A US Intergroup Trial of Response-Adapted Therapy of Stage III–IV Hodgkin Lymphoma using Early Interim FDG–PET imaging (SWOG S0816)

Press, et al

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Distribution Date: January 15, 2015
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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: Megan M. Hardin, Protocol Coordinator (E-mail: mhardin@swog.org)

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Chairs: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #15

Study Chair: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #15

The protocol referenced above has been revised as follows:

1. Pages 1 and 3, Title Page: The version date has been updated to the protocol and Model Consent Form. The participant list has been moved from Page 1 to Page 3 and revised to be consistent with the new NCTN/CTSU guidelines.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE

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November 1, 2014

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Megan M. Hardin, Protocol Coordinator (mhardin@swog.org)

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Chairs: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Chair: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
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- ( ) 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 of a change to the Master Forms Set for the above-noted study.

The **S0816** Hormone Level Form, Form #500001, has been updated as follows:

Data fields for decimals have been added to the lab value columns on this form. The form date has been updated to 11/1/14.

The 11/1/14 version of this form can be accessed from the Master Forms Set link on the **S0816** protocol abstract page of the SWOG website (http://swog.org).

This memorandum serves to notify the NCI and the SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Hongli Li, M.S.
Jeri Jardine
Iris Syquia

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Distribution Date: March 1, 2014
CTEP Submission Date: February 13, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Chairs: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #14

Study Chair: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #14

The protocol referenced above has been revised as follows:

1. Title Pages, Pages 1-3: The version date has been updated. "Study Coordinator" has been changed to "Study Chair". This change has also been made to Section 7.1 (Page 31), Section 7.2 (Page 32), Section 8.2a (Page 39), Section 8.6 (Page 43) and Section 11.3 (Page 53).

2. Page 2, Title Page: "Southwest Oncology Group" has been changed to "SWOG". This change has been made to the CTSU table (Page 6) and Sections 7.0 (Page 31), 14.3a (Page 57), 15.2 (Pages 59-61), 16.1b (Page 63) and 16.1f.2 (Page 65).

3. Pages 2-5, Title Page and Table of Contents: The Table of Contents has been labeled and moved behind the participant and Study Chair information per updated SWOG standard.

4. Page 47, Section 9.2: The "*" footnote has been revised as follows: "For patients who have not progressed,…" has been added to the beginning of the second sentence. The following sentence has been added to the end of this footnote: "For patients who have progressed, only hormone levels will be done annually until Year 7, other follow-up tests and CT scans are not required, and patients will be followed for survival." This change has also been made to Section 9.3 (Page 49).

5. Page 58, Section 14.4f: This section has been added to the protocol and the Hormone Level Form can be found in the forms packet which is available on the **S0816** abstract page (www.swog.org). See the attached letter from Dr. Press regarding this submission requirement. This section reads as follows:

   "f. AT BASELINE, AT THE TIME OF RESTAGING, DAY 365, THEN ANNUALLY UNTIL 7 YEARS AFTER REGISTRATION (for the first time submission include all measurements at prior time points):

   Submit the Hormone Level Form."

6. Page 63, Section 16.0: The following standard statement has been added to the end of this section:

   "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."

The protocol has been reformatted and repaginated to meet the current requirements for electronic protocol submission. This includes addition of second level headings in instances where they were previously absent, reformatting the title page to include all second level headings, reformatting the protocol calendar into M.S. Word, removal of form numbers and removal of the consent form and data collection forms as Section 18.0. References and page numbers affected by these changes have been updated throughout the protocol. Information in Section 11.0 has been rearranged to better fit with the new format but content was not affected.

The Version Date of the Model Consent Form has been added. There have been no additional changes to the Model Consent Form.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Hongli Li, M.S.
Jeri Jardine
Iris Syquia

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February 13, 2014

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Dear SWOG Investigator,

Thank you for enrolling patients on the SWOG Protocol **S0816**: "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". One of the secondary objectives of this protocol was to serially monitor hormone levels as a rough indicator of fertility. Unfortunately, the original protocol data submission forms did not capture this information and we are therefore requesting your assistance in completing the **S0816** Hormone Level Form (as per Section 14.4f) for patients you've enrolled on this study. All retrospective data will need to be submitted to the SWOG Data Operations Center no later than July 31, 2014.

Thank you very much for your cooperation with this important objective.

Sincerely,

Oliver W. Press, MD, PhD
Principal Investigator, SWOG Protocol **S0816**
Acting Senior Vice President, Fred Hutchinson Cancer Research Center
Acting Director and Member, Clinical Research Division, FHCRC
Recipient, Dr. Penny E. Peterson Memorial Chair for Lymphoma Research
Professor of Medicine and Bioengineering, University of Washington
Co-Chair, NCI Lymphoma Steering Committee

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November 15, 2012

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TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

STATUS NOTICE

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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

PERMANENT CLOSURE

The study referenced above has reached its accrual goal and will be permanently closed to accrual **effective December 1, 2012**. Registration will be open until 11:59 p.m. PST on Saturday, December 1, 2012.

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Hongli Li, M.S.
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Distribution Date: October 1, 2012
CTEP Submission Date: September 13, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #13

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #13

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated.

2. Page 49, Section 15.2: The url for the AG Mednet imaging workflow and instructions has been revised.

3. Master Forms Set: The **S0816** Prestudy Form (Form #47588) has been revised to allow for two digits plus a decimal for serum testosterone. This change does not require a new form number or date.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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Distribution Date: August 15, 2012
E-mailed Date: August 10, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
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- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

SWOG has been notified that several patients enrolled on the BEACOPP escalated arm of **S0816** have had difficulties acquiring procarbazine (Matulane) due to the fact that the drug is oral, expensive and coverage by several third party payors is sometimes inadequate. To address these concerns, please note the following drug ordering guidelines:

For patients with adequate insurance, procarbazine is ordered through Accredo Health Specialty Pharmacy by completing the online *Prescription & Enrollment Form* (Form posted online at http://www.accredo.com/referral/Matulane.pdf). The form must be completed by the physician and faxed to 888/302-1028. For questions, please call Accredo at 888/608-9010. Additionally, any pharmacy may order procarbazine to dispense to patients through Accredo's wholesale division at 877/900-9223. More information can be found online at www.matulane.com/obtain-matulane.asp.

Patients who are without insurance or are underinsured may apply for assistance by contacting NORD's medication assistance programs:

Matulane Reimbursement Assistance: 800/490-3262
Matulane Patient Assistance Program: 800/999-6673 ext. 336
Hodgkin Lymphoma Co-Pay Program for Matulane: 800/999-6673 ext. 457

If difficulties persist, please contact Dr. Oliver Press who will try to intervene and facilitate drug access.

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: July 15, 2012
CTEP Submission Date: July 5, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #12

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #12

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on **S0816**, and patients who sign a consent form prior to Institutional Review Board (IRB) approval and local implementation of the consent form changes **must** be informed of these changes. The manner of which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified at the next visit and this notification process must be documented in the patient chart.

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated. Hongli Li has replaced Bryan Goldman in the list of Biostatisticians.

2. Page 33, Section 7.10b: This section has been revised as follows:

   - Section 7.10b.1 - "…then every 4 months for Year 2, then every 4-6 months for Years 3-5, then annually." has been replaced with "…then every 6 months for Years 2-5, then annually until Year 7."

   - Sections 7.10b.2 and 7.10b.3 have been replaced with a new Section 7.10b2 as follows:

     "Follow-up tests at each time point will be the same as those listed above in Section 7.10a except:

     a) FSH, LH and estradiol or testosterone levels will be drawn once per year.
     b) Contrast-enhanced CT Scans will only be done every 6 months in Year 2 and annually in Years 3-5. CT scans are not required after Year 5. No PET/CT scans are required after the "end of treatment" scan."

     Previously CT scan was listed at Restaging and Day 365 only during follow-up, and CBC and chemistries were performed at every follow-up visit with no guidance listed for hormone level timing.

3. Pages 39-40, Sections 9.2 and 9.3: The "*" footnote has been revised to be consistent with Section 7.10b. The footnote now reads, "Follow-up evaluations will occur at Days 276 and 365, then every 6 months for Years 2-5, then annually, until Year 7. Follow-up tests at each time point will be the same as those listed at Day 365 except hormone levels will only be done once per year and CT Scans will only be done every 6 months in Year 2 and annually in Years 3-5. CT scans are not required after Year 5." Previously follow up was listed as every 4 months for Year 2, every 4-6 months for Years 3-5, then annually until Year 7; there was no guidance included for CT scans.

4. Page 48, Section 14.13: "EVERY SIX MONTHS FOR 2 YEARS…" has been revised to "EVERY SIX MONTHS FOR YEARS 2-5…" to be consistent with Section 7.10b.

5. Page 65, Model Informed Consent: "…then every 4 months for Year 2, then every 4-6 months for Years 3-5…" has been changed to "…then every 6 months for Years 2-5…" in the "How long will I be in the study?" section to be consistent with Section 7.10b.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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Distribution Date: February 15, 2012
E-mailed Date: February 2, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
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( ) Addition of tissue banking requirements
( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

MEMORANDUM

Due to the national shortage of vinblastine, institutions without appropriate vinblastine supply to treat currently enrolled patients according to the protocol schedule may substitute **vincristine** as follows:

- **Vincristine** 1.4 mg/m^2 with a cap of 2 mg.

If **vincristine** is given, it must be documented on the **S0816** Treatment Form (Form #11453) in the comment section. Start and end dates along with the total vincristine dose given for the reporting period must be recorded in the comments section. Documentation stating that this substitution is due to a vinblastine shortage is required.

This allowance is being made only for instances when vinblastine is not available due to the nation wide drug shortage. Any questions regarding this temporary allowance should be directed to the Study Coordinator.

This substitution is acceptable only for patients who are currently on study, which is defined as already having signed the consent form. New patients should not be consented to **S0816** if the local supply of vinblastine is not adequate to begin and complete the patient on vinblastine as described in the protocol.

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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Distribution Date: February 1, 2012
CTEP Submission Date: January 26, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Hardin, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #11

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #11

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated.

2. Page 25, Section 5.11: The following sentence has been revised for clarity: "Serum FSH, LH, estradiol (women only) and testosterone (men only) levels must be drawn within 60 days prior to registration, to obtain baseline values." The sentence now reads "Serum estradiol (women only), testosterone (men only), FSH and LH (both men and women) levels must be drawn within 60 days prior to registration, to obtain baseline values."

3. Pages 25-25a, Section 5.18: This section has been revised with new standard language for contraceptive methods in women of reproductive potential. Page 25a was added to prevent extensive repagination.

4. Page 48, Section 14.12: The Lymphoma Follow-Up Tumor Assessment form number has been changed from Form #64395 to Form #33912. This change has also been made to Section 18.2i (Page 60).

5. Master Forms Set: The Lymphoma Follow-Up Tumor Assessment Form (Form #64395) has been replaced with the Lymphoma Follow-Up Tumor Assessment Form (Form #33912). A section has been added to document any new lesions that may show up on restaging scans.

6. Pages 107-108, Section 19.5: The instructions for reporting adverse events in an expedited manner have been revised with new standard language which was prompted in response to the FDA's final ruling on reporting requirements.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Jeri Jardine
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swog.org

Distribution Date: December 15, 2011
CTEP Submission Date: November 29, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #10

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #10

Institutions **should** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated.

2. Page 71, Model Consent Form: For registrations occurring after December 15, 2011 funds are no longer available to reimburse for the Cycle 2 pet scan. Therefore, "for patients registered up to December 15, 2011" has been added to the first sentence of the second paragraph.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
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Distribution Date: December 1, 2011
E-mailed Date: November 29, 2011

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swog.org

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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

Effective for registrations occurring as of December 15, 2011, funds are no longer available to reimburse the Cycle 2 pet scan. As this test is now accepted as standard of care, this test should be billed to patient insurance where allowed by the individual insurance and local coverage rules. Please note, in the event that a patient has Medicare, the Secondary Payor Rule applies and Medicare cannot be charged for this.

A revision to the Model Consent Form is forthcoming.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: November 15, 2011
CTEP Submission Date: November 7, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #9

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #9

Institutions **should** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated. "Southwest Oncology Group" has been updated to "SWOG" above the title.

