008955, 2013.

6 Mocellin S, et al. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. J Natl Cancer Inst, 102(7): p. 493-501, 2010.

7 Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. Clin Cancer Res. Mar 1;10(5):1670-7, 2004.

8 Eggermont AM, Suciu S, Testori A, Santinami M, Kruit WH, Marsden J, Punt CJ, Salès F, Dummer R, Robert C, Schadendorf D, Patel PM, de Schaetzen G, Spatz A, Keilholz U. Long-term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. J Clin Oncol Nov 1;30 (31):3810-8, 2012.

9 Flaherty LE, Othus M, Atkins MB, Tuthill RJ, Thompson JA, Vetto JT, Haluska FG, Pappo AS, Sosman JA, Redman BG, Moon J, Ribas A, Kirkwood JM, Sondak VK. Southwest Oncology Group S0008: A Phase III Trial of High-Dose Interferon Alfa-2b Versus Cisplatin, Vinblastine, and Dacarbazine DTIC, Plus Interleukin-2 and Interferon in Patients With High-Risk Melanoma-An Intergroup Study of Cancer and Leukemia Group B, Children's Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. J Clin Oncol, Oct 20. Epub, 2014.

10 Eggermont AMM, Chiarion-Sileni V, Graf JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EDRTC 18071): a randomized double-blind, phase 3 trial. Lancet 16(5):522-530, 2015.

11 Eggermont AMM, Chiarion-Sileni V, Graf JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EDRTC 18071): a randomized double-blind, phase 3 trial. Lancet 16(5):522-530, 2015.

12 Mocellin S, Lens MB, Pasquali S, Pilati P, Chiarion Sileni V. Interferon alpha for the adjuvant treatment of cutaneous melanoma. Cochrane Database Syst Rev. Jun 18;6:CD008955, 2013.

13 Ribas A. Tumor Immunotherapy Directed at PD-1. N Engl J Med, 366(26): p. 2517-9, 2012.

14 Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, Mcdermott DF, Powderly JD, Carvajal RD, Sosman JA, Atkins MB, Leming PD, Spigel DR, Antonia SJ, Horn L, Drake CG, Pardol DM, Chen L, Sharfman WH, Anders RA, Taube JM, Mcmiller TL, Xu H, Korman AJ, Jure-Kunkel M, Agrawal S, McDonald D, Kollia GD, Gupta A, Wigginton JM, Sznol M. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med, 366(26): p. 2443-54, 2012.

15 Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, Drake CG, Camacho LH, Kauh J, Odunsi K, Pitot HC, Hamid O, Bhatia S, Martins R, Eaton K, Chen S, Salay TM, Alaparthy S, Grosso JF, Korman AJ, Parker SM, Agrawal S, Goldberg SM, Pardoll DM, Gupta A, Wigginton JM. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med; 366(26): p. 2455-65, 2012.

16 Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Elassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumeh PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med, 369(2): p. 134-44, 2013.

17 Hamid O, Robert C, Daud A, Hodi FS, Hwu WJ, Kefford R, Wolchok JD, Hersey P, Joseph RW, Weber JS, Dronca R, Gangadhar TC, Patnaik A, Zarour H, Joshua AM, Gergich K, Elassaiss-Schaap J, Algazi A, Mateus C, Boasberg P, Tumeh PC, Chmielowski B, Ebbinghaus SW, Li XN, Kang SP, Ribas A. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med, 369(2): p. 134-44, 2013.

18 Atefi, M, et al. Effects of MAPK and PI3K pathways on PD-L1 expression in melanoma. Clin Cancer Res, 20(13): p. 3446-57, 2014.

19 Pardoll DM. Immunology beats cancer: a blueprint for successful translation. Nat Immunol, 13(12): p. 1129-32, 2012.

20 Taube J., et al. Colocalization of inflammatory response with B7-h1 expression in human melanocytic lesions supports an adaptive resistance mechanism of immune escape. Sci Transl Med, 4(127): p. 127ra37, 2012.

21 Tumeh PC, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature, 27 November, 515:568-571, 2014.

22 Kilbridge, et al. Patient preferences for adjuvant interferon alfa-2b treatment. JCO, Vol:19 no. 3:812-823, 2001.

23 Webster K, Odom L, Peterman A, Lent L, Cella D. The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system: Validation of version 4 of the core questionnaire. Qual Life Res. 8:604, 1999.

24 Hauschild A, Gogas H, Tarhini A, Middleton MR, Testori A, Dreno B, Kirkwood JM. Practical guidelines for the management of interferon-alpha-2b side effects in patients receiving adjuvant treatment for melanoma: expert opinion. Cancer, Mar 1;112(5):982-94. doi: 10.1002/cncr.23251, 2008.

25 Spiessens B, Debois M. Adjusted significance levels for subgroup analyses in clinical trials. Contempoary Clinical Trials 31.6:647-656, 2010.

26 Sy JP, Taylor JMG. Estimation in a Cox proportional hazards cure model. Biometrics 56(1): 227-236, 2000.

27 Sy JP, Taylor JMG. Estimation in a Cox proportional hazards cure model. Biometrics 56(1): 227-236, 2000.

28 Little RJA. A class of pattern-mixture models for normal incomplete data. Biometrika, 81, 471-483, 1994.

29 Pauler DK, McCoy S, Moinpour C. Pattern mixture models for longitudinal quality of life studies in advanced stage disease. Stat Med, 22(5), 795-809, 2003.

30 Fairclough DL. Design and analysis of quality of life studies in clinical trials, Second Edition (2nd ed.). Boca Raton, FL: Chapman & Hall/CRC, Taylor & Francis Group, LLC, 2010.

31 Bacik J, Mazumdar M, Murphy BA, Fairclough DL, Eremenco S, Mariani T, Motzer RJ, Cella D. The functional assessment of cancer therapy-BRM (FACT-BRM): a new tool for the assessment of quality of life in patients treated with biologic response modifiers. Qual Life Res. 2004 Feb;13(1):137-54.

32 Trask, Peter C., et al. "Longitudinal course of depression, fatigue, and quality of life in patients with high risk melanoma receiving adjuvant interferon." *Psycho-Oncology* 13.8 (2004): 526-536.

33 Yost KJ, Sorensen MV, Hahn EA, Glendenning GA, Gnanasakthy A, Cella D. Using multiple anchor- and distribution-based estimates to evaluate clinically meaningful change on the Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) instrument. Value Health. 2005 Mar-Apr;8(2):117-27

18.0 APPENDIX

18.1 Surgical Management Guidelines

18.2 Guidelines for Self Administration of Interferon Alfa-2b Template

18.3 **S1404** Patient Interferon Diary (for patients who self-administer Interferon)

18.4 **S1404** Local Pathology Review Form

18.5 TNM Definitions for Pathologic Staging

18.6 QA Auditing and Monitoring

18.7 Instructions for PPD Requisition Form

18.8 Translational Medicine: Retrospective T-Cell Receptor Beta Chain (TCRβ) Sequencing of Banked Samples from **S1404**

18.9 Instructions for the SWOG Biospecimen Bank - Lab #201, Solid Tissue, Myeloma and Lymphoma Division

18.10 Translational Medicine: Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients

18.1 Surgical Management Guidelines

All patients must be free of disease at the time of registration. All surgery is to be completed prior to registration and meet the criteria outlined in Section 5.0, Eligibility Criteria. Patients must be registered within 98 days of the last surgery performed to render the patient free of disease.

a. Excision of the Primary Site

These guidelines apply to patients presenting with an intact primary and undergoing sentinel lymph node biopsy or regional lymph node dissection to establish eligibility. All such patients must undergo adequate wide excision of the primary tumor meeting the suggested criteria outlined below. In most cases, this must be a wide excision with 1 cm minimum margins. In all cases, the margins of excision must be histologically free of melanoma (including melanoma in-situ or atypical junctional melanocytic hyperplasia). For all sites except head & neck and extremities distal to the wrist or ankle, the primary melanoma must be excised with at least 1 cm margins of normal skin in all directions, measured either from the edge of the primary tumor or from the edge of the biopsy scar if prior excisional biopsy has been done. The excision should go down to the fascia; including the fascia in the resection is optional. Measurements of margins should ideally be done by the surgeon at the time of wide excision using a ruler; if the measurement is done by the pathologist, allowance of 33% for shrinkage will be made. In addition to the gross margin, a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained.

For primary melanomas on the head & neck or extremities distal to the wrist or ankle, the primary melanoma must be excised and a histologically negative margin (including histologic freedom from atypical junctional melanocytic hyperplasia) must be obtained. Measured margins of at least 1 cm are desirable, but not mandatory. Acral-lentiginous melanomas (including subungual primaries) may be resected by any procedure that yields a histologically negative margin, including amputation and digit-conserving surgery.

b. Excision of Recurrent Disease

All patients enrolled with regional disease, including recurrence after initial presentation, must have no evidence of active disease at the primary site or have undergone a re-excision of the primary site that meets the criteria outlined in Section 18.1a above (including histologically negative margins of excision) prior to registration. Patients presenting with satellite metastases (within 2 cm of the primary) or in transit metastases (beyond 2 cm from the primary but proximal to the regional lymph nodes) are eligible provided that all tumor has been excised with negative margins, they have undergone complete lymph node dissection meeting the criteria outlined below (if any histologic or clinical evidence of lymph node involvement), and they have NOT undergone prohibited systemic therapy for their satellite/in transit metastases (see Section 5.1b).

c. Regional Lymph Nodes

Regional lymph node dissection is mandatory for all patients with histologic or clinical evidence of regional lymph node involvement enrolled on this trial. (Patients with satellite/in transit disease and no evidence of nodal involvement may be enrolled without having undergone lymph node dissection.) The node dissection must be done in accord with the following guidelines; lymph node

sampling is not acceptable. Sentinel lymph node biopsy alone, without completion lymph node dissection, is not acceptable.

The number of tumor-involved nodes must be documented for all cases. Either H&E or immunohistochemical evidence of involvement is acceptable for determining the number of involved nodes, but RT-PCR or other molecular techniques are not. Patients with confluent nodal involvement that makes determination of the exact number of involved nodes difficult are eligible, and are considered to have "matted nodes" and classified as N3.