2. Page 25, Section 5.22: The references to Sections 15.5 and 15.6 have been updated to 15.2 and 15.3. This change has also been made throughout the protocol on Pages 27 (Section 7.2), 28-29 (Sections 7.5a, 7.5b and 7.5d), 38-40 (Sections 9.1-9.3, "Δ" footnotes), 47 (Section 14.8), 98 (Section 19.2), and Pages 100 and 102 (Section 19.2).

3. Pages 44-45, Sections 12.1 – 12.5: The following changes have been made:

   - Section 12.1 – The following language has been added to refer sites to the SWOG specimen submission website:

     "a. Pathology materials collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/Members/ClinicalTrials/Specimens/Lymphpath.asp)."

   - Sections 12.2-12.4 have been removed as all of the relevant information is on the SWOG Specimen Submission webpage.

   - Section 12.5 (previously on Page 45) has been moved to Section 12.1b.

4. Page 47, Section 14.5: The name of the SWOG Repository has been revised from "Southwest Oncology Group Lymphoma Repository-University of Arizona" to "SWOG Specimen Repository Solid Tumor, Myeloma and Lymphoma Division".

5. Pages 48-52, Sections 15.1 – 15.6: Section 15.1 (previously only containing the specimens to be collected and the collection timepoints) has been renamed "Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201) optional for patient:" The specimen submission timepoints have been retained as Section 15.1a but the specimen collection and shipping instructions from Sections 15.2-15.4 have been replaced by a reference to the SWOG specimen submission webpage in Section 15.1b and Sections 15.2-15.4 have been deleted. Section 15.1c has been added to instruct that no specimen collection kits are provided for this submission. Sections 15.5 and 15.6 have been renumbered to 15.2 and 15.3, respectively. Pages 51 and 52 have been left blank intentionally to prevent extensive repagination.

6. Page 74, Model Consent Form: The location and contact information for the SWOG Lymphoma Repository have been removed.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: August 1, 2011
CTEP Submission Date: July 14, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #8

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #8

Institutions **must** update their local consent forms to include the changes to the Model Consent Form.

SWOG considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes.

Patients currently on **S0816**, and patients who have signed a consent form but not yet started treatment, need not be informed of these changes unless required by the local Institutional Review Board (IRB).

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated.

2. Page 3, CTSU information: This page has been revised with new contact information for CTSU.

3. Page 13, Section 2.0: The ethnic/racial accrual table in this section has been revised to reflect the new accrual goal.

4. Page 43, Sections 11.2 and 11.4: These sections have been updated to include statistical information for a larger sample size. In order to obtain greater precision for the estimates of outcome and toxicity rate, especially among HIV-negative patients who are FDG-PET-positive after 2 cycles of ABVD, the number of eligible patients in this subgroup has been increased from 40 to 60. This will provide increased power to detect a potentially clinically meaningful result.

5. Page 63, Model Consent Form: The number of people who will take part in the study has been changed from "230" to "300".

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Distribution Date: June 15, 2011
CTEP Submission Date: May 31, 2011

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan M. Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #7

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #7

The protocol referenced above has been revised as follows:

1. Title Page: The version date has been updated. Section 14.0 begins on Page 46a instead of 46. The contact information for Andrew Evens, D.O. (ECOG Study Coordinator) has been updated (Page 2).

2. Page 24, Section 5.0: The **S0816** Prestudy Form number has been updated from #16295 to #47588.

3. Page 24, Section 5.5: The Lymphoma Baseline Tumor Assessment Form number has been updated from #48010 to #48031.

4. Page 25, Section 5.11: This section was moved from Section 7.1 because although the results of these tests do not determine eligibility, they must be completed to obtain a baseline for future comparison, and as such are required prior to registration. This section reads: "Serum FSH, LH, estradiol (women only), and testosterone (men only) levels must be drawn within 60 days prior to registration to obtain baseline values." Subsequent sections have been re-numbered respectively.

5. Page 25, Section 5.14: HIV positive patients are eligible if they have CD4 counts ≥ 150/mcL instead of 350/mcL. This section has been updated respectively. The last sentence had the following language added, "…at the time of enrollment OR if they had a documented CD4 count > 250 at any time within 8 months prior to HL diagnosis, …".

6. Page 26, Section 7.1: In the first sentence, "must be obtained" has been changed to "are recommended". The second sentence has been updated to state that "minor deviations from normal limits would be acceptable …". The following sentence has been updated to reflect new standard language for Good Medical Practice, "The Study Coordinator must be contacted if there are significant deviations in the values of these tests." The sentence now reads as follows, "If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering."

7. Page 26, Section 7.1f: This section was previously labeled 7.1g.

8. Page 33, Section 7.10b.2: "Each follow-up time-point" has been replaced with "Restaging and Day 365" for clarity.

9. Page 37, Section 8.6: This section has been updated to reflect new standard language for toxicity reporting. "Unexpected or fatal toxicities" has been replaced with "toxicities that meet the expedited reporting criteria". The rest of the sentence has been reworded but content not affected.

10. Page 38, Section 9.1: The "ß" footnote has been revised to indicate that the Good Medical Practice assessments at prestudy are recommended rather than required. The "ß" footnote has been removed form the "FSH, LH, and Estradiol or Testosterone Level" to be consistent with Section 5.11. The reference to Section 5.11 in the "∑" footnote has been updated to 5.12.

11. Pages 45-46b, Sections 13.2-13.5: All instructions contained in this section have been updated to contain the OPEN registration system instructions and to remove any other registration systems. The new information includes additional information that will be required by the OPEN system (Section 13.2), updated registration requirements including OPEN enrollment requirements and OPEN access requirements (Section 13.3) and OPEN registration procedures (Section 13.4). The phrase "for either method of registration" has been removed from Section 13.5 as only one registration method will be used now. Pages 46a and 46b have been added to prevent extensive repagination.

12. Page 47, Section 14.4b: The Lymphoma Baseline Tumor Assessment Form number has been updated from #48010 to #48031.

13. Page 47, Section 14.8: The following sentence has been added to this section: "Submit a copy of the interim and end of treatment radiology reports."

14. Page 48, Section 14.12: The Lymphoma Follow-Up Tumor Assessment Form number has been updated from #38305 to #64395.

15. Page 60, Section 18.2c: The **S0816** Prestudy Form (Form #16295) has been updated to Form #47588. The form date has been updated to 6/15/11.

16. Page 60, Section 18.2g: The Lymphoma Baseline Tumor Assessment Form (Form #48010) has been updated to Form #48031. The form date has been updated to 6/15/11.

17. Page 60, Section 18.2i: The Lymphoma Follow-Up Tumor Assessment Form (Form #38305) has been updated to Form #64395. The form date has been updated to 6/15/11.

18. Master Forms Set: The SWOG **S0816** Registration Worksheet-Step 1 (Form #16263) and the **S0816** Registration Worksheet-Step 2 (Form #43815) have been replaced by the **S0816** Registration Worksheet-Step 1 (Form #54892) and the **S0816** Registration Worksheet-Step 2 (Form #19171) to include OPEN registration. The form numbers have also been updated in Sections 18.2a and 18.2b, respectively (Page 60). The form dates have been updated to 6/15/11.

19. Master Forms Set: The **S0816** Prestudy Form (Form #16295) has been replaced with the **S0816** Prestudy Form (Form #47588).

20. Master Forms Set: The Lymphoma Baseline Tumor Assessment Form (Form #39601) has been replaced with the Lymphoma Baseline Tumor Assessment Form (Form #48031). NOTE: Form #39601 was errantly listed as #48010 throughout the protocol for the Lymphoma Baseline Tumor Assessment Form. The form numbers are now consistent throughout the protocol.

21. Master Forms Set: The Lymphoma Follow-Up Tumor Assessment Form (Form #27780) has been replaced with the Lymphoma Follow-Up Tumor Assessment Form (Form #64395). NOTE: Form #27780 was errantly listed as #38305 throughout the protocol for the Lymphoma Follow-Up Tumor Assessment Form. The form numbers have been corrected throughout the protocol.

22. Pages 97-97a, Appendix 19.1: The CTSU Procedures for Patient Enrollment have been updated to include the new OPEN registration system instructions and to remove all previous CTSU registration instructions. Page 97a has been added to prevent extensive repagination.

Please append this notice to the front of your copy of the protocol and insert the replacement pages.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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swog.org

February 1, 2011

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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

Due to the national shortage of bleomycin, institutions without appropriate bleomycin supply to treat currently enrolled patients according to the protocol schedule may omit the drug until available.

If bleomycin is omitted, it must be documented on the **S0816** Treatment Form (Form #11453) in the comment section. Documentation stating that this omission is due to a bleomycin shortage is required.

This allowance is being made only for instances when bleomycin is not available due to the nation wide drug shortage. Any questions regarding this temporary allowance should be directed to the Study Coordinator.

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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December 15, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS AND PATHOLOGISTS

FROM: SWOG Operations Office

RE: Myeloma/Lymphoma repository Closure

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 of the holiday closure schedule for the Lymphoma/Myeloma Specimen Repository. The repository will be closed from December 24, 2010 through January 2, 2011, and will not be accepting shipments between those dates. Please plan your specimen shipments accordingly.

The upcoming holiday closure schedule pertains to the following studies:

SWOG-8819 Lymphoma
SWOG-8947 Lymphoma
SWOG-9245 Lymphoma
S0120 Myeloma
S0777 Myeloma
S0801 Myeloma
S0806 Myeloma
S0816 Myeloma

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and SWOG Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
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Monica Toth
Michel Kelly – CALGB
Ryan Palmer – ECOG
Maddy Balois Oullette - CTSU
Kathleen DeRose – GlaxoSmithKline
Millenniium – CTEP Updates Desk
Tom Street – Celgene
Laura cannon- AG Mednet

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Distribution Date: December 1, 2010
E-mailed: November 18, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

MEMORANDUM

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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

Due to the national shortage of doxorubicin, institutions without appropriate doxorubicin supply to treat currently enrolled patients according to the protocol schedule may substitute pegylated liposomal doxorubicin (Doxil) for doxorubicin as follows:

1. ABVD regimens - pegylated liposomal doxorubicin 20 mg/m^2.
2. Standard BEACOPP regimens (HIV positive population) - pegylated liposomal doxorubicin 20 mg/m^2.
3. Dose escalated BEACOPP (HIV negative population) - pegylated liposomal doxorubicin 28 mg/m^2.

If pegylated liposomal doxorubicin is given, it must be documented on the **S0816** Treatment Form (Form #11453) in the comment section. Start and end dates along with the total pegylated liposomal doxorubicin dose given for the reporting period must be recorded in the comments section. Documentation stating that this substitution is due to a doxorubicin shortage is required.

This allowance is being made only for instances when doxorubicin is not available due to the nation wide drug shortage. Any questions regarding this temporary allowance should be directed to the Study Coordinator.

This substitution is acceptable only for patients who are currently on study, which is defined as already having signed the consent form. New patients should not be consented to **S0816** if the local supply of doxorubicin is not adequate to begin and complete the patient on doxorubicin as described in the protocol.

Please append this notice to the front of your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Jeri Jardine
Scott Kurruk
Iris Buchanan
Maddy Balois – CTSU

SWOG
Leading cancer research. Together.

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swog.org

Distribution Date: November 15, 2010
CTEP Submission Date: November 5, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS, CTSU

FROM: Megan Wardeski, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #6

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #6

The protocol referenced above has been revised as follows:

1. Title page: The version date has been updated.

2. Pages 33-33a, Section 8.1: The criteria for reporting Adverse Events have been updated. **Effective January 1, 2011** the CTCAE Version 4.0 will be utilized for SAE reporting. The CTCAE Version 3.0 will continue to be utilized for routine toxicity reporting. Page 33a was added to prevent extensive repagination.

3. Pages 55-55a, Section 16.1f: This section has been updated to reflect new standard language for reporting secondary AML/ALL/MDS. Page 55a was added to prevent extensive repagination.

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Jeri Jardine
Scott Kurruk
Iris Buchanan
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: October 1, 2010
Submitted to CTEP: September 22, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Southwest Oncology Group Operations Office

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #5

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #5

The protocol referenced above has been revised as follows:

1. Title page: The version date has been updated.

2. Page 24, Section 5.7: The following statement has been added to this section: "Combined PET/CT scans are required for this study, and older "stand-alone" FDG-PET scans are not adequate for entry to this study."

3. Page 26, Section 7.1: In the first sentence of this section, "should" has been corrected to "must".

4. Page 38, Section 9.1: CT scan of the neck has been added to the list of pre-study x-rays and scans (see Section 7.1). The "*" footnote has been added and it reads, "Advisable in patients with cervical disease. If performed at baseline, however, a neck CT scan MUST be repeated at completion of therapy (if initially abnormal)".

5. Page 47, Section 14.4: The time allowance for submission of prestudy data has been changed to 7 days.

6. Page 101, Section 19.2: The following sentence has been updated to be consistent with Section 7.10a: "To assess the final response after completion of all therapy, patients should have repeat whole body PET/CT scans and diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (and neck, if done at baseline), between 30 and 45 days after completion of the last dose of chemotherapy." It now reads, "To assess the final response after completion of all therapy, patients should have repeat whole body PET/CT scans and diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (and neck, if done at baseline), between 6 and 8 weeks after completion of the last dose of chemotherapy".

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
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Jeri Jardine
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Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: July 1, 2010
Submitted to CTEP: June 21, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #4

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #4

The protocol referenced above has been revised as follows:

1. Title page: The version date has been updated. The participant list has been revised to include the AIDS Malignancy Clinical Trails Consortium (AMC) that will be enrolling patients through the CTSU. A list of appendices was added to the table of contents.

2. Page 2a: Page 2a has been added to prevent extensive repagination. The study coordinators for the AMC and the AMC protocol number have been added to this page.

3. Page 3, CTSU information: This page has been updated to add the AMC to the list of organizations that may participate through the CTSU. Instructions for accessing the members' section of the CTSU website have been added.

4. Page 34, Section 8.2d: "Vincristine" has been corrected to "vinblastine" throughout this section.

5. Page 40, Section 9.3: Under the restaging column of the calendar, "Day 190" has been corrected to "Day 211" as restaging tests are to be done 6-8 weeks after last chemotherapy treatment.

6. Page 70-70a, Model Consent Form: The Cancer Trials Support Unit (CTSU) and the AIDS Malignancy Clinical Trials Consortium (AMC) were added to the list of organizations that may look at or copy patients' medical records. Language specific to AMC sites regarding their certificate of confidentiality was added. Page 70a was added to prevent extensive repagination.

7. The **S0816** Prestudy Form (Form #6085) has been updated to Form #16295. Beta 2 microglobulin has been removed from the Prestudy Form as it does not need to be collected. Form numbers have been updated on Pages 24, 47, and 60.

Institutions **must** update their local consent forms to include the addition of CTSU to the list of organizations that may look at or copy patients' records to the Model Consent Form.

The Southwest Oncology Group considers that the changes to the Model Consent Form **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual **does not** need to be suspended pending implementation of these changes.

Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
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Jeri Jardine
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Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: April 15, 2010
Submitted to CTEP: April 7, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #3

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #3

The above-referenced protocol has been revised as follows:

1. Title page: The version date has been updated.

2. Page 60, Section 18.0: The version date of the **S0816** Adverse Event Form (Form #30313) has changed from 4/1/09 to 7/1/09.

3. Master Forms Set: The **S0816** Adverse Event Form (Form #30313) has been updated. The version date of the updated form is 7/1/09.

4. Pages 97-98, Appendix 19.1: The URL for the CTSU web site has been updated to www.ctsu.org throughout this section.

Also please note: Revision #2 (distributed 4/15/10) included changes to the Model Consent Form but did not provide instructions regarding these changes. Institutions **must** update their local consent forms to include the changes to the Model Consent Form. The Southwest Oncology Group considers that the Model Consent Form changes **do not** represent an alteration in risk-benefit ratio. Therefore, local accrual does **not** need to be suspended pending implementation of these changes. Patients currently on treatment need not be informed of these changes unless required by the local Institutional Review Board (IRB).

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Jeri Jardine
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Iris Buchanan
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: April 15, 2010
Submitted to CTEP: March 29, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #2

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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 #2

The above referenced protocol has been revised as follows:

1. Title Page: The version date has been updated.

2. Page 3: The CTSU member's website has been updated to https://www.ctsu.org.

3. Page 12, Section 2.0: The reference to frozen tissue has been removed from the background section for the correlative study portion of the study as the study does not collect frozen tissue.

4. Page 25, Section 5.22: It has been clarified that the ten day requirement between the interim PET/CT scan and continued ABVD or BEACOPP is from when the PET/CT scan was done and not when the results are sent back to the site.

5. Page 26, Section 7.1: A statement has been inserted that if a test required for Good Medical Practices is deemed unnecessary by the treating physician, rationale for not doing the test must be documented in the patient research record.

6. Page 27, Section 7.3: The **S0816** Treatment Form number has been changed from Form #15524 to #11453.

7. Pages 28-29, Section 7.5: Any references to "PET" scan have been replaced with "PET/CT." In Section 7.5b, the CALGB Imaging Core Lab direct phone number has been inserted along with a statement to call the direct phone number in the event an immediate review is necessary.

8. Page 30, Section 7.7b.3: The typo "cystis" has been corrected to "cystitis."

9. Page 32, Section 7.9 and 7.10: Formatting errors not affecting content have been corrected in these sections.

10. Page 33, Section 7.11a: The reference to Section 10.2f has been corrected to Section 10.2d.

11. Page 33, Section 7.13: It has been clarified that patients are to be followed for a maximum of seven years from registration or until death.

12. Page 38, Section 9.1: The footnote "ß" was updated to reflect the change in Section 7.1.

13. Page 45, Section 13.3: The Southwest Oncology Group Operations office phone number has been updated.

14. Pages 47 and 48, Section 14: The SWOG Operations Office phone number has been updated. The form number for the **S0816** Treatment Form has been changed from #15524 to #11453.

15. Pages 49 and 50, Sections 15.3a and 15.4a: It has been clarified that this is an optional specimen submission and that specimens will be submitted with patient consent.

16. Page 54, Section 16.1e: The SWOG Operations office phone number has been updated.

17. Page 55, Table 16.1 and Section 16.1f: The SWOG Operations office FAX number and address has been updated respectively.

18. Page 63, Model Consent Form: Under "Why is this study being done…" "Blood" has been removed from specimens that are submitted to confirm diagnoses. It has been added that blood may be submitted for research purposes only if patients consent to the optional submission.

19. Page 65, Model Consent Form: Under "How long will I be in the study?" It is clarified that patients will return to their doctor's office for up to 7 years from registration during the follow-up period.

20. Page 60, Section 18.2d: The form number for the **S0816** Treatment Form has been changed from #15524 to #11453.

21. Master Form Set: The **S0816** Treatment Form has been revised.

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
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Scott Kurruk
Iris Buchanan
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

Distribution Date: October 15, 2009
Submitted to CTEP: September 16, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Amanda Vidlak, Protocol Coordinator

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza and J. Cook.

REVISION #1

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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

The above referenced protocol has been revised as follows:

1. Title Page: the version date has been updated.

2. Fast Facts Sheet: The title of the study has been corrected and the dosing has been deleted.

3. Page 5, Section 1.0: The term “secondary endpoints” has been changed to “secondary objectives” to standardize wording.

4. Page 24, Section 5.2: The last sentence indicating that specimen submission is not required has been deleted, as specimen submission is required for pathology review.

5. Page 24, Section 5.7: The section reference for the FDG-PET scan was changed from 7.3 to 7.4.

6. Page 51, Section 15.5: Instructions for submitting FDG-PET/CT scans have been updated for clarification. A reference to Appendix 19.2 has been added to the AG Mednet instructions.

7. Page 52, 53, Section 15.6: The instructions for electronic submission of Digital PET/CT images by CALGB FTP have been updated for clarification. The CALGB Imaging Core Laboratory direct line and fax numbers have been corrected. Page 53a was added to prevent extensive repagination.

8. Page 100, Section 19.2: The timeline for submission of baseline scans and interim response scans has been changed to say "within 24 hours upon image acquisition," and not "immediately."

   Under the interim response scan heading a reference has been added for the AG Mednet service.

9. Page 101, Section 19.2: The timeline for submission of the final response scan has been changed to say within 72 hours upon image acquisition.

   The sentence saying the "baseline" scan must be submitted has been corrected to say "final response scan."

10. Page 102, Section 19.2: The detailed scanning protocol has been revised. Instructions have been added to promote consistency. Page 102a has been added to prevent extensive repagination.

Replacement pages are enclosed for the revised pages referenced above. Please insert them into your copy of the protocol.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
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Joseph Unger, M.S.
Jeri Jardine
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Iris Buchanan
Maddy Balois – CTSU

Southwest
Oncology Group
A National Clinical Research Group

July 1, 2009

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: Southwest Oncology Group Operations Office

RE: **S0816** "A Phase II Trial of Response Adapted Therapy of Stage III-IV Hodgkin Lymphoma Using Early Interim FDG-PET Imaging". Study Coordinators: Drs. O. Press, J. Friedberg, R. Brown, L. Rimsza, J. Cook, N. Bartlett, A. LaCasce, E. Hsi, H. Schoder, J. Sweetenham, A. Evens, R. Gascoyne and A. Iagaru.

STATUS NOTICE

Study Coordinator: Oliver W. Press, M.D., Ph.D.
Phone number: 206/667-1872
E-mail: press@u.washington.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. The entire protocol is attached or your use.

This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: PROTOCOL & INFORMATION OFFICE
Michael LeBlanc, Ph.D.
Bryan Goldman, M.S.
Joseph Unger, M.S.
Jeri Jardine
Scott Kurruk
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Maddy Balois – CTSU

PRIVILEGED COMMUNICATION Activated July 1, 2009
FOR INVESTIGATIONAL USE ONLY

SWOG

A PHASE II TRIAL OF RESPONSE-ADAPTED THERAPY OF STAGE III-IV HODGKIN LYMPHOMA USING EARLY INTERIM FDG-PET IMAGING

SWOG STUDY CHAIRS:

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AGENTS:

Bleomycin (NSC-125066)
Cyclophosphamide (Cytoxan®) (NSC-26271)
Dimethyl Triazeno Imidazole Carboximide (DTIC), (Dacarbazine), (NSC-45388)
Doxorubicin (NSC-123127)
Etoposide (VP-16)(Vepesid)(Ethylidene-Lignan P.) (NSC-141540)
Prednisone (NSC-10023)
Procarbazine (Matulane) (NSC-77213)
Vinblastine Sulfate (Velban) (NSC-49842)
Vincristine (Oncovin) (NSC-67574)

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AMC STUDY CHAIRS:

AMC Protocol **AMC-073**

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PARTICIPANTS

ALLIANCE/Alliance for Clinical Trials in Oncology

ECOG-ACRIN/ECOG-ACRIN Cancer Research Group

SWOG/SWOG

AMC/AIDS Malignancy Consortium

TABLE OF CONTENTS

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

The following institutions will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix:

- **Cooperative Group institutions not aligned with SWOG**
- **AIDS Malignancy Consortium (AMC) institutions**

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the Members section of the CTSU site located at https://www.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by SWOG. **Case report forms** (with the exception of patient enrollment forms)**, clinical reports, and transmittals** must be sent to the SWOG Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by SWOG. Please send query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations.
- Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

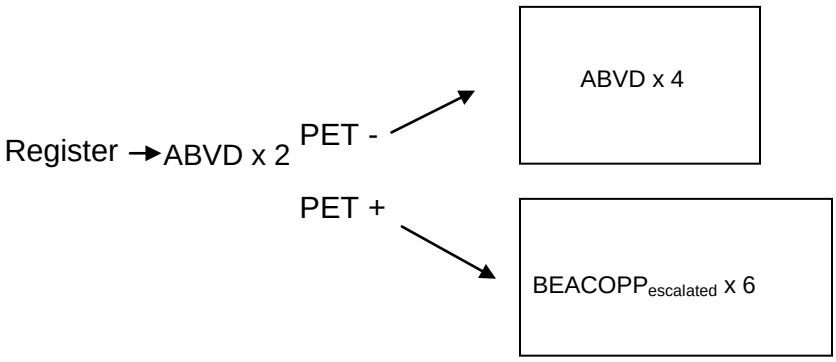
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-866/651-CTSU Fax: 215/569-0206	CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 9:00 am – 5:30 pm EST, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 am and 5:30 pm.]	SWOG Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.
For treatment- or toxicity-related questions contact the Study PI of the Coordinating Group.		
For eligibility questions contact the SWOG Data Operations Center by phone or email: Phone: 206/652-2267; E-mail: lymph@crab.org		
For questions unrelated to patient eligibility, treatment, or 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 Public web site is located at: www.ctsu.org. To access the members section, enter your user ID and password where indicated in the upper left portion of the page.		