Micrometastasis versus macrometastasis - As outlined in Section 4.0 Staging Criteria, the status of regional lymph node involvement will be determined by histopathologic assessment and by the clinical presentation of those nodes. By definition, micrometastases are diagnosed by sentinel node biopsy or elective lymph node dissection. Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically. Note: Patients with extranodal extension are eligible for the trial, and for the purposes of this protocol are considered to have macrometastatic involvement (i.e., eligible even if only one tumor-involved node).

1. Cervical Lymph Node Dissection

   A classic radical neck dissection is not required and is discouraged. In cases with clinically negative nodes, less than a full neck dissection is permissible, including modified dissections such as supraomohyoid or posterior triangle dissections. In such cases, the entire triangle should be dissected. Preservation of the internal jugular vein, sternocleidomastoid muscle, and eleventh cranial nerve ("functional neck dissection") should be performed whenever possible. Radionuclide lymphatic drainage scans may be helpful in delineating lymph node groups at risk for tumor involvement. Consideration should be given to the parotid gland nodes, particularly for melanomas of the face, anterior ear and temporal region, which should be removed by superficial or if necessary total parotidectomy if there is evidence of involvement by tumor. The facial nerve (seventh cranial nerve) should be spared unless invaded by tumor.

2. Axillary Lymph Node Dissection

   Removal of at least the level I and II axillary lymph nodes is the minimum acceptable operation. Level III nodes must be removed if clinically suspicious. The minimum borders of the dissection are the latissimus dorsi muscle laterally, the axillary vein superiorly, and the medial border of the pectoralis minor muscle medially. The nerves to the serratus anterior (long thoracic nerve) and latissimus dorsi (thoracodorsal nerve) should be identified and preserved if possible. If the primary tumor is on the trunk, consideration should be given to remove the low axillary nodes (at or below the level of the nipple) by following the latissimus dorsi muscle down to its origin on the chest wall and dissecting the node-bearing tissue between it and the serratus anterior muscle.

3. Inguinal or Ilioinguinal Lymph Node Dissection

   The minimum operation for groin node dissections is a superficial inguinal lymph node dissection (inguinal or inguinofemoral lymphadenectomy). A pelvic (iliac and obturator) node dissection is also necessary (ilioinguinal lymphadenectomy) if these nodes are felt to be involved by imaging studies or intraoperative palpation. The borders of a superficial inguinal

lymph node dissection are the adductor muscles medially, the sartorius laterally, the junction of these two muscles caudally, the femoral vessels posteriorly, and a line connecting the pubic tubercle and the anterior superior iliac spine superiorly. The node-bearing tissue superficial to the external oblique fascia and superior to the inguinal ligament should be included with the specimen, up to the level of this line. Removal of the pelvic nodes, if required, may be accomplished through the same or a separate incision; "sampling" of the deep nodes rather than a radical dissection is adequate. Minimally invasive surgical approaches, such as robotic-assisted pelvic lymphadenectomy, are acceptable provided the operation otherwise conforms to the standards described.

d. Other Sites of Nodal Involvement

Lymph node dissections at sites other than those mentioned (e.g., popliteal or epitrochlear) should be carried out only if involvement of the nodes with melanoma is documented or if the primary site lies directly over the node group and node dissection is necessary to allow adequate wide excision. Patients with nodal involvement in these sites, as well as those with recurrent disease in the regional nodal basin after a previous complete lymphadenectomy, are eligible for this trial provided that all evidence of disease has been resected with histologically negative margins. Failure to document the margin status may lead to the patient being declared ineligible.

e. Resection of Distant Metastatic Disease

Patients with Stage IV melanoma metastatic to skin, subcutaneous sites, distant lymph nodes or lung or other visceral sites are allowed provided all sites are resected with histologically negative margins, they have NOT undergone prohibited systemic therapy for their metastatic disease (see Section 7.2) and the patient otherwise meets the eligibility criteria outlined in Section 5.0. Patients with resected brain metastases are not eligible. Minimally invasive surgical approaches, such as video-assisted thoracotomy, are acceptable. Failure to document the margin status may lead to the patient being declared ineligible. Stereotactic radiosurgery or ablative techniques that do not involve resection of the tumor to negative margins are not acceptable.

18.2 Guidelines for Self-Administration of Interferon Alfa-2b Template

For emergency contact:

Insert Site Contact Information.

Instructions for Self-Administering Medication

1. Preparation

   a. Wash hands well. Take acetaminophen (Tylenol®) as premedication if directed by your doctor.

2. Assemble necessary supplies. The Interferon should be kept refrigerated until several minutes before each treatment. You also need a syringe with a needle, at least 3 alcohol prep pads, and a container* for used materials.

   *An unbreakable, leak-proof, reclosable container - milk carton, coffee can.

3. Reconstituting the Interferon Powder

   a. If this is the first dose that will be coming from a vial, the Interferon powder must be dissolved, using the diluent provided. Snap the plastic cap off both vials, and cleanse both rubber stoppers with an alcohol pad and allow to air dry.

   b. There may be a different syringe/needle provided that you will use to reconstitute the Interferon. Open the package containing one of these syringes and attach (or tighten) the appropriate needle to it. Pull back the plunger of the syringe so that the top of it rests right on the line representing the volume of diluent that you are to add to the Interferon powder.

   c. Insert the needle through the stopper of the diluent vial, and invert the vial/syringe in front of you at eye level, holding the syringe in your dominant hand and the vial in the other.

   d. Inject the air from the syringe into the vial slowly. If you feel like you are forcing it, pull back the plunger to allow some solution into the syringe, then push the remaining air into the vial. Ultimately, your syringe should be filled with diluent solution up to the correct line and no air will be left in the syringe. If you have bubbles, tap the syringe with your finger until they rise to the top, push them up into the vial and recheck the plunger to insure that it is still at the correct volume mark.

   e. Withdraw the needle from the diluent vial and insert it into the vial containing the Interferon powder. This time keep the vial on the surface and push the plunger down to inject the diluent into the powder vial. If you meet resistance, allow some air to rise into the syringe before pushing down and expelling the remaining solution into the vial.

      Eventually, all the solution will be in the vial. Pull back the plunger to return it to the line that is the same as the volume of solution that you injected. This will prevent pressure build-up in the Interferon vial. Remove the needle and discard it appropriately.

f. To help dissolve the Interferon powder, you may need to roll the vial between your palms or swirl the solution around. DO NOT shake the vial. Be sure that all the powder is dissolved before proceeding to #3.

4. Withdrawing Your Dose From the Vial

a. Cleanse the rubber stopper of the vial containing the Interferon solution with an alcohol pad and allow to air dry.

b. Open syringe package and needle package (if separate) and attach or tighten needle by twisting until tight. Pull back the plunger to the mark that represents your dose (i.e., 3 MU/0.5 ml, top of plunger should rest at the 0.5 ml mark). This fills the syringe with air in a volume equal to the volume of your dose.

c. Uncap the needle and push it through the stopper, at least half-way into the vial. Now pick up the vial (with syringe/needle in it) with your left hand and turn it upside down, holding it at eye-level, about 12 inches from your face. You should now have the vial in one hand and your other hand free to manipulate the syringe. (Note: Left-handed persons should have the vial in their right hand, so that they can manipulate the syringe with their left hand.)

d. Inject air from the syringe into the vial slowly, and then withdraw the plunger. The syringe will gradually fill with drug solution. Repeat this procedure until only solution is in the syringe, solidly, to the mark that indicates your dose. Withdraw needle and recap it.

5. Administration

a. Thoroughly clean the area to be injected with an alcohol pad. Areas appropriate for this type of injection have been shown to you. A new site should be used for each injection whenever possible.

b. As demonstrated, pinch 1 1/2 to 2 inches of loose skin from the site to be injected.

c. Uncap the needle, and insert the needle approximately 1/4 inch into the skin and push the syringe plunger in all the way, thereby giving the dose of Interferon.

d. Remove needle and wipe injection site with a new alcohol pad, but do not massage the area to any great extent.

e. Carefully recap needle and return needle and syringe to the clinic pharmacy for disposal.

If the interferon vial is a multidose vial (eg., solution for injection vial) and contains more than one dose, write the date on the label. It is usable for 30 days. Unused doses in a multidose vial must be discarded after one month.

Reconstituted vials (eg., powder for injection vials) must be discarded after one dose has been withdrawn from the vial. Do not re-use reconstituted vials, as bacterial contamination may occur.

f. If a drug administration diary has been provided, remember to complete it after each dose. Enter the date and time of day given, along with any notable side effects that you may have experienced since the previous dose was given.

18.3 **S1404** Patient Interferon Diary (for patients who self-administer Interferon)

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #**_____

Institution/Affiliate _____ Physician _____

Instructions for the participant:
This is a monthly calendar on which you are to record the number of injections you self-administer. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from interferon alfa-2b, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____
Your next appointment is: _____

Special instructions: The dose of interferon alfa-2b for maintenance is 10 MU/m^2/d.

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature: _____

18.4 **S1404** Local Pathology Review Form

SWOG
S1404 LOCAL PATHOLOGY REVIEW FORM

Patient Identifier | | | | | | | **Study Identifier** | S | 1 | 4 | 0 | 4 | **Registration Step** | 1 |

Patient Initials _____ (L, F M)

Instructions: This form must be completed and signed by a local pathologist prior to registration for confirmation of eligibility per S1404 protocol Section 5.1e. Upload the completed form via Medidata Rave™ in the Source Documentation-Baseline form, include a copy with the tissue submission, and retain the original in the patient's research record. Please see protocol Section 15 for complete information regarding tissue submission.