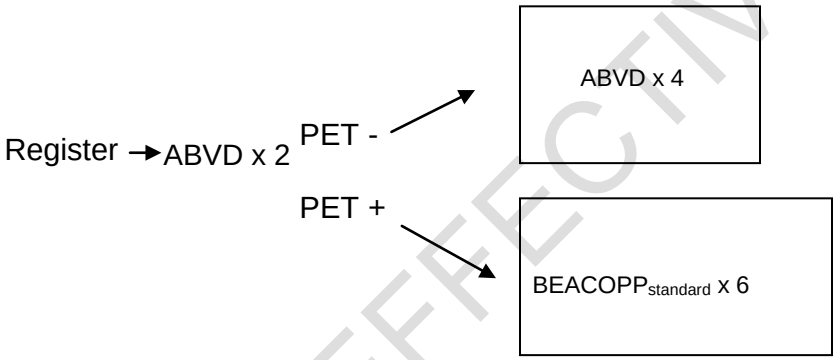
CTSU logistical information is located in Appendix 18.1

SCHEMA

S0816 Schema for HIV-negative patients



S0816 Schema for HIV-positive patients



1.0 OBJECTIVES

1.1 Co-Primary Objectives

a. To estimate the 2-year progression-free survival (PFS) in HIV-negative patients with advanced stage Hodgkin Lymphoma (HL) treated with response-adapted therapy based on FDG-PET imaging after 2 cycles of adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD).

b. To estimate the 2-year PFS in the subset of HIV-negative patients with advanced stage HL who are PET-positive after 2 cycles of ABVD and are subsequently treated with escalated dose BEACOPP.

1.2 Secondary Objectives

a. To estimate the 2-year overall survival (OS) for HIV-negative patients treated with response- adapted therapy.

b. To estimate the response rate (complete and partial) for HIV-negative patients treated with response- adapted therapy.

c. To evaluate the toxicity of this response-adapted regimen.

d. To document the feasibility of centralized, real-time review of FDG-PET imaging for U.S. cooperative group studies.

e. To prospectively evaluate the overall response rate, complete response rate, PFS, and OS of a cohort of HIV-positive patients with HL treated with response-adapted therapy. The use of cycle-2 PET scanning in HIV infection will be done to provide preliminary data for this strategy in HIV-infected patients.

f. To prospectively identify serum and tissue biomarkers associated with progression-free and overall survival of patients with HL treated with response-adapted therapy. Biologic features meriting specific investigation include the degree of tumor cell infiltration with T-regulatory cells, the FOXP3/Granzyme B ratio, and the expression of MAL or Bcl-2 in biopsy samples, and TARC levels in serum specimens.

g. To prospectively evaluate HIV viral load and CD4 cells in the cohort of HIV-positive patients with HL treated with response-adapted therapy.

2.0 BACKGROUND

Introduction: Hodgkin Lymphoma

Hodgkin Lymphoma (HL) is a lymphoid neoplasm that is diagnosed in approximately 8190 Americans annually and results in approximately 1070 deaths each year in the USA. *(1)* HL typically affects young adults and presents with painless lymphadenopathy with or without splenomegaly, fevers, drenching night sweats, weight loss and pruritus. The diagnosis is best established by an excisional lymph node biopsy demonstrating large, atypical lymphoblasts surrounded by a heterogeneous infiltrate of non-neoplastic inflammatory and accessory cells. The World Health Organization's classification of lymphomas distinguishes two major subtypes of HL, namely, "classical HL" and "nodular lymphocyte predominant HL".

Classical HL is characterized pathologically by the presence of bizarre monoclonal lymphoid cells that may be either mononuclear (Hodgkin cells) or multinucleate (Reed-Sternberg cells). The malignant Hodgkin and Reed Sternberg cells (HRS) cells of classical HL express CD15 and CD30 surface antigens, but usually not typical B cell markers such as surface immunoglobulin, CD20, CD79a, or the common leukocyte antigen, CD45. *(2)* The B-cell origin of HRS cells is nevertheless demonstrable by the expression of the B-cell specific activator protein (BSAP) derived from the PAX 5 gene in 90% of cases. *(2)* Immunoglobulin genes are rearranged in 98% of HRS cells but are not transcribed due to the absence of the transcription factor Oct-2 and its co-activator BOB-1. The malignant (HRS) cells are typically surrounded by a heterogeneous infiltrate of reactive T and B lymphocytes, eosinophils, macrophages, fibroblasts, and variable amounts of collagen deposition (sclerosis). *(2)* Four discrete histologic subtypes of classical HL are currently recognized by the WHO classification including lymphocyte rich classical HL (LRCHL), nodular sclerosing HL, mixed cellularity HL, and lymphocyte depleted HL.

Nodular lymphocyte predominant HL (NLPHL) is a monoclonal indolent B-cell neoplasm that is distinguished from classical HL by histologic and immunophenotypic features, including the presence of large neoplastic cells known as "popcorn" or "L and H" cells residing in large nodular meshworks of follicular dendritic cell processes filled with non-neoplastic lymphocytes. In marked contrast to the HRS cells of classical HL, the malignant L and H cells of NLPHL express typical B-cell surface antigens including CD20 and CD79a as well as the common leukocyte antigen, CD45, but do not express CD15 or CD30. *(2)* NLPHL is responsible for approximately 5% of all cases of HL, typically affects men 30-50 years old, usually presents with localized lymphadenopathy (Stage I-II), progresses slowly, and is associated with prolonged survival despite frequent relapses. *(3)* Because of the marked differences between the behavior of NLPHL and classical HL, this protocol will confine its accrual to classical HL.

Workup and Staging of Hodgkin Lymphoma

The National Cancer Center Network has established standards for the evaluation and therapy of patients with HL. *(4)* Recommended diagnostic tests include a history, physical examination, excisional lymph node biopsy with evaluation for histology and immunophenotype, complete blood cell count (CBC) with differential, chemistry panel including liver function tests, albumin, lactate dehydrogenase, erythrocyte sedimentation rate, chest radiograph, computed tomography (CT) of the chest abdomen and pelvis, fluorodeoxyglucose positron emission tomography (FDG-PET), bone marrow aspirate and biopsy (if B symptoms or advanced stage), and fertility counseling. Other tests useful in selected cases include pulmonary function tests, determination of the cardiac ejection fraction, HIV testing, neck CT scans, and vaccination for encapsulated bacteria. After completion of the diagnostic workup, the extent of involvement with HL is designated using the Ann Arbor staging criteria (see Section 4.0). Patients with Stage IA and IIA are considered to have "early stage" HL and are generally treated with short courses (2-4 cycles) of combination chemotherapy, usually with doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), followed by involved field radiotherapy which affords a cure rate of 90-95%. *(5)* Patients with Stages III-IV disease are considered to have advanced HL and are generally treated with 6-8 cycles of combination chemotherapy as outlined below. Treatment of patients with Stages IB, IIB, and bulky Stage II HL is variable and will not be addressed in the current protocol.

Standard Therapy for Advanced Hodgkin Lymphoma

Although HL is one of the most curable of all human neoplasms, approximately 30% of patients in the United States with Stage III-IV HL still die of the disease with current management. *(6)* Since HL typically afflicts patients between the ages of 14-40, many years of productive life are tragically lost to this lymphoma each year. The development of the MOPP (mechlorethamine, Oncovin, procarbazine, prednisone) regimen in the 1960s permitted hematologists/oncologists to cure a significant proportion of patients with advanced stage Hodgkin disease for the first time and represented a major milestone in medical oncology. *(7)* After the introduction of MOPP, a number of MOPP-like chemotherapy regimens based on alkylating agents were developed to reduce acute toxicity. These "MOPP-variant" regimens were equivalent to MOPP in efficacy and

were associated with less early treatment-related toxicity; however, the major late morbidities of MOPP, sterility and an increased incidence of acute myeloid leukemia, persisted with the derivative regimens. *(8)* The ABVD regimen (adriamycin, bleomycin, vinblastine, and dacarbazine) was developed by Bonadonna and colleagues in Milan in the 1970s containing drugs considered to be non-cross resistant with those in the MOPP regimen. *(9)* Early studies by this group demonstrated the ability of ABVD to successfully treat patients with recurrence after MOPP and the efficacy of ABVD as primary therapy. Randomized trials subsequently proved that ABVD was more effective and less toxic than MOPP. *(6)* Alternating (MOPP-ABVD) and hybrid (MOPP-ABV) regimens were developed but proved to be no more effective than ABVD alone and were more toxic. *(6, 10-12)* Based on these studies, ABVD became the standard of care in the United States and most other countries in the world. Administration of full doses of ABVD without treatment delays, dose reductions, or growth factors appears to optimize cure rates with this regimen. *(13,14)*

Stanford V

Several groups have recently placed emphasis on developing novel, brief duration regimens for the treatment of advanced HL. The rationale behind the development of these regimens is to increase dose-intensity of chemotherapy by reduction in the total duration of treatment (based on retrospective analyses suggesting a relationship between treatment outcome and dose intensity), reducing cumulative doses of several drugs thought to be responsible for long term toxic effects, including alkylating agents, doxorubicin and bleomycin, and reducing the extent of radiation therapy, with an anticipated further reduction in cardiac and pulmonary toxicity. Such alternative treatment regimens include Stanford V and BEACOPP.

Stanford V is an abbreviated 12 week course of treatment in which myelosuppressive and nonmyelosuppressive treatments are alternated weekly. *(15-17)* The dose intensity of individual drugs is maintained or increased compared with standard chemotherapy while the cumulative doses of bleomycin (30 Units/m^2) and adriamycin (150 mg/m^2) are reduced compared to ABVD or hybrid programs. Procarbazine is omitted and the cumulative dose of mustard is reduced to 18 mg/m^2. It was anticipated that pulmonary and cardiac dysfunction, sterility and leukemogenesis might be reduced or avoided with the Stanford V chemotherapy program. A major advantage of the chemotherapy program is its relative brevity. Consolidative irradiation is given to sites of bulky disease (> 5 cm) or macroscopic splenic disease. However, in the Stanford V regimen, the radiotherapy dose is reduced to 3600 cGy and the axillae and high neck are omitted from treatment unless they are the sites of bulky disease. Omission of axillary irradiation significantly reduces the risk of secondary breast cancer. In a study of 142 patients with Stage III or IV or bulky stage I-II disease, the 5-year freedom-from-progression (FFP) was 89% and overall survival (OS) 96% after a median follow-up of 5.4 years. *(17)* These results compared favorably with the historical FFP achieved at Stanford University with alkylator-based combination chemotherapy and total lymphoid irradiation or alternating chemotherapy (MOPP/ABVD) (72%), although they did not achieve statistical significance (p = 0.14). Stanford V was well tolerated acutely and there were no treatment related deaths. All women under the age of 40 years continued to have regular menses after the completion of treatment. Although male fertility was not regularly assessed, semen analyses post-treatment revealed normo- or oligo-spermia. Twelve normal live births occurred subsequent to Stanford V ± RT. One patient with recurrent Hodgkin disease died of lung cancer; she had received no radiotherapy. Stanford V ± RT was also studied in a limited institution pilot by the Eastern Cooperative Oncology Group (ECOG) in 50 patients with locally extensive or advanced stage disease. With 47 evaluable patients and a median follow-up of 4.8 years, the estimated freedom from progression was 87% at 2 years and 85% at 5 years. Overall survival was 96% at 2 and 5 years. There was one death from Hodgkin disease and one death from an M5 acute leukemia. Stanford V was well tolerated acutely with no major morbidity. Because of the early favorable results with Stanford V, a major U.S. intergroup trial was recently conducted randomizing patients with advanced HL to either standard ABVD therapy or the Stanford V regimen. This study completed accrual in 2006, but results are not yet available.