Pathologic Diagnosis: _____

Preliminary Data Specimen Submission (select all that apply):

☐ Primary ☐ Lymph Nodes ☐ Satellite/In-Transit Metastases ☐ Distant Metastases

Specimen Type Submitted:

☐ Unstained Slides – Local Surgical Pathology Number(s) _____

Specimen Review

Tumor Cells Available (PLEASE CHECK ONLY ONE):

☐ Adequate: ≥ 100 viable tumor cells (ELIGIBLE) ☐ Inadequate: < 100 viable tumor cells (INELIGIBLE)

_____ _____
Signature of Interpreting Pathologist **Date**

_____
Printed Name of Interpreting Pathologist

Comments:

Page 1 of 1 **Version 1.0**

18.5 TNM Definitions for Pathologic Staging

Table 1 TNM Definitions for Stage III Melanoma: Pathologic Staging[b]

Stage	TNM	Description
IIIA	T1–4a	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
	N1a	1 regional lymph node metastasis with micrometastasis[c]
	N2a	2–3 regional lymph node metastases with micrometastasis[c]
	M0	No detectable evidence of distant metastases
IIIB	T1–4b	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N1a	1 regional lymph node metastasis with micrometastasis[c]
	N2a	2–3 regional lymph node metastases with micrometastasis[c]
	M0	No detectable evidence of distant metastases
IIIB	T1–4a	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration

Stage	TNM	Description
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
	N1b	N1b = 1 regional lymph node metastasis with macrometastasis[d]
	N2b	N2b = 2–3 regional lymph node metastases with macrometastasis[d]
	N2c	N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
	M0	No detectable evidence of distant metastases
IIIC	T1–4b	T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N1b	N1b = 1 regional lymph node metastasis with macrometastasis[d]
	N2b	N2b = 2–3 regional lymph node metastases with macrometastasis[d]
	N2c	N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
	M0	No detectable evidence of distant metastases
IIIC	Any T	TX = Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
		T0 = No evidence of primary tumor
		Tis = Melanoma *in situ*
		T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
		T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
		T2a = Melanomas 1.01–2.0 mm in thickness without ulceration.

Stage	TNM	Description
		T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
		T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
		T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
		T4a = Melanomas >4.0 mm in thickness without ulceration
		T4b = Melanomas >4.0 mm in thickness with ulceration
	N3	≥4 regional lymph node metastases; or matted nodes; or in transit met(s)/satellite(s) with metastatic lymph node(s)
	M0	No detectable evidence of distant metastases
T = primary tumor; N = regional lymph nodes; M = distant metastasis.		
Adapted with permission from AJCC: Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 325-44.		
The explanations for superscripts b–d are at the end of Table 2.		

Table 2 TNM Definitions for Stage IV Melanoma

Stage		TNM	Description
Clinical[a]	**Pathological[b]**		
IV	IV	Any T	TX = Primary tumor cannot be assessed (e.g., curettaged or severely regressed melanoma)
			T0 = No evidence of primary tumor
			Tis = Melanoma *in situ*
			T1a = Melanomas ≤1.0 mm in thickness without ulceration; mitosis <1/mm^2
			T1b = Melanomas ≤1.0 mm in thickness with ulceration or mitoses ≥1/mm^2
			T2a = Melanomas 1.01–2.0 mm in thickness without ulceration
			T2b = Melanomas 1.01–2.0 mm in thickness with ulceration
			T3a = Melanomas 2.01–4.0 mm in thickness without ulceration
			T3b = Melanomas 2.01–4.0 mm in thickness with ulceration
			T4a = Melanomas >4.0 mm in thickness without ulceration
			T4b = Melanomas >4.0 mm in thickness with ulceration
		Any N	NX = Regional lymph nodes cannot be assessed (e.g., previously removed for another reason)
			N1a = 1 regional lymph node metastasis with micrometastasis[c]
			N1b = 1 regional lymph node metastasis with macrometastasis[d]
			N2a = 2–3 regional lymph node metastases with micrometastasis[c]
			N2b = 2–3 regional lymph node metastases with macrometastasis[d]
			N2c = In transit met(s)/satellite(s) without metastatic lymph nodes
			N3 = ≥4 regional lymph node metastases; or matted nodes; or in transit met(s)/satellite(s) with metastatic lymph node(s)
		M1	M1a = Metastases to skin, subcutaneous, or distant lymph nodes and normal serum LDH
			M1b = Metastases to lung and normal serum LDH

Stage		TNM	Description
			M1c = Metastases to all other visceral sites and normal serum LDH; or distant metastases to any site and elevated serum LDH

Stage		TNM	Description
Clinical[a]	**Pathological[b]**		
LDH = Lactate dehydrogenase; T = primary tumor; N = regional lymph nodes; M = distant metastasis.			
Adapted with permission from AJCC: Melanoma of the skin. In: Edge SB, Byrd DR, Compton CC, et al., eds.: AJCC Cancer Staging Manual. 7th ed. New York, NY: Springer, 2010, pp 325-44.			
[a]Clinical staging includes microstaging of the primary melanoma and clinical and/or radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.			
[b]Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy. Pathologic Stage 0 or Stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.			
[c]Micrometastases are diagnosed after sentinel lymph node biopsy and complete lymphadenectomy (if performed).			
[d]Macrometastases are defined as clinically detectable nodal metastases confirmed by therapeutic lymphadenectomy or when nodal metastasis exhibits gross extracapsular extension.			

18.6 QA Auditing and Monitoring

The Quality Assurance Program of the Groups participating in the NCTN was developed to enhance the reliability and validity of clinical trials data through the use of routine monitoring procedures which includes auditing as one component. The purpose of an audit is to document the accuracy of data submitted to the Data Operations Center and to verify compliance with protocol and regulatory requirements. The program also surveys data management practices at each institution in order to provide educational support to the sites regarding issues related to data quality, data management, and other aspects of quality assurance.

Audits are conducted according to FDA regulations and NCI guidelines for Auditing Clinical Trials for the National Clinical Trials Network (NCTN) Program, NCI Community Oncology Research Program (NCORP) and Research Bases:
http://ctep.cancer.gov/branches/ctmb/clinicalTrials/docs/ctmbauditguidelines.pdf.

Each institution is audited at least once every three years, but remains at annual risk of an audit. Routine monitoring of Institutional Performance Review reports and timeliness of reporting of Serious Adverse Events (SAEs) is conducted to identify institutions that may require more frequent audits.

The audit team consists of qualified individuals capable of providing a medical assessment of the patient cases (Quality Assurance, physician, nurse or experienced clinical research associate [CRA]). A number of patients equal to 10% of the accrual since the last audit with a minimum of three are randomly selected for review at each institution. In addition, a limited review of eligibility and consent only is conducted for at least one unannounced case at each on site audit.

The major objective of the audit process is to verify study data that could affect the interpretation of primary study endpoints. This is done through independent verification of study data against the source documents. Primary source documentation reviewed during an audit includes the following: research records, hospital charts, clinic charts, lab reports, x-rays, scans, radiotherapy reports, operative reports, pathology reports and other special studies required by protocol.

By comparing the data collection forms submitted to the Data Operations Center with the primary records and referring to the protocol, the audit team reviews the records to determine compliance with protocol requirements for eligibility, treatment administration, response assessment, toxicity reporting and general data quality. Auditors verify that the current IRB-approved version of the consent form was signed prior to registration and that subjects were informed of new findings that could affect their willingness to participate in the study. NCTN investigators and institutions are expected to follow the protocol and lead Group policies in treating patients registered on Group protocols. Among other requirements, investigators/institutions must follow SWOG's policies for dosing principles, reporting of SAEs, and follow-up of all patients.

The audit team also verifies that the protocol and its amendments received initial and continuing IRB review and approval and that safety reports and serious adverse events were submitted to the IRB. Investigational drug accountability record forms (DARFs) are reviewed and random patients are cross referenced against the medical record. A tour of the pharmacy is conducted to verify security and storage conditions as well as the physical inventory.

The audit report is comprised of three components: 1) conformance to IRB and informed consent requirements, 2) the pharmacy and use of NCI DARFs, and 3) patient case review. An acceptable rating requires no deficiencies, few lesser deficiencies, or major deficiencies that were addressed prior to the audit. Institutions found to be “unacceptable” or

"acceptable, needs follow-up" on any component are required to submit a written response and/or corrective and preventative (CAPA) action plan. Failure to submit a written response including a corrective and preventative action plan within the required timeframe will result in suspension of registration privileges. A re-audit of any component rated as unacceptable will be conducted within one year after the unacceptable audit. An unacceptable rating for the same audit component on two consecutive audits will result in probation. Accrual will be suspended pending submission of a site improvement plan that addresses key infrastructural issues contributing to poor performance. An unacceptable rating at the second re-audit may result in termination from the group. If systematic misrepresentation of data is identified, an immediate repeat audit is scheduled by the representatives from the Group with the NCI and/or the FDA present.

In some cases, non-compliance for issues such as timeliness of data submission, SAE reporting and submission of specimens is monitored off site rather than scheduling a re-audit. Failure to show improvement may result in scheduling of a re-audit or other disciplinary action.

Results of all Quality Assurance Audits are reported to the NCI, the Principal Investigator of the institution that was audited, and representatives of the Group. Protocol specific audit results are also sent to the Statistical Center to inform the statisticians, data chairs and study chairs of any significant discrepancies involving eligibility, treatment, toxicity or response assessment.

The Quality Assurance Program performs their educational role through several mechanisms including presentations during the Group Meetings, online Clinical Trials Training Courses, collaboration with others such as the Pharmacy Committee and Statistical Center to develop training tools, and memos and newsletter articles that are distributed to all Group institutions to educate research staff about changes in regulatory and quality assurance issues and audit procedures.

Additional Monitoring

In addition to the standard auditing process outlined above, the following additional requirements will be implemented for this study:

- Routine monitoring by Data Coordinators at the Statistics and Data Management Center**.**
- Risk-based monitoring by Monitors at the Statistics and Data Management Center**.**
- Additional on-site monitoring visits by Quality Assurance Auditors at the Operations Office.

Routine Monitoring at the SWOG Statistics and Data Management Center

Data Coordinators at the SWOG Statistics and Data Management Center (SDMC) will perform routine monitoring with the following actions:

- Monitor data quality through routine review of submitted data such as on-study, baseline and follow up tumor assessment, lab, treatment, off treatment, and follow up case report forms to identify and follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors in data collection and reporting at a site.

- Analyze site characteristics, performance metrics and clinical data to identify trial sites with characteristics correlated with poor performance or noncompliance through the SWOG Institutional Performance Reporting mechanism and other available reports.

- Verify critical source data remotely via the collection and review of pathology, radiology and applicable lab reports. This includes the review and confirmation of appropriate disease classification as determined by the pathology report, and assessment of

response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the Electronic Data Capture (EDC) system and submitted follow-up tumor assessment forms.

- To assure data are as consistent, complete and accurate as possible, all subject data must undergo careful review by Data Coordinators (DCs). After verifying that all data forms required to determine eligibility have been received or at a time point designated when all the required forms should have been received, the DC reviews the data and completes an initial evaluation.