An independent European multicenter trial was recently conducted randomizing patients to Stanford V ± RT, ABVD, or MOPP/EBV/CAD (MEC). *(18)* The complete response rates for ABVD, Stanford V, and MEC were 89%, 76%, and 94%, respectively; 5-year failure-free survival (FFS) and progression-free survival (PFS) rates were 78%, 54%, 81% and 85%, 73%, and 94%, respectively ($p < .01$ for comparison of Stanford V with the other two regimens). Corresponding 5-year overall survival rates were 90%, 82%, and 89% for ABVD, Stanford V, and MOPP/EBV/CAD, respectively. *(18)* Stanford V was more myelotoxic than ABVD but less myelosuppressive than MEC, which required larger reductions in the prescribed drug doses. Although this study concluded that the Stanford V regimen was inferior to ABVD, interpretation of the study is flawed because radiotherapy was not administered as intended for the Stanford V regimen. As a consequence, uncertainty persists regarding the relative merits of ABVD and Stanford V and the results of the intergroup randomized trial of Stanford V and ABVD are highly anticipated. In the interim, most American physicians continue to use ABVD as their preferred regimen for HL.

BEACOPP

The BEACOPP regimen (Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Oncovin, Procarbazine and Prednisone). devised by the German Hodgkin Lymphoma Study Group (GHSG), under the leadership of Volker Diehl, substitutes etoposide for dacarbazine and vinblastine and encompasses two main intensification principles: dose escalation of the putative most important drugs (cyclophosphamide, etoposide, and doxorubicin) and time intensification accomplished by shortening the respective chemotherapy cycles from 4 to 3 weeks. *(19,20)* Two different variants of BEACOPP were initially designed: BEACOPP in baseline dosage (BEACOPP-21) and BEACOPP in escalated dosage with granulocyte colony-stimulating factor (G-CSF) support (escalated BEACOPP-21). In 2003, Diehl and colleagues published a large randomized clinical trial randomizing 1,201 subjects between the ages of 15-65 with Stages IIB, III, or IV HL to treatment with either COPP-ABVD (the "standard of care"), $BEACOPP_{standard}$, or $BEACOPP_{escalated}$. *(20)* The majority of patients also received consolidative radiotherapy. Accrual was terminated early in the COPP-ABVD arm by the data safety monitoring board due to inferior survival and progression-free survival compared to the two BEACOPP arms. In the initial report, 5-year overall survival was 83% in the COPP-ABVD arm, 89% with $BEACOPP_{standard}$, and 91% with $BEACOPP_{escalated}$ ($p = 0.16$ for COPP-ABVD vs $BEACOPP_{standard}$, $p = 0.06$ for $BEACOPP_{standard}$ vs $BEACOPP_{escalated}$, and $p = 0.002$ for COPP-ABVD vs $BEACOPP_{escalated}$). Freedom from treatment failure was 69% at 5 years for COPP-ABVD, 76% for $BEACOPP_{standard}$, and 87% for $BEACCOPP_{escalated}$ ($p < 0.001$ for $BEACOPP_{escalated}$ vs COPP-ABVD). Hematologic toxicity was similar between $BEACOPP_{standard}$ and COPP-ABVD but greatly increased with $BEACOPP_{escalated}$ with Grade 4 leukopenia seen in 90% of patients with the latter regimen compared with 19% with COPP-ABVD. Grade 4 thrombocytopenia was seen in 47% of patients with $BEACOPP_{escalated}$ compared to 2% with COPP-ABVD. Myelodysplasia or secondary acute myeloid leukemia was seen in one of 260 evaluable patients treated with COPP-ABVD compared with 4 of 469 treated with $BEACOPP_{standard}$ and 9 of 466 with $BEACOPP_{escalated}$. Reliable long term data on gonadal toxicity are not yet available, however early studies suggest that nearly all subjects receiving BEACOPP regimens will become infertile, compared with < 5% receiving ABVD. *(6,21)* The therapeutic superiority of $BEACOPP_{escalated}$ (and to a lesser degree $BEACOPP_{standard}$) compared to COPP-ABVD has persisted with longer follow-up of this study, now with a median of 10 years since study entry. *(22,23)* At 10 years, freedom from treatment failure rates were 64%, 70%, and 82% and overall survival rates were 75%, 80%, and 86% for COPP-ABVD , $BEACOPP_{standard}$, and $BEACOPP_{escalated}$, respectively ($p < 0.001$).

A subsequent randomized study in Germany (HD9) compared COPP-ABVD to $BEACOPP_{standard}$ in 75 elderly patients from ages 66-75. *(24)*There were no differences in complete remission rates (76%), overall survival (50% at 5 years), or freedom from treatment failure (46% at five years) between the two arms on this study, but 21% of elderly patients treated with $BEACOPP_{standard}$ died of acute toxicity compared with 6% with COPP-ABVD. The BEACOPP regimens are therefore not recommended for patients over age 65.

To mitigate the toxicity of $BEACOPP_{escalated}$, the GHSG investigated an alternative approach by further shortening the cycle duration instead of dose escalation. This time-intensified variant of the BEACOPP regimen is repeated every 14 days (BEACOPP-14) with G-CSF support. (25) In a multi-center pilot study BEACOPP-14 was shown to be both feasible and effective in 94 patients with advanced HL, with 94% of patients achieving a complete remission. The overall survival and freedom-from-treatment-failure (FFTF) at 34 months were 97% and 90%, respectively. Acute toxicity was moderate, with World Health Organization Grade 3/4 leukopenia in 75%, thrombocytopenia in 23%, anemia in 65%, and infection in 12% of patients. These results showed that dose intensification of BEACOPP-21 by shortening of cycle duration from 3 weeks to 2 weeks with G-CSF support is possible, acute toxicity of BEACOPP-14 is moderate and comparable to that of BEACOPP-21, and treatment results are promising with a low rate of progressive disease (4%) and a FFTF rate of 90% at 34 months. However, further follow-up and a randomized comparison will be required before BEACOPP-14 can be considered equivalent in efficacy to $BEACOPP_{escalated}$.

Although the $BEACOPP_{escalated}$ regimen has become the standard of care for advanced HL in Germany, the regimen has been rarely employed in the United States or other countries due to concerns about its acute and late toxicities. While $BEACOPP_{escalated}$ may result in better survival, it remains to be determined whether the increased toxicity of this regimen (3% treatment induced mortality, 100% infertility in men, 100% infertility plus premature menopause in most women over the age of 25, risk of myelodysplasia) can be justified for good-risk patients. To further define the role of $BEACOPP_{escalated}$ compared with ABVD, a randomized comparison is being conducted in Europe by the EORTC for patients with advanced HL.

The Role of Radiotherapy in Advanced Stage Hodgkin Lymphoma

The rationale for the use of radiation therapy as an adjuvant to chemotherapy in Stage III and IV patients has been based on observations that relapse frequently occurs in previously involved sites even in patients with Stage IV disease. Given the reliability of radiation therapy to provide local control, many studies have incorporated combined modality therapy. Despite this sound rationale, randomized, cooperative group trials have failed to show a convincing benefit for consolidative irradiation in patients with Stage III-IV HL. (26-29) Consequently, consolidative radiotherapy will not be incorporated in the current protocol.

Prognostic Factors in Hodgkin Lymphoma

A variety of prognostic factors have been described for patients with locally extensive or advanced stage Hodgkin disease. In order to facilitate the reporting of clinical trials and to assist in the design of future studies, an international effort was organized to characterize prognostic factors in a large number of patients. (30) Data from twenty-three cooperative groups or treatment centers were collected on 5,141 patients who were considered to have advanced disease and were treated with "modern" therapy according to a defined protocol. Twenty factors were considered including age, gender, histology, stage, mediastinal mass size, inguinal involvement, extranodal disease, B symptoms, and the laboratory measurements of albumin, hemoglobin, leukocytes, lymphocytes, platelets, creatinine, alkaline phosphatase, lactate dehydrogenase and erythrocyte sedimentation rate. Seven factors were identified, each of which reduced tumor control by 7-8% at 5 years. These included age > 45 years, male sex, Stage IV, serum albumin < 4 mg/dL, hemoglobin < 10.5 mg/dL, WBC > 15,000 cells/mcL, and lymphocytes < 600 cells/mcL. Freedom from progression (FFP) at 5 years was related to the number of factors present as indicated below. The 5-year FFP for patients with 3+ factors, who comprised 42% of the population, was 55%, compared to 74% for those with 0-2 factors, who comprised 58% of the population. Clinical investigations designed to reduce toxicity or improve FFP could be based on such a grouping.

Unfortunately, the impact of the HL international prognostic factor score (IPS) developed by this working group has been less than anticipated and its predictive value has been challenged. *(31,32)* Only 19% of HL patients have four or more risk factors as defined by this index; the other 81% of patients have a progression-free survival rate ≥ 60% with standard ABVD. Attempts to pursue risk-adapted therapy based upon the international prognostic score have therefore been plagued by concerns that a substantial fraction of patients will be over-treated using algorithms based on the IPS score. *(33)* A recent study investigated the relative value of the IPS as opposed to early interim FDG-PET imaging after two cycles of chemotherapy (mainly ABVD) to predict outcome of HL patients and demonstrated convincingly that interim FDG-PET imaging was far superior to the IPS in predicting patient outcome (PFS, OS). *(33)*

FDG-PET Imaging in Evaluation of Hodgkin Lymphoma

PET scanning has been used in HL at diagnosis for staging, during treatment to assess response, and to evaluate residual masses after completion of treatment for prediction of relapse. *(34)* 2-(^{18}F)fluoro-2-deoxy-D-glucose (FDG) PET is a functional imaging technique, which relies on the detection of a higher rate of glucose metabolism in malignant cells compared with normal cells. Conventional radiological methods, e.g. CT scanning, have significant limitations in assessing response to therapy. A reduction in tumor size is used as the most important determinant, but this is not an accurate predictor of outcome as the malignant cells in HL often make up only a small proportion of the tumor volume, and it takes time for a reduction in tumor size to occur. Thus, size reduction cannot be used accurately for response assessment and therapy adjustment until late during treatment. FDG-PET allows evaluation of metabolic rather than morphological or volume changes, allowing earlier assessment of tumor response during therapy.

Several studies have assessed the role of PET imaging in response assessment in HL. Friedberg et al. reported a study of 22 patients with de novo HL who were imaged by FDG-PET after three cycles of chemotherapy. *(35)* After a median follow-up of two years, four of five interim PET positive patients had progressed and 15 of 17 PET-negative patients remained in remission. Hutchings et al. retrospectively assessed the prognostic value of early interim PET in 85 patients with HL. *(36)* At a median follow-up of more than three years, PET imaging had a strong positive predictive value in advanced HL, independent of the other known prognostic factors. In a further study, the same group studied 77 newly diagnosed patients with HL, who underwent FDG-PET at staging, after two and four cycles of chemotherapy, and after completion of chemotherapy. *(37)* After two cycles of chemotherapy, 61 patients had a negative PET scan and 16 patients a positive one. After a median 2-year follow up, 11 of 16 PET-positive patients had progressive lymphoma and two died. Three of 61 PET-negative patients had recurrences, although all remained alive. In this study there was a strong association between early PET response after two cycles and PFS and OS. For prediction of PFS, interim FDG-PET was as accurate after two cycles as later during treatment and superior to CT at all times. In regression analyses, early interim FDG-PET was stronger than established baseline prognostic factors. Similarly, an Italian group reported the results of PET imaging after two cycles of ABVD. *(38)* The scan was positive in 20 patients, of whom 17 progressed during therapy, one relapsed and two remained in CR. By contrast, 85 of 88 patients (97%) with a negative scan remained in CR. These studies suggest that early PET is predictive of complete response and particularly suggest that interim assessment of response by PET imaging is superior to assessment after completion of treatment for prediction of disease progression, with a very low false-negative rate. Thus, PET is a strong and independent predictor of PFS and allows early identification of those patients with a suboptimal response to initial therapy. The results of continued treatment with ABVD in the group remaining PET-positive after two cycles are extremely poor, justifying an early switch to more intensive treatment in the hope of salvage. These exceedingly poor outcomes for patients with positive FDG-PET scans after 2-3 cycles of ABVD as reported by Gallamini and Hutchings suggest that randomizing such patients to either continued therapy with ABVD or switching to $BEACOPP_{escalated}$ is no longer feasible due to ethical concerns. *(33, 36-38)*