The initial review includes the following:
- Determine that all required data fields on each form were completed and are consistent with other data.
- Determine if all prestudy tests and exams were performed within protocol specified time limits.
- Determine if each eligibility criterion was met and properly documented.
- Review and confirm pathology based on the pathology report uploaded to the EDC system.
- Verify that stratification and/or descriptive factors (if applicable) were correctly identified at registration.
- Verify that the subject received the assigned study treatment and correct dose(s).
- Verify that the treatment was started within the time limit indicated in the protocol (if applicable).
- Determine if adverse events reported are consistent with other data and entered as required by study specifications.
- Post internal notes to add additional information which may be useful to the study sponsor, monitors, or statisticians, but which do not require action by site personnel.
- Use the query tool to request additional data classifications and corrections of the CRA.

The DC will perform subsequent review of data when new data become available or queries are answered. Regular review will also occur while patients are still on-study, at the time of progression, once they are removed from study and at the time of death.
Subsequent reviews include the following:
- Determine if all required data fields on each newly submitted form were completed and consistent with other data.
- Evaluate all new treatment documentation for correct treatment and dose.
- Conduct assessment of response to treatment utilizing RECIST 1.1 based on scan reports uploaded to the EDC and submitted follow-up tumor assessment forms.
- Review and code any new concomitant medications as required by study specifications.
- Evaluate if the subject is or should be off protocol treatment per protocol criteria.
- Review and evaluate death if death of subject is reported.
- Use the query tool to request additional data classifications and corrections.
- Post internal query notes to add additional information that may be useful to the study sponsor, monitor, or statisticians but which do not require action by site personnel.
- Review site responses to the queries and the corrected or amended eCRF pages. When corrections and responses are considered satisfactory, queries are closed by the data coordinators. Unsatisfactory responses are re-queried and tracked.
- Perform re-evaluations promptly after responses to queries are received

<u>Centralized Risk-based Monitoring at the Statistics and Data Management Center (SDMC)</u>
Monitors at the Statistics and Data Management Center (SDMC) will support the risk based monitoring approach for this trial through off-site monitoring to include auditable elements through administration of eight weeks of treatment for the first two patients randomized at each site. Within 10 weeks of randomization, the Head CRA (or Data Manager) at the study site will be contacted by a SDMC monitor via email with instructions for uploading the auditable elements including:

- Copy of the signature page of the patient informed consent signed prior to registration.

- Documentation to support all eligibility criteria including:
  - Copy of the signed and dated eligibility checklist (unless previously uploaded into RAVE)
  - Operative and pathology reports to support histology and stage of disease
  - An H & P including vital signs, height and weight, review of symptoms, performance status and past medical history. The medical history should include details of the malignancy, prior surgical procedures, prior chemotherapy and/or radiotherapy, history of relevant medical disorders and concomitant medications
  - Lab reports to support all required prestudy tests. Lab reports must include institutional normal limits.
  - Reports of baseline scans, brain CT/MRI, and EKG
  - Documentation of baseline toxicities

- Documentation for the first eight weeks of treatment including:
  - An H & P including weight, BP, performance status, concomitant medications and toxicity notation
  - Lab reports prior to each cycle
  - Drug orders and documentation of drug administration through chemo flowsheets, progress notes, etc.
  - Documentation to support dose modifications or treatment delays

<u>Onsite Monitoring by the Quality Assurance Program</u>

- Additional on-site monitoring visits will be conducted with the first site visit within 6 months of first patient randomization.
- Monitoring visits will be combined with other routine audits whenever possible. The initial monitoring visit may be postponed up to 3 months to coincide with a routine audit or to coincide with a routine audit of another institution in the same geographic area. Monitoring visits may also be postponed if no accrual or activity has occurred beyond the timeframe covered by the off-site central monitoring.
- Subsequent monitoring visits will be conducted according the following criteria:
  - If > 10 patients per year (~ 10% of sites) – annually
  - 5 – 10 patients per year (~ 20% of sites) – every 2 years
  - < 5 patients per year – every 3 years or as part of routine audit cycle
- More frequent monitoring visits to a site may be scheduled in response to several factors – high rate of accrual, unacceptable monitoring visit results, centralized electronic monitoring outcome, turnover in staff, etc.
- All sites that receive and dispense investigational agents must be monitored on site to allow <u>at least one</u> visit to the pharmacy with the following exceptions:
  - Sites that use a centralized pharmacy may be monitored at this central location.
  - After an initial onsite visit, NCORP sites and LAPS/Main Member Affiliates may be monitored at a central location.
  - Pharmacies monitored during SWOG site visits for other studies will suffice for the on site monitoring requirement.
  - The need for subsequent onsite visits will be determined on a case by case basis including past audit results, number of patients on the investigational agent, etc.

Communication of Monitoring Results

The monitoring team will meet routinely to share all aspects of monitoring (on site, centralized, safety, for-cause). When needed, the SWOG Executive Officer for Quality Assurance will be consulted.

All monitoring visits results will be reported according to NCI-CTMB requirements via the CTMB-AIS data base and regularly reviewed by SWOG monitoring staff.

Summarized results of all monitoring visits will be provided semi-annually to the SWOG Board of Governors and the study team. Any problems or issues of concern will be reported to the Data and Safety Monitoring Committee on an as-needed basis.

Safety Specific Centralized Monitoring
Each Serious Adverse Event (SAE) report submitted (via CTEP-AERS) will be reviewed by the SWOG SAE Coordinator at the Operations Office. Supporting documentation for any deaths on study will be requested and compiled with the report and sent to the Physician Reviewer. As mentioned below all sites will undergo mandatory training and this will include training regarding SAE reporting. SWOG regularly monitors timeliness of SAE reporting and addresses any issues of poor performance with individual sites.

The study will be monitored for under reporting/missed Serious Adverse Events: The SWOG SAE Coordinator receives a weekly report from the data base that includes all adverse events that are submitted through routine submission that potentially also meet expedited reporting criteria but for which no CTEP-AERS report is found. The Coordinator is responsible for following up with the responsible site to ensure that SAEs are not missed/under-reported.

The study will be monitored for trends in Serious Adverse Events: A "new SAE on study" report is generated each time a new Serious Adverse Event is entered into the SWOG data base. It is a cumulative report that lists all SAEs reported for the protocol. This allows those who review the report to identify concerning trends in reported events; events that may be occurring at greater intensity (higher toxicity grade) or frequency than expected. The SAE Coordinator, Physician Reviewer, Study Chair, and assigned Statisticians are responsible for regularly monitoring this report.

Additional Approaches to be Used
- Mandatory training of key site personnel prior to first patient registration.
- Timely review of all monitoring reports to identify sites that require additional training, monitoring, disciplinary action, etc.
- Mentoring visits and additional communication between monitor and site staff to assess potential problem areas, provide feedback on data submission quality and timeliness, identify staff turnover, etc.
- Additional mandatory centralized training to be provided to all sites if major changes to the protocol occur or common problem areas are identified.

Management of Noncompliance

Issues of particular concern related to patient safety and questions of site fraud will be managed according to SWOG standard policies and the policies of the NCI CTMB for auditing of clinical trials under the NCI National Clinical Trials Network (NCTN) Program. Where important deviations are discovered, additional site training components will be developed and implemented.

As with standard NCTN procedures, sites will be required to develop and implement corrective action plans in response to any major deficiencies identified at a monitoring visit

Ensuring Quality Monitoring

All staff involved in monitoring are required to undergo training in the principles of clinical investigations and human subjects protection. They are also required to complete the same protocol specific training required of the site staff.
All monitoring and auditing processes for the study will be reviewed by study leadership twice per year to ensure conformance to the monitoring plan.

Monitoring Plan Amendments

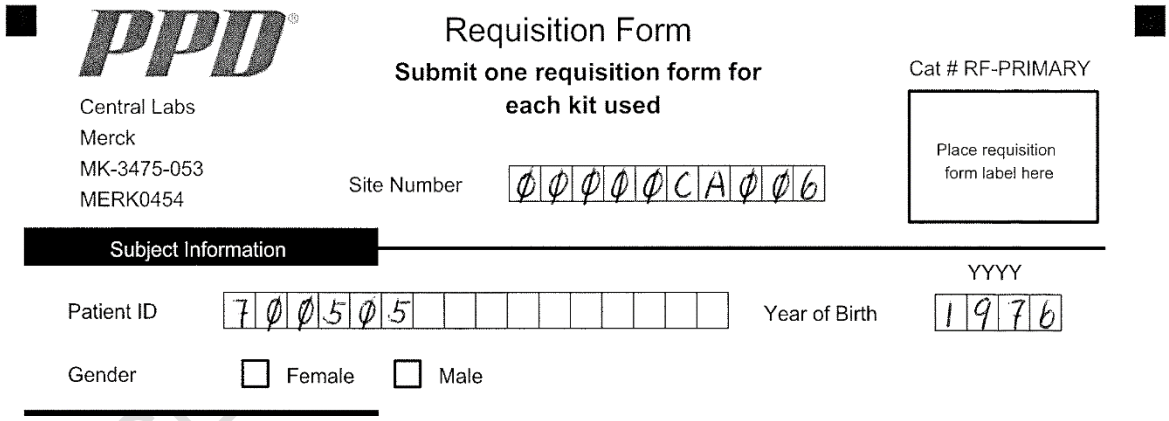
At each formal review of the monitoring plan and conformance to it, the study leadership will make a recommendation regarding the need for amendments to the monitoring plan. These amendments will be reviewed and approved by the NCI and provided in this protocol section and will be submitted to the FDA.

18.7 Instructions for PPD Requisition Form

Instructions for filling out the PPD Requisition Form.
Every PPD/ADA specimen submission must include a copy of the PPD Requisition Form. This form is supplied along with the kit. In addition, PPD will send you a copy of their Laboratory Manual.

Subject Information Section	
Site Number:	Fill in the NCI code for your institution. In addition, PPD requires that you add leading zeros so that all 10 spaces are filled. Do not leave any blank spaces or it will delay processing of your specimen. For example, if your NCI code is CA006, then you would enter "00000CA006" in this field.
Patient ID:	Enter the 6-digit SWOG patient identification number assigned at registration.
Year of Birth:	Enter all 4 digits of the patient's year of birth. For example, "1976".
Gender:	Place a mark in the appropriate box.

Below is an example of how this would look:



Visit Information Section

PK and ADA sampling should be done based on the treatment cycles for pembrolizumab, not on calendar weeks. However, PPD has created visit labels assuming that there will be no treatment delays or variation in schedule. The following table is intended to help you pick the most appropriate visit label for your PK/ADA specimen submission:

Visit Label	Specimen to be submitted
Week 1	Sample collected prior to the first infusion on Cycle 1
Week 4	Sample collected prior to the second infusion during Cycle 1.
Week 10	Sample collected prior to the second infusion during Cycle 2
Week 19	Sample collected prior to the third infusion on Cycle 3
Week 25	Sample collected prior to the first infusion on Cycle 4
Week 49	Sample collected prior to the infusion on Cycle 6
Post Treatment FU 30 Days	Sample collected 30 days after discontinuation of pembrolizumab (provided patient has not started a new anti-cancer therapy prior to this time)
Unscheduled	PPD has provided 10 “unscheduled visit” labels. These should be used sparingly if at all. Using the guide provided above, you should be able to identify the correct visit label for your submission.

18.8 Translational Medicine: Retrospective T-Cell Receptor Beta Chain (TCRβ) Sequencing of Banked Samples from S1404

a. Objectives

1. Primary
To evaluate the association between TCRβ variable gene (TRBV) haplotype and Grade 3-4 immune-related adverse events (irAEs) among Stage III melanoma patients treated with adjuvant Ipilimumab or Pembrolizumab.

2. Secondary
To describe the TRBV haplotype distribution among this cohort of patients studied.

To assess associations between baseline patient demographics and TRB haplotype.

b. Background

Checkpoint blockade immunotherapy (CPI) can elicit anti-cancer T cell responses mediating durable progression free survival but may also promote T cell destruction of healthy tissue to elicit irAEs. Efforts to identify germline variants associated with irAEs using whole genome sequencing (WGS) or microarrays have yet to reveal markers predictive of adverse events following immunotherapy. Identifying such biomarkers could allow for personalized drug selection and dosing to ultimately enable safer and more effective immunotherapy, particularly in light of the increasing use of combination CPI regimens having a significant incidence of severe adverse events. *([1])*

Despite previous efforts, three lines of reasoning support the notion that germline encoded TRBV polymorphism could be a key determinant of adverse events during CPI. First, the TCR locus is repetitive and structurally complex, impeding the measurement of variation by traditional short read WGS or microarray-based methods. *(2)* Second, single amino acid substitutions within the framework or complementarity-determining region (CDR) 1 and 2 regions of the rearranged TCRβ chain are known to significantly alter TCR affinity for human leukocyte antigen (HLA). *(3)* Third, adverse events during immunotherapy may manifest as acute versions of chronic autoimmune diseases (i.e. fulminant type 1 diabetes) that have been separately linked to TRBV polymorphism. *(4)* To circumvent the challenge in measuring TRBV polymorphism by WGS, Thermo Fisher has developed a cost-efficient and rapid method for detection of TRBV polymorphism by next-generation sequencing (NGS) of rearranged TCRβ chains from peripheral blood leukocytes. *([5])* Based on current knowledge, this represents the first NGS-based method to permit haplotype-level resolution of the TRB locus.

A pilot study involving haplotype analysis of the TRB locus by TCRβ sequencing was previously conducted at the University of Texas MD Anderson Cancer Center (MDACC) under the PI, Aung Naing, MD, using the peripheral blood of 81 Caucasians who had graded adverse events following immunotherapy. The results of this analysis revealed the presence of 6 major haplotype groups within the study cohort. Strikingly, members of one haplotype group, accounting for 33% of patients, appear to be protected against severe (Grade 3-5) adverse events (0% frequency) while 14% to 44% of patients in other haplotype groups had severe adverse events (p=7.1E-4, Fisher's 2x2 exact test). Should this finding be confirmed in the larger SWOG cohort, this would indicate that TRBV allele profiling

may serve as a predictive biomarker for adverse events to enable personalized checkpoint blockade drug selection and dosing.

c. Experimental Research Technique

Baseline banked blood samples from Caucasian patients on **S1404**
Preferred source of sample: buffy coat

Total RNA extracted from PBL or whole blood will be used as input for TCRβ sequencing using the Thermo Fisher Scientific product Oncomine TCRB-LR (SKU A35386). This assay utilizes a long-amplicon approach (up to 400 bp) to capture the sequences of all 3 CDR regions of the TCR Beta chain. Sequencing assays for up to 240 patients (details of patient selection provided in the statistical section) will be performed at the University of Texas MD Anderson Cancer Center (MDACC) under the supervision of Mingxuan Xu, PhD. The de-identified data output from the analyses will be provided to Thermo Fisher (Tim Looney) to complete the haplotype analyses. Results from the haplotype analyses will be provided to the PI, Aung Naing, MD and the SWOG Statistical Center. No specimens, demographic data, or PHI will be provided to Thermo Fisher. Limited de-identified clinical data, including tumor type, may be provided to Thermo Fisher from the assays. This protocol will allow for extraction of both DNA and RNA from the cryopreserved cell pellets. Total RNA will then be used for TCRB-LR library preparation in Aung Naing's laboratory.

d. Statistical Plan

Sample selection: the pilot haplotype work has been in Caucasian patients, so we will use baseline blood samples from Caucasian patients enrolled on S1404. We note that melanoma incidence is higher among Caucasian patients than other races, and 95% of patients enrolled on **S1404** were Caucasian. In addition, we will restrict analyses to the subset of patients who planned to receive Ipilimumab as their control arm regimen prior to randomization. First, we will analyze 120 patients who were randomized to the control arm and treated with Ipilimumab on **S1404**; we will select 60 patients with Grade 0-2 irAEs and 60 patients with Grade 3-4 irAEs (selection will be random among all patients with appropriate consent who have baseline samples meeting these criteria [>150 patients available for each irAE cohort]). We note that the Grade 3-4 irAE rate is 35% among patients treated with Ipilimumab on the control arm. We choose to over-sample Grade 3-4 irAE because the incidence of haplotype 2 among this subset is expected to be small, and we want adequate power to evaluate the incidence (further details of expected incidence below in the primary analysis section). If the pilot data results are validated among these Ipilimumab patients (details of primary analysis below), we will select 120 patients randomized and treated with pembrolizumab; we will select 60 patients with Grade 0-2 irAEs and 60 patients with Grade 3-4 irAEs (selection will be random among all patients with appropriate consent who have baseline samples meeting these criteria [>150 patients available for each irAE cohort]). We note that the Grade 3-4 irAE rate is 15% on the pembro arm.

Primary analysis: TRBV haplotype analysis will be performed as described in Looney et al. by T. Looney (at Thermo Fisher) and the results of the analysis will be provided to the SWOG statistical center. The association between haplotype Group 2 and the incidence of severe Grade 3-4) adverse events will be assessed using Fisher's exact test; haplotypes 1, 3, 4, 5, 6 will be grouped together for this analysis (i.e., we will compare haplotype 2 versus all other haplotypes). *(6)* In the pilot data, the haplotype 2 incidence was 33%. We assume the Grade 3-4 irAE to be 12% among haplotype 2 patients (was 0% in the pilot data) and to be 46% among other haplotype patients. Given these incidence assumptions, we expect

that 11% (0.33*0.12/ (0.33*0.12+0.67*0.46)) of patients with a Grade 3-4 irAE in the Ipilimumab cohort of S1404 will be haplotype 2, and that 89% will have another haplotype. Similarly, we expect that 43% (0.33*0.88/ (0.33*0.88+0.67*0.54)) of patients with a Grade 0-2 irAE in the Ipilimumab cohort of **S1404** will be haplotype 2, and that 92% will have another haplotype. With 60 patients with Grade 3-4 irAE and 60 patients with Grade 0-2 irAE, under these assumptions Fisher's exact test has 92% power with a two-sided alpha of 5%.

If a significant association between haplotype 2 and Grade 3-4 irAE is observed in the Ipilimumab cohort, we will process samples on the 120 Pembro patients and perform the same analysis (Fisher's exact test with two-sided alpha = 5%). If we assume the same incidence of haplotype 2 (33%), and that 2% of of the Grade 3-4 AE cohort will be haplotype 2, this test has 86% power.

Secondary analysis: Associations between haplotype and baseline patient characteristics (age, performance status, stage, primary tumor characteristics, LDH) will be evaluated using Fisher's exact test and Wilcoxon-rank sum tests.

Analyses and interpretation of data output will be completed within 1 year of the receipt of specimens.

e. Data Analysis

The data will be analyzed by the SWOG Statistics and Data Management Center (Megan Othus, Ph.D.). The Haplotype Analysis will be performed by Thermo Fisher (Tim Looney).

f. Specimen Information

Laboratory Performing Analysis:
Aung Naing, MD (c/o Mingxuan Xu, PhD)
The University of Texas MD Anderson Cancer Center
Investigational Cancer Therapeutics
1515 Holcombe Blvd., Room Y3.5623, Box 387
Houston, Texas 77030
713-745-9805
Mxu2@mdanderson.org

Specimens used:
Preserved frozen pelleted peripheral blood leukocytes (PBL), peripheral blood mononuclear cells (PBMC) are highly preferred, though whole peripheral blood is also acceptable.

2 ml of whole peripheral blood, from which peripheral blood leukocyte (PBL) total RNA will be extracted in the laboratory of Dr. Naing. 50 ng of PBL RNA will be used for library preparation and sequencing via the Oncomine TCRB-LR assay.

Baseline (pretreatment) samples are highly preferred, though any timepoint is acceptable.

g. References

1 Larkin, J et al. Combined Nivolumab and Ipilimumab or monotherapy in untreated melanoma. NEJM 373:23-34, 2015.

2 Watson, C et al. Comment on 'A database of human immune receptor alleles recovered from population sequencing data'. J Immunol 198:3371-3373, 2017.

3 Robbins, P et al. Single and dual amino acid substitutions in TCR CDRs can enhance antigen-specific T cell functions. J Immunol 180:6116-6131, 2008.

4 Pierce, B et al. The missing heritability in T1D and potential new targets for prevention. J Diabetes Res 737485, 2013.