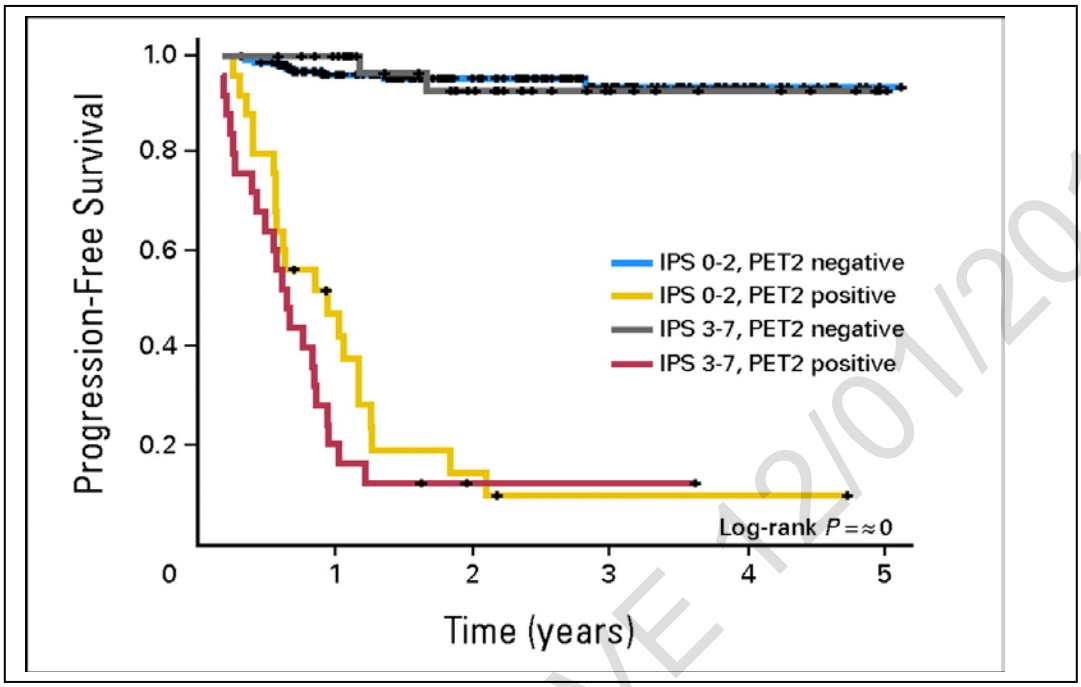


Fig 3. Kaplan-Meier plot showing the progression-free survival according to International Prognostic Score (IPS) group and positron emission tomography results after two cycles of ABVD. Reproduced from Gallamini, A. et al. *(33)*

Response-Adapted Therapy for HL Based on FDG-PET Imaging

A preliminary test of the value of response-adapted therapy of HL based on early interim functional imaging was conducted by Dann et al. in a study of 108 patients. *(39)* Those with adverse prognostic factors (IPS ≥ 3) were initially treated with two cycles of $BEACOPP_{escalated}$ therapy and the rest were treated with $BEACOPP_{standard}$. After two cycles, early interim ^{67}Gallium scans (n=54) or FDG-PET/CT imaging (n=54) was performed. Those with a positive interim scan received four more cycles of $BEACOPP_{escalated}$ whereas those with a negative scan were given four cycles of $BEACOPP_{standard}$. The complete remission rate was 97% with a 5-year event-free survival of 85% and 5-year OS of 90%. Relapse or progression occurred in 27% of patients with a positive interim scan compared to only 2% of patients with a negative scan (2%). These favorable findings suggest that early interim FDG-PET scanning is a useful tool for adjustment of chemotherapy that permits cure of the majority of patients with advanced HL. However, interpretation of the study is somewhat confounded by the heterogeneity of the study population (48 patients were Stage I-II, only 39 had IPS 3-7). In the current study, we propose to initiate treatment with the less toxic ABVD regimen and to escalate to $BEACOPP_{escalated}$ after two cycles in those with positive interim PET scans, since this sequence will maximize the preservation of fertility and minimize acute and late toxicities.

Hodgkin Lymphoma in Patients Infected with the Human Immunodeficiency Virus

Recent studies have convincingly demonstrated that patients infected with the human immunodeficiency virus (HIV) have a significantly increased risk of developing HL. *(40-45)* Unfortunately, few data are available concerning the optimal treatment of such patients. Most reported series contained small numbers of patients treated at single institutions and were analyzed retrospectively. Early studies suggested that HL occurring in HIV-infected patients was

an aggressive tumor with a relatively low complete response rate and an unfavorable clinical outcome. *(42)* However, most of these series were compromised by the inclusion of patients with long-standing HIV and pre-existing opportunistic infections, predisposing them to unfavorable outcomes. *(42)* Furthermore, many of the patients in early series had not received highly active anti-retroviral therapy (HAART). Provocative recent series of HIV+ patients with aggressive non-Hodgkin lymphomas suggest that complete remission rates and progression-free survivals can approach those of non-HIV infected patients with comparable prognostic factors if CD4 T-cell counts are > 350 per mm^3, if patients are treated with HAART either concurrently with chemotherapy or immediately after conclusion of chemotherapy, if no other AIDS-defining conditions are present, and if standard curative drug regimens are used without reduction of doses of drugs. *(46)*

Precise delineation of the optimal therapy for HIV-infected patients with malignancies has been confounded by the explicit exclusion of HIV+ patients from nearly all clinical protocols. The Cancer Therapy Evaluation Program of the NIH has recently proposed that patients with HIV infections be deliberately included in cancer clinical trials, including specifically HL. *(47)* In accordance with this mandate from the NIH, we propose to include otherwise healthy HIV-infected patients with HL in this trial, but will evaluate them independently as a separate cohort. However, because of the absence of any published data on the tolerability of $BEACOPP_{escalated}$ in HIV+ patients and concerns about the tolerability of this intensified regimen in this population, we will utilize $BEACOPP_{standard}$ in HIV+ patients who remain FDG-PET positive after two cycles of ABVD. The $BEACOPP_{standard}$ regimen has been tested in a small cohort of HIV+ HL patients in Germany and found to be effective and reasonably tolerable. In this small series, nine of 12 patients achieved long term disease-free survival, two died of opportunistic infections, and one died of recurrent HL. *(48)* In view of these results, further investigation of the $BEACOPP_{standard}$ regimen seems justified, but amplification of therapy to $BEACOPP_{escalated}$ seems unwise because of the 17% incidence of fatal infections with the $BEACOPP_{standard}$ regimen. *(48)*

Rationale for Current Study

Although prognosis at diagnosis can be estimated using established pre-treatment prognostic indices such as the IPS, response to treatment is the most important single predictive factor for an individual patient. *(30,33)* It is therefore desirable to identify these patients as early as possible during treatment so that response-adapted, individually-tailored treatment can be administered, aiming to lower the risk of treatment failure, avoid unnecessary toxicity for those in the best prognosis group while increasing the probability of long-term survival for the poor-prognosis group. Response-adapted therapy, aiming to achieve high cure rates with minimal long-term morbidity and mortality, requires reliable prognostic stratification. 2-(^{18}F)fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging has a number of potential advantages in refining and improving the management of patients with HL. *(33)* By using early interim FDG-PET imaging it may be possible to identify those patients in whom initial standard treatment (e.g. ABVD chemotherapy) is ineffective, initiating an earlier switch to more intensive treatment (e.g. the $BEACOPP_{escalated}$ regimen). This approach may improve cure rates while simultaneously minimizing the magnitude of treatment related morbidity (myelosuppression, sterility, myelodysplasia, acute myeloid leukemia) and mortality.

Correlative Studies

Improving the ability to determine which patients with HL require dose intensification and which patients will be cured with less intense and less toxic approaches is an important priority. The International Prognostic Score (IPS) based on clinical features at diagnosis has been disappointing in its ability to predict outcome for patients and to select patients for dose-intense regimens. *(30,31)* We hypothesize that biologic features of a patient's tumor and of the non-neoplastic immune cell infiltrate, as detected by immunohistochemistry, will predict outcome with therapy much better than the clinical features utilized in the IPS. We will collect paraffin blocks on all patients as a requirement for study entry to facilitate performance of exploratory biologic

studies on the diagnostic tumor specimens and correlate findings with the outcomes of patients enrolled on this trial. In addition, we will collect serum samples at study entry, after Cycle 2 of chemotherapy (at the time of initial response assessment with PET), and at the conclusion of chemotherapy (at the time of final response assessment). Upon acquisition of funding for the correlative studies, we will construct tumor microarrays and investigate features of both the immune infiltrate (e.g. regulatory T-cells identified by CD4, CD25 and FOXP3 staining; infiltrating cytotoxic T-lymphocytes identified by T-cell restricted intracellular antigen (TIA) and granzyme B staining, and features of HRS cells such as MAL and Bcl-2 expression. *(49,50)* We will assess the significance of the previously reported prognostic factors for HL identified in retrospective analyses including expression of MAL, Bcl-2, and the FOXP3/Granzyme B ratio prospectively in this large multi-center trial. *(50)* The glucocorticoid-induced tumor necrosis factor receptor family-related gene (GITR) and Cytotoxic T-Lymphocyte Antigen 4 (CTLA4) will also be studied as markers of down modulated T-effector cells indicative of a hypoactive immune response and EBER positivity as a marker of latent Epstein-Barr virus infection. Serial serum biomarker findings (TARC, etc.) will be correlated with tumor immunohistocytochemistry results and with response assessments.

Specific hypotheses being addressed by these correlative studies include:

1. Patients with fewer than 25 FoxP3 regulatory T-cells (T_{reg} cells) per high power field will have a worse failure-free and overall survival than patients with more than 25 T_{reg} cells per high power field.

2. Patients with a FOXP3/Granzyme B ratio ≤ 1 will have a worse failure-free and overall survival than patients with a ratio > 1.

3. Expression of MAL or Bcl-2 and the FOXP3/Granzyme B ratio will be independent prognostic factors for failure-free and overall survival.

Inclusion of Women and Minorities

This study was designed to include women and minorities. Based on recent registrations to studies involving Hodgkin Lymphoma studies, it is anticipated that accrual in the race and 13 sec subgroups will be as shown below:

Ethnic Category	Sex/Gender		
	Females	**Males**	**Total**
Hispanic or Latino	9	13	22
Not Hispanic or Latino	136	142	278
Total Ethnic	145	155	300

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	3	4
Black or African American	16	14	30
Native Hawaiian or other Pacific Islander	0	0	0
White	128	138	266
Racial Category: Total of all subjects	145	155	300

3.0 DRUG INFORMATION

3.1 Bleomycin (NSC-125066)

a. DESCRIPTION

Bleomycin is an antitumor antibiotic which seems to act by inhibiting DNA synthesis with some evidence of lesser inhibition of RNA and protein synthesis.

b. TOXICOLOGY

Human Toxicity: Toxicities observed with bleomycin include fever, chills, nausea, vomiting, anorexia, alopecia, stomatitis, phlebitis, skin rash, erythema, nail changes and hyperpigmentation. Occasional acute anaphylactic-like reactions to bleomycin have been seen. The most serious toxicity is that of pneumonitis progressing to pulmonary fibrosis (with dry cough and labored breathing) which can be fatal. The occurrence of pulmonary fibrosis is dose related. Renal and hepatic toxicity, beginning as deterioration in renal or liver function tests, have been reported. Vascular toxicity includes myocardial infarction, cerebrovascular accident, thrombotic microangiopathy and cerebral arteritis. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: Tumor cells of the skin and lungs have been found to have high concentrations of bleomycin in contrast to the low concentrations found in the hematopoietic tissue. Low concentrations in bone marrow is related to degradative enzymes in this tissue. Sixty to 70% of administered dose is recovered in the urine as active bleomycin. With adequate renal function, half life is 115 minutes.

Formulation: Bleomycin is supplied in 15 U vials as a lyophilized powder which is stored at room temperature. Each vial is diluted in 5 ml of injectable sterile water, sodium chloride, 5% dextrose, or bacteriostatic water.