5 Looney, T et al. Haplotype analysis of the TRB locus by TCRB repertoire sequencing. bioRxiv 406157, 2018.

6 Looney, T et al. Haplotype analysis of the TRB locus by TCRB repertoire sequencing. bioRxiv 406157, 2018.

18.9 Instructions for the SWOG Biospecimen Bank - Lab #201, Solid Tissue, Myeloma and Lymphoma Division

a. **General Banking Instructions**

The SWOG Biospecimen Bank will store formalin-fixed paraffin-embedded (FFPE) tissue blocks or slides at room temperature.

Aliquots of frozen, processed plasma, buffy coat, and serum are banked in -80°C freezers for long-term storage.

b. **Instructions Related to RNA Extraction and T-Cell Receptor Beta Chain (TCRβ) Sequencing (Appendix 18.8)**

The SWOG SDMC will provide a list of patients and time points to the Bank for distribution to Dr. Naing's laboratory. For each patient, the Bank will ship 1 vial of frozen buffy coat (from Baseline time point, if possible) on dry ice for RNA extraction and T-Cell Receptor Beta Chain (TCRβ) Sequencing.

c. **Instructions Related to circulating tumor DNA (ctDNA) (Appendix 18.10)**

The SWOG SDMC will provide a list of patients and time points to the Bank for distribution to the Natera laboratory. For each patient, an H&E slide from the primary tumor or lymph node metastasis will be scanned to a 40X digital image for digital pathology review by Dr. Allie Grossmann, who will provide specimen quality data (e.g., %tumor vs. necrosis, %tumor vs. normal, confirmation of concordance with institutional diagnosis, and comments when applicable) and will digitally annotate slides, as needed, for specimens that will require macrodissection to enrich tumor content. Following pathology QA review, the Bank will either scrape unstained slides (macrodissected as needed), or section FFPE blocks. All tissue will undergo co-extraction for DNA and RNA.

DNA will be extracted from buffy coat from one time point for each patient.

All nucleic acids will undergo quantitation and QC before storage in a -80°C freezer.

For each patient, the Bank will ship the following specimens to Natera on dry ice for overnight delivery:

- At least 500 ng DNA from primary tumor or lymph node metastasis and DNA from buffy coat
- A minimum of 4 ml of frozen plasma from Baseline
- A minimum of 4 ml of frozen plasma at start of cycle 3 (if relapsed after start of cycle 3),
- A minimum of 4 ml of frozen plasma at start of cycle 4 (if relapsed after start of cycle 4),
- A minimum of 4 ml of frozen plasma at removal from protocol therapy or relapse

18.10 Translational Medicine: Association of Circulating Tumor DNA (ctDNA) with Relapse-Free Survival in High-Risk, Resected Melanoma Patients

a. Objectives

1. Primary (integrated): To evaluate associations between pretreatment ctDNA (present versus absent) and relapse within 2 years of randomization in a case-control analysis across treatment arms
2. Secondary (integrated): To evaluate associations between pretreatment ctDNA and relapse within 2 years of randomization in a case-control analysis within each treatment arm (after treatment arm data are unblinded to investigators).
3. Secondary (integrated): To evaluate associations between "early-on treatment" ctDNA levels and relapse within 2 years of randomization
4. Secondary (integrated): To describe ctDNA levels at end of therapy and time of relapse

b. Background

From a double-blind, randomized, placebo-controlled trial, Eggermont, AMM et al. reported improved relapse free survival with adjuvant pembrolizumab in high risk, resected, Stage III melanoma patients compared to placebo. Specifically, pembrolizumab therapy was associated with a one-year rate of recurrence-free survival of 75.4% [95% confidence interval CI, 71.3 to 78.9] vs. 61.0% [95% CI, 56.5 to 65.1] in the placebo cohort. Thus, while anti-PD-1 therapy reduces the risk of disease progression of Stage III melanoma, 25% of patients are predicted to relapse within 1-year. For those untreated, up to 39% will relapse. At present, there are no biomarkers available to predict which of these patients are most likely to relapse. Improving outcomes for these patients in the future will require significant advancements in risk stratification tools.

The Signatera test, offered by Natera, is an emerging biomarker that has shown promising clinical utility for the detection of minimal residual disease and early detection of relapse. *(1, 2, 3, 4)* The assay quantifies cell free, circulating tumor DNA (ctDNA) present in plasma, down to a 0.1% mutant allele fraction. In patients with non-small cell lung cancer, colorectal cancer, muscle-invasive bladder cancer and breast cancer, studies with Signatera have shown an unprecedented positive predictive value (PPV) for relapse ranging from 93%-100%with an average lead time of 2.8-9.5 months compared to radiographic detection. *(5, 6,. 7*, 8)

The **S1404** Stage III melanoma cohort includes post-operative plasma samples collected prior to the initiation of immunotherapy. With these samples, we may be able to discern if baseline ctDNA levels can risk stratify patients. The overall goal is to determine if highly sensitive, tumor-guided ctDNA testing can distinguish **S1404** patients who remain disease free from those who have relapsed. We hypothesize that the Signatera test results will be associated with relapse outcomes in the trial (and within each treatment arm) and that nondetectable ctDNA levels will be associated with lack of relapse within 2 years. For patients who have detectable ctDNA at time zero, we hypothesize that reduction in ctDNA levels will be associated with a lack of relapse within 2 years.

c. Experimental Research Technique

The Natera Signatera assay is a personalized medicine approach for cancer patients that allows for serial testing of peripheral blood for monitoring of minimal residual disease and molecular relapse. Sixteen patient tumor-specific, somatic, non-driver mutations are selected based on exome sequencing comparisons of

germline (buffy coat) to tumor (FFPE tissue). Through a proprietary algorithm, Natera chooses truncal, founder mutations that persist throughout the clonal phylogeny of the heterogeneous tumor population. Each patient plasma sample is then tested with a custom-designed assay that quantifies the 16 unique somatic mutations. For this study, germline and tumor exome data files will be provided to SWOG for future studies.

Dr. Allie Grossmann (PI) is board certified in both Anatomic Pathology and Molecular Genetic Pathology. She is a Medical Director of Molecular Oncology at ARUP Laboratories, a national reference laboratory owned by the University of Utah, where she oversees the design, validation and routine clinical testing of a variety of molecular, genomic and immunohistochemical clinical assays, including ctDNA assays. She is an independent investigator at the Huntsman Cancer Institute (Department of Pathology, University of Utah), with an NCI and American Cancer Society-funded melanoma research laboratory. She is Co-Director of the Biospecimen Pathology Core for the HCI Melanoma SPORE initiative. She is a quality control anatomic pathologist for HCI Biorepository – providing histomorphologic review of melanoma and sarcoma tumor banking. Dr. Grossmann is ideally suited to lead this study.

d. Statistical Plan

The case-control pairs will be selected randomly among eligible patients with all required samples. Cases will be patients who relapsed within 2 years of randomization. Controls will be patients who were alive without relapse for at least 2 years after randomization. To the degree possible with the sample sizes available, case-control patients will be matched based on the randomization stratification factors stratification factors stage (stage IIIA and IIIB versus IIIC and IV) and PD-L1 status (positive versus negative versus indeterminate). Also, to the degree possible with the sample sizes available, we will restrict to patients who received ipilimumab on the control arm, and restrict to patients on the pembrolizumab arm who declared before randomization that they would have received ipilimumab if randomized to the control arm.

With 100 total patients, 50 cases and 50 controls, and assuming 24% of control patients (no relapse or death within first two years) have detectable baseline ctDNA levels, we will have 90% power with a two-sided alpha of 5% to detect an odds ratio (OR) of 5.3 or more extreme if the correlation between cases and controls is 0.5. If the correlation is lower than 0.5, we have additional power. For example, if the correlation is 0.2, we have 90% power to detect an OR of 4.26 or more extreme.

For secondary analyses we will:

- evaluate baseline ctDNA as a quantitative covariate in a conditional logistic regression model,
- evaluate associations between presence/absence of ctDNA and quantitative ctDNA levels at the third and fifth cycles and relapse within 2 years using conditional logistic regression and landmark analyses,
- descriptively summarize changes in ctDNA levels over time using descriptive statistics including means, medians, and inter-quartile ranges and spaghetti plots
- perform all the above analyses within each treatment arm, and fit regression models with a treatment arm interaction covariate (to be performed after results by treatment arm from the trial are released by the DSMC).

No information on arm label will be provided during the processing, labeling, or analyses of this project until the DSMC releases results of the trial.

Analyses and interpretation of data are planned to be completed within 1 year of the receipt of specimens.

e. Data Analysis

Natera will report ctDNA levels to SWOG Statisticians. SWOG statisticians will perform all analyses linking ctDNA results with patient-level data.

f. Specimen Information

Exome sequencing and ctDNA detection will be performed by Natera and statistical testing will be performed by SWOG statisticians ctDNA and outcome correlation data will be reported to Dr. Allie Grossmann (PI).

The SWOG Biospecimen Bank - Lab #201 will ship the following specimens to Natera on dry ice for overnight delivery as outlined in Section 18.9.c:

1) DNA from FFPE tumor
2) DNA from germline (buffy coat)
3) frozen plasma aliquots

Natera
201 Industrial Road, Suite 420San Carlos, CA 94070

Natera study contact:
Alexey Aleshin, MD, MBA (Medical Director, Oncology)
aaleshin@natera.com
858-335-6526

Specimens used:

Eligible patients who received ipilimumbab or pembolizumab on **S1404**. This proposal requires:

- primary tumor or lymph node metastasis AND plasma AND buffy coat from baseline,
- plasma at start of cycle 3 (if relapsed after start of cycle 3),
- plasma at start of cycle 4 (if relapsed after start of cycle 4),
- plasma at removal from protocol therapy or relapse.

50 patients from each arm will be selected with a 1:1 case control design as follows:

- control arm (patients who received IFN)
  - n=25 patients who relapsed within 2 years
  - n=25 patients who were alive without relapse at 2 years
- pembrolizumab arm
  - n=25 patients who relapsed within 2 years
  - n=25 patients who were alive without relapse at 2 years

We note that treatment arm information will not be released until the DSMC releases the treatment arm results of the trial.

References for 18.10

1 Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.05282.

2 Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma [published online ahead of print May 6, 2019]. *J Clin Oncol*. 2019. doi:10.1200/JCO.18.02052.

3 Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.

4 Coombes RC, Page K, Salari R, et al. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence [published online ahead of print April 16, 2019]. *Clin Cancer Res*. 2019. doi:10.1158/1078-0432.CCR-18-3663.

5 Reinert T, Henriksen TV, Christensen E, et al. Analysis of plasma cell-free DNA by ultradeep sequencing in patients with stages I to III colorectal cancer. *JAMA Oncol*. 2019. doi:10.1001/jamaoncol.2019.05282.

6 Christensen E, Birkenkamp-Demtröder K, Sethi H, et al. Early detection of metastatic relapse and monitoring of therapeutic efficacy by ultra-deep sequencing of plasma cell-free DNA in patients with urothelial bladder carcinoma [published online ahead of print May 6, 2019]. *J Clin Oncol*. 2019. doi:10.1200/JCO.18.02052.

7 Abbosh C, Birkbak NJ, Wilson GA, et al. Phylogenetic ctDNA analysis depicts early-stage lung cancer evolution. *Nature*. 2017;545(7655):446-451.

8 Coombes RC, Page K, Salari R, et al. Personalized detection of circulating tumor DNA antedates breast cancer metastatic recurrence [published online ahead of print April 16, 2019]. *Clin Cancer Res*. 2019. doi:10.1158/1078-0432.CCR-18-3663.

Informed Consent Model for **S1404**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	61.2 (targeted above 55)
Flesch-Kincaid Grade Level	8.9 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices about participating in research. The consent form provides a summary of the study, the individual's rights as a study participant, and documents their willingness to participate. The consent form is, however, only one piece of an ongoing exchange of information between the investigator and study participant. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Study Title for Study Participants: **Testing MK-3475 (Pembrolizumab) Compared to Standard Treatment for High Risk Resected Melanoma** *(updated 2/19/16)*

Official Study Title for Internet Search on http://www.ClinicalTrials.gov: ***S1404*** *A Phase III Randomized Trial Comparing Physician/Patient Choice of Either High Dose Interferon or Ipilimumab to MK-3475 (Pembrolizumab) in Patients with High Risk Resected Melanoma.*

What is the usual approach to high risk melanoma?

You are being asked to take part in this study because you have melanoma, which, although it has been successfully treated with surgery, has a high probability of coming back.

There are several treatment options for high risk resected melanoma. These include: 1) high dose interferon alfa-2b, 2) a different version of interferon (called "pegylated" interferon), and 3) ipilimumab which was recently approved by the FDA. However, only some patients benefit from these treatments. Though a choice of either high dose interferon alfa-2b or ipilimumab has been selected as the standard treatment option for this study, please talk with your doctor about alternatives before finalizing your decision to take part in this study. We hope to find a more effective and long-lasting treatment for your type of cancer.

What are my other choices if I do not take part in this study?

Your other choices may include:

- **You may choose to have the usual approach, described above**
- **You may choose to take part in a different study, if one is available**
- **You may choose not to have treatment at this time, but continue to have your disease checked periodically.**

Talk to your doctor about your choices before you decide if you will take part in this study.

Why is this study being done?

The purpose of this study is to compare the effects, good and/or bad, of the experimental drug MK-3475 (also called pembrolizumab) to the usual treatment of either interferon alfa-2b or ipilimumab. This study will allow the researchers to know whether treatment with MK-3475 (pembrolizumab) is better, the same, or worse than usual treatment. In this study, you will get either MK-3475 or a choice of either interferon alfa-2b or ipilimumab. There will be about 1,378 people taking part in this study.

What are the study groups?

This study has two study groups (also called study "arms"). A computer will by chance assign you to one of the two study arms. This is called randomization. This is done by chance because no one knows if one study arm is better, the same, or worse than the other arm. Once you are put on one arm, you cannot switch to the other arm. Neither you nor your doctor can choose which arm you will be in.

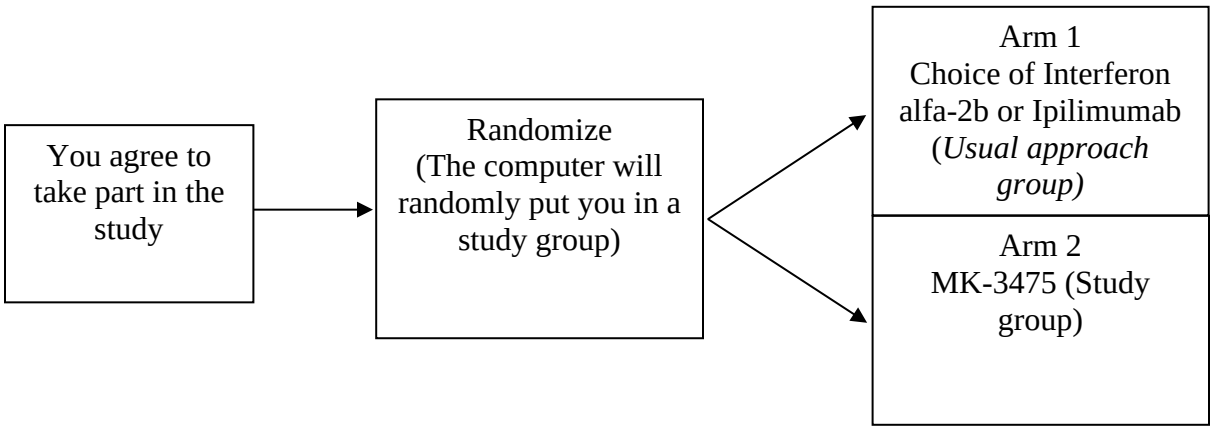
If you are in Arm 1, you will receive either interferon alfa-2b or ipilimumab in two stages, called the induction phase and the maintenance phase.

If you choose to get interferon alfa-2b, in the induction phase you will receive interferon alfa-2b for 5 consecutive days (Mon-Fri) out of 7 days, for four weeks. This will be done by intravenous infusion (given through a vein in your arm) over a 20 minute period. These infusions will be given in an outpatient setting. In the maintenance phase, you will receive interferon alfa-2b three times weekly, every other day (Mon, Wed, Fri) for 48 weeks. This will be done by subcutaneous injection (just below the skin). You will be taught how to self administer the interferon subcutaneous injections. You will be asked to keep track of your injections with a written interferon calendar which will be reviewed during visits to your doctor's office or clinic.

If you choose to get ipilimumab, in the induction phase you will get ipilimumab by an infusion into your vein over 90 minutes. This infusion will be given as an outpatient. During the induction phase you will get the infusion once every three weeks for four doses. In the maintenance phase, you will get ipilimumab by an infusion into your vein over 90 minutes. This infusion will be given as an outpatient. During the maintenance phase you will get the infusion once every twelve weeks for about twelve doses (total treatment time will be a maximum of three years).

If you are in Arm 2 you will receive MK-3475 (pembrolizumab) by intravenous infusion over a 30 minute period. This infusion will be in the outpatient setting. You will receive MK-3475 (pembrolizumab) infusions every three weeks for eighteen doses (approximately one year).

Another way to find out what will happen to you during the study is to read the chart below. Start reading at the left side and read across to the right, following the lines and arrows.



How long will I be in the study?

You will receive study drugs for one year if you get interferon alfa-2b or MK-3475 (pembrolizumab) or three years if you get ipilimumab. After you are finished with study treatment, the doctor will ask you to visit the office for follow-up exams. For interferon alfa-2b or MK-3475 (pembrolizumab), the first visit will be 6 weeks (-/+ 1 week) after the last dose of the study drug. The next visit will be 12 weeks (-/+ 1 week) after the last dose of the study drug, then there will be a visit every 3 months for the first two years, then every 6 months for Years 2-5, then every 12 months for the next 5 years. For ipilimumab, the first visit will be 6 weeks after the last dose of the study drug, then every 6 months for Years 4-5, then every 12 months for the next 5 years. Follow-up exams will take place for up to 10 years as long as your disease does not reoccur. If you come off of study treatment because your disease comes back, your overall condition will be followed every 6 months for 1 year, then annually until 10 years from the date you began the study. We would like to keep track of your medical condition for 10 years from the date the study started to look at the long-term effects of the study treatment.

What extra tests and procedures will I have if I take part in this study?

Before you begin the study:

All of the exams, tests, and procedures you will have before you begin the study are part of the usual approach for your cancer. The one test that is not standard is a test to determine a biomarker* called PD-L1.

It is likely that your melanoma was removed through surgery and it is customary for the melanoma tissue to be preserved in a paraffin embedded block. This study requires that a minimum of five slides, made from the tissue block, be sent to a central laboratory for staining and determination of a biomarker called PD-L1. (*A biomarker can be a genetic feature or specific protein found in the tumor sample). Submission of these slides is required because the research on the tissue sample is an important part of the study.

In addition to the slides submitted to the central lab for testing, you will be given the option to submit slides for banking for future studies. You can indicate whether you will allow your specimens to be banked for future studies in the section called "Optional Studies".

Neither you nor your health care plan/insurance carrier will be billed for the collection of the tissue that will be used for this study.

During the study:

If the exams and tests show that you can be in the study, and you choose to take part, then you will need the following extra tests and procedures. They are not part of the usual approach for your type of cancer and are being done because you are participating in this study.

- If you are on Arm 2 (MK-3475), you will be required to provide blood samples for additional testing to measure the amount of study drug that is in it and for antibody testing. These blood samples will be collected before you receive your study treatment the day of your infusion before the infusion at Week 1, Week 4, Week 10, Week 19, Week 25, and Week 49. Additionally, a sample will be obtained 30 days after you are off protocol treatment. The total amount of blood taken each time for this testing is about two teaspoons. This is not part of regular cancer care, but is being done as part of this research study.
- Questionnaires – You will complete three questionnaires (which will take about 10 minutes to complete) to collect information about how you are feeling physically and emotionally during your treatment and how you are performing your daily activities. These questionnaires are required for patients who can fill out the questionnaires in English, Spanish or French. The questionnaires will be given to you at the beginning of the study (before you start treatment), Weeks 1, 4, 13, 25, 37 and 48 then 24 and 48 weeks after the date of your last treatment. If any questions make you feel uncomfortable, you may skip those questions and not give an answer. We will do our best to make sure that your personal information will be kept private. This is not part of regular cancer care, but is being done as part of this research study.