Storage and Stability: As supplied, the drug is stable under refrigeration at 2 - 8^{o}C. Reconstituted drug can be stored in glass for 24 hours at room temperature in NaCl or 5% Dextrose.

Administration: The bleomycin solution may be further diluted for IV use with normal saline or D5W and may be given slowly over ten minutes. It may also be given IM or SQ.

Supplier: This drug is commercially available for purchase by the third party. This drug will NOT be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.2 Cyclophosphamide (Cytoxan®) (NSC-26271)

a. DESCRIPTION

2-[bis (2-chloroethyl) amino] tetrahydro-2H-1, 3,2-oxazaphosphorine 2-oxide monohydrate. Cyclophosphamide is biotransformed principally in the liver to active alkylating metabolites, which cross-link to tumor cell DNA.

b. TOXICOLOGY

Human Toxicology: Toxicity from cyclophosphamide includes bone marrow suppression which usually occurs 10 to 12 days after administration, nausea, vomiting, anorexia, abdominal discomfort, diarrhea, stomatitis, hemorrhagic colitis, jaundice, reversible alopecia, hemorrhagic cystitis which can frequently be prevented with increased hydration, hematuria, ureteritis, tubular necrosis, fibrosis of the bladder, cardiac toxicity which may potentiate doxorubicin-induced cardiotoxicity, rare anaphylactic reaction, skin rash, hyperpigmentation of the skin and nails, interstitial pulmonary fibrosis, and cross sensitivity with other alkylating agents. Treatment with cyclophosphamide may cause significant suppression of the immune system. With the combination therapy the most frequent adverse event observed to date is neutropenia. Prophylactic G-CSF for subsequent cycles has been necessary. Dose reductions have been necessary for neutropenia and mucositis. For further details, refer to Section 2.0, Background.

Second malignancies, most frequently of the urinary bladder and hematologic systems, have been reported when cyclophosphamide is used alone or with other anti-neoplastic drugs. It may occur several years after treatment has been discontinued. Increased myelosuppression may be seen with chronic administration of high doses of phenobarbital. Cyclophosphamide inhibits cholinesterase activity and potentiates effect of succinylcholine chloride. If patient requires general anesthesia within 10 days after cyclophosphamide administration, the anesthesiologist should be alerted. Adrenal insufficiency may be worsened with cyclophosphamide. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy. The occurrence of acute leukemia has been reported in patients treated with anthracycline/alkylator combination chemotherapy.

For prescribing information and a comprehensive list of adverse events associated with cyclophosphamide, refer to the drug package insert.

c. PHARMACOLOGY

Pharmacokinetics: Cyclophosphamide is activated principally in the liver by a mixed function microsomal oxidase system. PO administration is well absorbed, with bioavailability greater than 75%. Five to twenty-five percent of unchanged drug is excreted in the urine. Several active and inactive metabolites have been identified with variable plasma protein binding. There appears to be no evidence of clinical toxicity in patients with renal failure, although elevated levels of metabolites have been observed.

Formulation: Cyclophosphamide is supplied in 100 mg, 200 mg, 500 mg, 1 gram and 2 gram vials as a white powder. The drug should be reconstituted with Sterile Water for Injection, USP, and may be diluted in either normal saline or D5W.

Storage and Stability: Although the reconstituted cyclophosphamide is stable for six days under refrigeration, it contains no preservatives and therefore should be used within 6 hours.

Administration: The drug should be diluted in about 150 cc of normal saline or D5W and infused IV. An added dose of IV fluids may help prevent bladder toxicity.

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.3 Dimethyl Triazeno Imidazole Carboxamide (DTIC), (Dacarbazine), (NSC-45388)

a. DESCRIPTION

The chemical structure of DTIC is 5-(3,3-dimethyl-1-triazeno)-imidazole-4-carboxamide. Three hypotheses have been offered as the mechanism(s) of action of DTIC: inhibition of DNA synthesis by acting as a purine analog, action as an alkylating agent, and/or interaction with SH groups.

b. TOXICOLOGY

Human Toxicology: Myelosuppression is the dose-limiting toxicity. The predominant side effect observed in humans has been anorexia, nausea and vomiting. This occurs with maximal intensity on the first day of a five-day course, and in many patients, it is less with each subsequent day. Myelosuppression consisting of thrombocytopenia and leukopenia occurs in approximately one-quarter of patients after a five-day course of 250 mg/m^2. The time course for this myelosuppression is generally maximal approximately three weeks after administration with the period of recovery variable. Other side effects reported included infrequent flu-like syndrome associated with fever and myalgia, phlebitis, tissue necrosis, hepatic toxicity, anaphylaxis, photosensitivity, alopecia, and facial flushing. Rarely, DTIC has caused diarrhea.

c. PHARMACOLOGY

Kinetics: After IV administration, plasma disappearance is biphasic with the initial half-life of 19 minutes and terminal half-life of 5 hours. In patients with renal and hepatic dysfunction half-life is lengthened to 55 minutes and 7.2 hours. 40% of unchanged DTIC is excreted in the urine in 6 hours. The drug is not apparently bound to plasma proteins.

Formulation: 100 and 200 mg ampules containing a white powder.

Storage and Stability: The drug must be stored in a refrigerator 2°C to 8°C (36°F - 46° F) at a temperature of 4° C or less and protected from the light while stored. Once reconstitution occurs, the drug should be utilized within an 8-hour period.

Administration: Dacarbazine 100 mg/vial and 200 mg/vial are reconstituted with 9.9 ml and 19.7 ml, respectively, of Sterile Water for Injection, USP. The resulting solution contains 10 mg/ml of dacarbazine. The reconstituted drug may be given as a rapid intravenous injection (although this may be quite painful) or more preferable as an infusion in 150-200 cc of diluent over a 15-30 minute period. This latter form of administration is rarely associated with any pain along the infusion site.

Supplier: DTIC is commercially available, and therefore should be purchased by the third party. This drug will not be provided by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.4 Doxorubicin (NSC-123127)

a. DESCRIPTION

Mechanism of Action: Doxorubicin is a cytotoxic anthracycline antibiotic different from daunorubicin by the presence of a hydroxyl group in the C-14 position. Doxorubicin is produced by fermentation from S. *Peucetius* var. *caesius*. Its mechanism of action is thought to be the binding of nucleic acids, preventing DNA and possibly RNA synthesis.

b. TOXICOLOGY

Human Toxicology: Studies with doxorubicin have shown that the major toxic effects of this drug are alopecia, which is often total but always reversible; nausea and vomiting, which develops shortly after drug administration, occasionally persisting for 2 - 3 days; fever on the day of administration; and phlebitis at the site of the drug's injection. Extravasation of the drug will lead to soft tissue necrosis. Phlebosclerosis, cellulitis, vesication and erythematous streaking have also been seen. Mucositis may be seen 5 - 10 days after administration. Ulceration and necrosis of the colon, particularly the cecum, with bleeding and severe infection have been reported with concomitant administration of cytarabine. Anorexia and diarrhea have also been observed. Hyperpigmentation of nail beds and dermal creases, onycholysis and recall of skin reaction from prior radiotherapy may occur. Cardiac toxicity manifested as acute left ventricular failure, congestive heart failure, arrhythmia or severe cardiomyopathy has been reported, but appears to occur predominantly in patients who receive total doses in excess of 550 mg/m^2. Myelosuppression, predominantly neutropenia, is common with nadir occurring approximately two weeks after a single injection; lesser degrees of anemia and thrombocytopenia have been reported. Rapid recovery of the blood counts approximately two and a half weeks after a single injection generally permits an every three week schedule. Patients with obstructive liver disease have more severe myelosuppression due to impaired drug excretion. Thus, patients with hepatic dysfunction may need to have reduced dosage or to be excluded from therapy. Renal excretion of doxorubicin is minimal, but enough to color the urine red; thus impaired renal function does not appear to increase the toxicity of doxorubicin. Other side effects include fever, chills, facial flushing, itching, anaphylaxis, conjunctivitis and lacrimation. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Pharmacokinetics: Intravenous administration is followed by a rapid plasma clearance with significant tissue binding. Urinary excretion is negligible; biliary excretion accounts for 40 to 50% of the administered dose being recovered in the bile or the feces in 7 days. The drug does not cross the blood-brain barrier.

Formulation: Doxorubicin is supplied in 10, 20 and 50 mg single-use vials, and 150 mg multidose vials as a red-orange, lyophilized powder, which has a storage stability of at least two years - see expiration date on vial. Doxorubicin should be reconstituted with 5, 10, 25 and 75 ml respectively, of Sodium Chloride Injection, USP (0.9%) to give a final concentration of 2 mg/mL.

Storage and Stability: The reconstituted doxorubicin is stable for 24 hours at room temperature and 48 hours under refrigeration (2°-8°C). It should be protected from exposure to sunlight. Discard any unused solution from the vials.

Bacteriostatic diluents with preservatives are NOT recommended as they might possibly worsen the reaction to extravasated drug.

Administration: Doxorubicin may be further diluted in 5% dextrose or sodium chloride injection and should be administered slowly into tubing of a freely flowing **intravenous infusion with great care taken to avoid extravasation.**

Supplier: This drug is commercially available for purchase by the third party. This drug will not be supplied by the NCI.

3.5 Etoposide (VP-16) (Vepesid) (Ethylidene-Lignan P.) (NSC-141540)

a. DESCRIPTION

Chemistry: VP-16 is a semi-synthetic podophyllotoxin derivative from the plant podophyllum pletatum, and has antineoplastic properties in experimental animals and in man. The empiric formula $C_{29}H_{32}O_{13}$ has a molecular weight of 588.

Mechanism of Action: The epipodophyllotoxins exert phase specific spindle poison activity with metaphase arrest, but in contrast to the vinca-alkaloids, have an additional activity of inhibiting cells from entering mitosis. Suppression of tritiated thymidine, uridine, and leucine incorporation in human cells in tissue culture suggests effects against DNA, RNA and protein synthesis.

Animal Tumor Data: Significant antitumor effect has been demonstrated in L1210, mouse sarcoma 37 and 180, Walker carcinosarcoma and Ehrlich ascites tumor. With the L1210 system, activity was schedule-dependent, having greater effect with a twice weekly administration than with daily dosing or the administration of single large doses. The drug is active given intraperitoneally or orally in L1210. No effect was demonstrated against intracerebrally inoculated L1210.

b. TOXICOLOGY

Animal Toxicology: The predominant toxicities of VP-16 in animal studies involve the hematopoietic system, with toxicity to the liver and GI tract occurring only at doses producing profound myelosuppression. Anemia, leukopenia, and lymphoid involution occur in mice, rats and monkeys. Acute toxicity investigations have been complicated by the toxicity of the solvent system. The LD-50 of the solvent plus drug approached that of the solvent alone. Immunosuppressive effects occur with an inhibition of antibody production in mice and monkeys, and prevention of experimental allergic encephalomyelitis in rats (cell-mediated immunity).

Human Toxicology: Reversible myelotoxicity has been uniformly observed to be the major toxicity of VP-16 and to represent the only clinically significant side effect. Following a single IV injection, peak myelotoxicity occurs at seven to nine days. Following daily IV injections for five to seven days, myelotoxicity is maximal between 12 - 16 days from the initiation of therapy. Bone marrow suppression is mainly manifested as granulocytopenia, with thrombocytopenia and anemia occurring to a lesser extent. Gastrointestinal toxicities including transient modest nausea, vomiting and diarrhea, are common. Other reactions could include aftertaste, rash, pigmentation, pruritus, abdominal pain, constipation and dysphagia. Occasional alopecia is reported. VP-16 does not produce phlebitis or nephrotoxicity. Rarely, anaphylactic-like reactions have been reported, as well as, hypotension. Hypotension can be managed by infusing the drug over at least a 30 minute period. Occasionally, chills, fever, peripheral neurotoxicity,

stomatitis, hepatotoxicity, transient cortical blindness and radiation recall dermatitis may be a result of VP-16 administration. The occurrence of acute leukemia has been reported rarely in patients treated with VP-16 in association with other antineoplastic agents. VP-16 can cause fetal harm when administered to pregnant women.