What possible risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **The study approach may not be better, and could possibly be worse, than the usual approach for your cancer.**
- **You may be asked sensitive or private questions which you normally do not discuss**

The drugs used in this study may affect how different parts of your body work, such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Possible Side Effects of interferon alfa-2b (Table Version Date: March 16, 2017)

COMMON, SOME MAY BE SERIOUS In 100 people receiving interferon alfa-2b, more than 20 and up to 100 may have:
• **Infection, especially when white blood cell count is low** • **Diarrhea, nausea, vomiting** • **Flu-like symptoms including body aches, muscle pain** • **Tiredness** • **Weight loss** • **Loss of appetite** • **Anemia which may require blood transfusions** • **Headache** • **Depression, thoughts of suicide** • **Hair loss** • **Pain** • **Fever, Chills**

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving interferon alfa-2b, from 4 to 20 may have:
• **Heart failure or attack which may cause shortness of breath, swelling of ankles, cough or tiredness** • **Abnormal heartbeat** • **Low blood pressure** • **Change in skin color, numbness or pain in fingers and toes** • **Diabetes** • **Internal bleeding, which may cause black tarry stool, blood in vomit** • **Liver damage which may cause yellowing of eyes and skin, or confusion** • **Bruising, bleeding** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Damage to organs** • **Swelling of the body** • **Confusion** • **Stroke, coma** • **Blurred vision with chance of blindness, visual loss** • **Bleeding of the eye** • **Blockage of the lungs or lung collapse** • **Damage to the blood vessel in lungs** • **Blood clot**

RARE, AND SERIOUS In 100 people receiving interferon alfa-2b, 3 or fewer may have:
• **None**

Possible Side Effects of Ipilimumab

Special precautions

Side effects of ipilimumab (MDX-010) may happen anytime during treatment or even after your treatment has ended. Some of these problems may happen more often when ipilimumab (MDX-010) is used in combination with BMS-936558 (nivolumab). **Call or see your healthcare provider right away if you develop any problems listed below or the symptoms get worse.**

COMMON, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), more than 20 and up to 100 may have:

- **Diarrhea, nausea**
- **Tiredness**

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Skin: itching; rash, blisters including inside the mouth (can be severe); hives**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving ipilimumab (MDX-010), from 4 to 20 may have:

- **Abnormal heartbeat**
- **Hearing loss**
- **Swelling and redness of the eye**
- **Pain**
- **Difficulty swallowing, eating**
- **Constipation, vomiting**
- **Weight loss, loss of appetite**
- **Fever**
- **Dehydration**
- **Pain or swelling of the joints**
- **Reaction during or following a drug infusion which may cause fever, chills, rash**
- **Low blood pressure which may cause feeling faint**

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Lung problems (pneumonitis). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling.**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine.**
- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs and facial muscle movement.**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.**

RARE, AND SERIOUS

In 100 people receiving ipilimumab (MDX-010), 3 or fewer may have:

- **Bleeding**
- **Blockage of the bowels which may cause constipation**
- **Fluid around heart**
- **Severe illness with multiorgan failure**
- **Confusion**

Ipilimumab (MDX-010) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in coma**
- **Heart problems including swelling and heart failure. Symptoms and signs of heart problem may include: Shortness of breath, swelling of the ankle and body.**
- **Complications associated with stem cell transplant using donor stem cells (allogeneic stem cell transplant). These complications are caused by attack of donor cells on the host organs (inducing liver, skin and gut), and can lead to death. If you are considering an allogeneic stem transplant after participating in this study, please tell your doctor that you have received ipilimumab therapy, since the risk and severity of transplant-associated complications may be increased.**
- **Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck.**

*This is applicable for patients who have undergone a stem cell transplant.

You should tell your doctor if you develop any diarrhea, constipation, any change in your bowel movements, have blood in your stool, or have abdominal pain or pain when swallowing. Your doctor may want to perform tests to better understand why you have these symptoms. These tests will allow your doctor to look at your intestine for damage. It may also help determine the type of treatment you might need, which may include the use of steroids. You may have to go into the hospital for doctors to investigate and treat the diarrhea or other stomach/intestinal symptoms.

Ipilimumab may increase your chance of bowel perforation. A bowel perforation means that your bowel has developed a hole which allows the contents of your intestine to leak into the abdomen. This is considered a medical emergency as it causes a severe infection which can result in death. It has also been reported that patients with bowel metastasis of melanoma (melanoma cancer which has spread to the bowel) might be at higher risk of bowel perforation, which could also result in death. If you know you have diverticulum (protrusion of soft tissue through the colonic wall) and/or diverticulitis (inflammation in

the diverticulum), you need to tell your doctor and your doctor will evaluate whether it is appropriate to treat you with ipilimumab.

Contact your doctor if you experience weakness of your limbs with or without numbness or tingling. Some patients may experience a sensation of tingling, tickling, prickling or burning of a person's skin with unknown long-term physical effect. In rare cases, the immune system may attack skeletal muscles (myasthenia gravis) or the nerves that control muscles (Guillain-Barre Syndrome), which could be life-threatening if not treated appropriately.

Risk Profile for MK-3475 (pembrolizumab)

(CAEPR Version 2.5, December 27, 2019)

COMMON, SOME MAY BE SERIOUS
In 100 people receiving MK-3475 (pembrolizumab), more than 20 and up to 100 may have:
• **Tiredness**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), from 4 to 20 may have:

- **Nausea**
- **Infection**
- **Loss of appetite**
- **Pain in back**
- **Joint stiffness**
- **Cough**
- **Swelling and redness of the skin**

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Anemia which may require blood transfusion**
- **Pain in lymph nodes**
- **Blood clot which may cause bleeding, confusion, paralysis, seizures and blindness**
- **Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting**
- **Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness**
- **Diarrhea**
- **Sores in the mouth which may cause difficulty swallowing**
- **Pain in belly**
- **Sores in the bowels**
- **Chills, fever**
- **Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly**
- **Pain or swelling of the joints**
- **Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine**
- **Fluid in the joints**
- **Pain in chest**
- **Lung problems (pneumonitis and other conditions). Symptoms may include: new or worsening cough, chest pain, shortness of breath.**
- **Skin: itching; acne; rash (can be severe); blisters and peeling on the skin, mouth; skin changes; hives**

RARE, AND SERIOUS

In 100 people receiving MK-3475 (pembrolizumab), 3 or fewer may have:

- **A syndrome starting with flu-like symptoms and followed by swelling, tenderness which may cause flu-like symptoms, blurred vision, ringing in the ears, changes in hair or hair loss**
- **Swelling of the spinal cord**
- **Feeling of "pins and needles" in arms and legs**
- **Redness, pain or peeling of palms and soles**

MK-3475 (pembrolizumab) may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- **Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: Shortness of breath, swelling of the ankles and body**
- **Swelling and redness of the eye**
- **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat**
- **Reaction during or following a drug infusion which may cause fever, chills, rash**
- **Damage to organs in the body when donor cells attack host organs which may cause yellowing of eyes and skin, itchy dry skin**
- **Damage to organs in the body when the body produces too many white cells**
- **A condition with high blood sugar which leads to tiredness, frequent urination, excessive thirst, headache, nausea and vomiting, and can result in a coma**
- **Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs**
- **Swelling of the brain (encephalitis/meningitis) which may cause headache, confusion, sleepiness, seizures, and stiff neck**
- **Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling**
- **Swelling or tenderness of blood vessels**

Pembrolizumab works by helping your immune system to fight your cancer. However, pembrolizumab can also cause your immune system to attack normal organs and tissues in your body and can affect the way they work, which can result in side effects. These side effects may be serious (i.e. causing hospitalization or be life-threatening), may result in death, and/or may occur after you stop taking pembrolizumab. These side effects can affect more than one of your normal organs and tissues at the same time.

Risks of Venipuncture/Intravenous Needle Insertion:

Occasional, some may be serious: Mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Rare: Severe pain, swelling, infection from the actual injection, and fainting.

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. With regard to interferon alfa-2b, ipilimumab or MK-3475, women of childbearing potential and men must agree to use adequate contraception (barrier method of birth control or abstinence) prior to study entry and for the duration of study participation through 120 days after receiving the last dose of treatment. If you become pregnant while receiving treatment on this study, you should inform your doctor immediately and stop the study drug. Two birth control methods are required for MK-3475 (two barrier methods, barrier method plus hormonal method, or barrier method plus IUD).

What possible benefits can I expect from taking part in this study?

This study may or may not help you because it is not possible to know at this time if the study drug is better than the usual approach. This study may help researchers learn things that may help people in the future.

Can I stop taking part in this study?

Yes, you can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The MK-3475 (pembrolizumab) will be supplied at no charge while you take part in this study. It is possible that the drug may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options. Interferon alfa-2b and ipilimumab are commercially available and will not be supplied for this study.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The study sponsors will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The study sponsor, SWOG, Alliance, ECOG-ACRIN, CCTG, NRG and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- IROC - Your medical images will be transferred to the Ohio State University in Columbus, Ohio. Your medical images will be reviewed by investigators at this organization as part of the quality control for this study.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

ADDITIONAL STUDIES SECTION:

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of “yes” or “no” for each of the following studies.

Optional Research Studies that Involve Specimens

Please note: This section of the Informed Consent Form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be part of the main study even if you say “no” to taking part in the additional studies.

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part, samples of your tissue and blood will be used. The researchers ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called “biobanking”. The Biobank is being run by SWOG and supported by the National Cancer Institute.

What is involved?

If you agree to take part, here is what will happen next:

1) A sample from the tissue that was collected at the time of your surgery or biopsy will be sent to the Biobank for use in future studies. A sample of tissue will also be sent at the time of relapse should this occur. Blood samples will also be collected at the following times: Before you begin study treatment, at the start of Cycle 3 (Weeks 13 if there are no dose delays), at the start of Cycle 4 (Week 25 if there are no dose delays), at the time you are removed from study treatment for any reason and at relapse. *(9/29/16)*
2) Your samples will be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.
3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will Information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. Your samples may be helpful to research. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial).*

Please circle your answer to show whether or not you would like to take part in each option:

SAMPLES FOR FUTURE RESEARCH STUDIES:

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

2. My samples and related information may be kept in a Biobank for use in future health research.

Yes No

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature

_____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).