Pregnancy and Lactation: Etoposide can cause fetal harm when administered to a pregnant woman. Etoposide has been shown to be teratogenic in mice and rats. In these studies, etoposide caused dose-related maternal toxicity, embryotoxicity, and teratogenicity. Fetal abnormalities included decrease weight, major skeletal abnormalities, exencephaly, encephalocele, anophthalmia, and retarded ossification. No information is available on excretion of this drug in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, it is recommended that nursing be discontinued.

c. PHARMACOLOGY

Kinetics: After IV administration, disposition is biphasic with initial half-life of 1.5 hours and terminal half-life of 4 - 11 hours. Drug does not accumulate in plasma following daily administration of 100 mg/M^2 for 4 - 5 days. Drug crosses blood-brain barrier poorly. Recovery after IV administration of radio-labeled etoposide in the urine ranges from 42 - 67% and feces from 0 - 16%. The mutagenic and genotoxic potential has been established in mammalian cells.

Formulation: 100 mg of VP-16 is supplied as 5 ml of solution in Sterile Multiple Dose Vials for injection. The pH of the yellow clear solution is 3 - 4. Each ml contains 20 mg VP-16, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg polysorbate 80/tween 80, 650 mg polyethylene glycol 300, and 30.5% (v/v) alcohol. VP-16 must be diluted prior to use with either 5% Dextrose Injection, USP, or 0.9% sodium Chloride Injection, USP. The time before precipitation occurs depends on concentration, however, when at a concentration of 0.2 mg/ml it is stable for 96 hours at room temperature and at 0.4 mg/ml it is stable for 48 hours.

PO form is available as 50 mg capsules.

Storage and Stability: The drug is available as a box of 10 vials that are stored at room temperature. Each vial should be kept in the box to protect it from light. VP-16 is less stable in 5% Dextrose injection and precipitation is reported. Capsules must be stored under refrigeration 2°-8°C (36°-46°F). The capsules are stable for 24 months under such refrigerated conditions.

Administration: IV or PO. VP-16 has a minimum infusion time of 30 minutes to reduce hypotension.

Supplier: VP-16 is commercially available and should be obtained through a third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.6 Prednisone (NSC-10023)

a. DESCRIPTION

Prednisone is a glucocorticoid rapidly absorbed from the GI tract.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of prednisone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, mood swings, depression, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin, phenobarbitol, and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Prednisone is very slightly soluble in water. Glucocorticoids have salt-retaining properties. The anti-inflammatory property of this drug is its ability to modify the body's immune system. On the other hand, glucocorticoids suppress the body's response to viral as well as bacterial infections. Equivalent doses are as follows:

Prednisone/ Prednisolone	Cortisone	Hydrocortisone	Methylprednisolone	Dexamethasone
20 mg	100 mg	80 mg	16 mg	2 mg

Ref: Knoben JE, Anderson PO. *Handbook of Clinical Drug Data*, 6th ed. Drug Intelligence Pub, Inc. 1988.

Formulation: Prednisone is available in 2.5 mg, 5 mg, 10 mg, 20 mg and 50 mg tablets.

Storage and Stability: Prednisone should be stored at room temperature.

Administration: Prednisone is administered orally.

Supplier: Prednisone is commercially available and should be purchased by third party. Prednisone will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.7 Procarbazine (Matulane) (NSC-77213)

a. DESCRIPTION

Procarbazine (matulane) is N-isopropyl-□-(2-methylhydrazino)-p-toluamide monohydrochloride. The cytotoxic action of procarbazine has not been clearly defined. The drug inhibits protein, RNA and DNA synthesis. Studies suggest that

the drug may inhibit transmethylation of methyl groups of methionine into t-RNA. In addition, the drug may directly damage DNA. Hydrogen peroxide formed during the auto-oxidation of the drug may attack protein sulfhydryl groups contained in residual protein which is tightly bound to DNA.

b. TOXICOLOGY

Human Toxicity: Side effects seen include myelosuppression, nausea and vomiting, skin rash and central nervous system depression.

WARNINGS: Because procarbazine exhibits some amine oxidase inhibitory activity, sympathomimetic drugs, tricyclic antidepressant drugs (amitriptyline, imipramine) and other drugs and foods with known high tyramine content (cheese, bananas, wine, yogurt, figs, liver) should be avoided.

Ethyl alcohol should be avoided since there may be a disulfiram (Antabuse) like reaction.

To minimize CNS depression and possible synergism, barbiturates, antihistamines, narcotics, hypotensive agents or phenothiazines should be used with caution. Caution must be observed in patients with impairment of renal or hepatic function.

c. PHARMACOLOGY

Kinetics: Procarbazine is rapidly and completely absorbed. Following oral administration, peak plasma concentration is reached at 30 minutes. Procarbazine is primarily metabolized in the liver and kidney. After IV administration, plasma half-life is 10 minutes. 70% is excreted in the urine as N-isopropylterph-thalamic acid. Procarbazine readily crosses the blood-brain barrier.

Formulation: Procarbazine is supplied in 50 mg capsules. The capsules can be stored at room temperature. The encapsulated drug is stable at room temperature for two years.

Administration: Oral.

Supplier: Procarbazine is commercially available for purchase by the third party. This drug will NOT be provided by the NCI.

3.8 Vinblastine sulfate (Velban) (NSC-49842)

a. DESCRIPTION

Chemistry: Vinblastine is the salt of an alkaloid derived from Vinca Rosea Linn., a common flowering herb known as the periwinkle. It has the empirical formula of $C_{46}H_{58}O_9H_4H_2SO_4$.

Mechanism of Action: Tissue culture studies suggest an interference with metabolic pathways of amino acids leading from glutamic acid to the citric acid cycle and to urea. A number of studies in vitro and in vivo have demonstrated its stathmokinetic effect and various atypical mitotic figures. Other studies indicate an effect on cell energy production required for mitosis and the interference with nucleic acid synthesis. Reversal of antitumor effect by glutamic acid and tryptophan has been observed.

b. TOXICOLOGY

Human Toxicology: Leukopenia is the usual dose-limiting side effect, with the nadir falling four to seven days post-injection. Thrombocytopenia and anemia may occur. Gastrointestinal toxicities include nausea, vomiting, diarrhea or constipation, abdominal pain, ileus, peptic ulcer, rectal bleeding and anorexia. Fever and phlebitis have also been seen when the drug is given as an infusion. Extravasation may lead to tissue necrosis. Ten percent of the patients will experience peripheral neuropathy. Alopecia can also occur. Vincristine can also cause paresthesia, loss of deep tendon reflexes, depression, headache, dizziness and convulsions. Other toxicities include bronchospasm, dyspnea, chills, stomatitis, pharyngitis, jaw pain, bone pain, pain in organs containing tumor tissue, malaise, and weakness. When vinblastine is administered in combination with bleomycin and cisplatin, cardiac toxicities have occurred. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Kinetics: After rapid IV administration, a triphasic serum decay pattern followed. The respective half-lives were 3-7 minutes, 1.6 hours, and 24.8 hours. Toxicity of the drug is increased with hepatic excretory insufficiency suggesting that the biliary system is the major route of excretion.

Formulation: 10 mg/vial, saline diluent.

Storage and Stability: Vials should be stored in a refrigerator (2° to 8°C or 36° to 46°F) to assure extended stability. Refrigerate unreconstituted drug. Reconstituted drug is stable for 30 days, if refrigerated. Solvents that raise or lower pH of the resulting solution from between 3.5-5.0 should not be used.

Administration: The daily dose of vinblastine will be given by intravenous injection.

Supplier: Vinblastine sulfate is commercially available, and should therefore be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the Physician Desk Reference and package insert for complete information.

3.9 Vincristine (Oncovin) (NSC-67574)

a. DESCRIPTION

Chemistry: Vincristine is one of the so-called vinca-alkaloids and is extracted from the plant cantharanthus roseus (vinca rosea).

Biochemistry: This drug appears to produce the arrest of mitosis in animal cells by interfering with microtubule function.

b. TOXICOLOGY

Human Toxicology: The primary toxic effects of vincristine are neurological with paresthesia, weakness, muscle wasting, motor difficulties including difficulty walking and slapping gait, loss of deep tendon reflexes, sensory loss, neuritic pain, paralytic ileus, bladder atony, and constipation. Rarely, it produces myelosuppression. Other side effects may include alopecia, allergic reactions,

(including rare anaphylaxis, rash and edema), jaw pain, hypertension, hypotension, nausea, vomiting, diarrhea, fever, headache, oral ulceration, optic atrophy with blindness, ptosis, diplopia and photophobia. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy.

c. PHARMACOLOGY

Pharmacokinetics: After IV administration, a triphasic serum decay pattern follows with half-lives of 5 minutes, 2 - 3 hours, and 85 hours. The range of terminal half-life is 19 - 155 hours. Excretion is 80% in the feces and 10 - 20 % in the urine.

The liver is the major excretory organ in humans and animals, and biliary obstruction causes increased toxicity in man.

Formulation: 1 mg/1 mL, 2 mg/2 mL, and 5 mg/5 mL vials containing solution. It is also available in 1 mg/mL and 2 mg/2 mL disposable syringes.

Storage and Stability: It should be stored under refrigeration. Vincristine is available with and without preservatives so the time-frame for use once the vial has been entered varies. The intact vials have a labeled expiration date. Protect from light. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

Administration: Vincristine should be administered intravenously through a freely-running IV. If it extravasates, it produces a severe local reaction with skin slough. FATAL IF GIVEN INTRATHECALLY, FOR INTRAVENOUS USE ONLY.

Supplier: Vincristine is commercially available, and should be purchased through a third party. This drug will NOT be supplied by the NCI.

4.0 STAGING CRITERIA

4.1 Staging Criteria

The Ann Arbor staging criteria will be used. Stage is based on extent of disease at the time of diagnosis. Only patients with Stage III or IV disease are eligible for this protocol.

4.2 Ann Arbor Classification (AJCC Manual for Staging of Cancer, 6th ed., 2002)

STAGE III Involvement of lymph node regions on both sides of the diaphragm (III), which may be accompanied by localized involvement of an associated extralymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE).

STAGE IV Diffuse or disseminated involvement of one or more extra lymphatic organs with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement).

4.3 International Prognostic Score (30)

Age	≥ 45 years	
Gender	Male	
Stage	IV	Note: Stage IV is defined as diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.
Hemoglobin	< 105 g/L	
Albumin, serum	< 40 g/L	
WBC	≥ 15.0 x 10^9/L	
Lymphocytes	Count < 0.6 x 10^9/L or percent < 8% of WBC	

High Risk Disease: 3 or More Adverse Risk Factors

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 spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the **S0816** Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 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 two weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14 or 28 falls on a weekend or holiday, the limit may be extended to the next working day.**

SWOG Patient No. _____

Patient Initials (L, F, M) _____

5.1 FIRST REGISTRATION

_____ a. All patients must have previously untreated Stage III or IV classical Hodgkin lymphoma (nodular sclerosing, mixed cellularity, lymphocyte-rich, or lymphocyte depleted). **Nodular lymphocyte predominant Hodgkin Lymphoma is not eligible.** All histology will be reviewed centrally.

_____ b. Pathology Review: Adequate sections and a paraffin block from the original diagnostic specimen must be available for submission for review by the lymphoma pathology group as outlined in Section 12.0. If the entire paraffin block cannot be sent, cores or punches from these blocks are acceptable. An adequate biopsy requires sufficient tissue to establish the architecture and a WHO histologic subtype with certainty. Thus, core biopsies, especially multiple core biopsies MAY be adequate; whereas, needle aspirations or cytologies are not adequate.

_____ c. Patients must be offered the opportunity to consent to the correlative science studies as outlined in Section 15.0. Patients are encouraged to submit tissue and serum for the correlative science studies as outlined in Section 15.0; however, specimen submission is not a requirement for participation in the study.

_____ d. Patients must be age 18-60, inclusive. Due to concerns about the toxicity of the BEACOPP regimen, patients over the age of 60 are not eligible.

_____ e. All patients must have bidimensionally measurable disease (defined in Section 10.1a) documented on the Lymphoma Baseline Tumor Assessment Form within 28 days prior to registration. Patients with non-measurable disease (defined in Section 10.1b) in addition to measurable disease must have all non-measurable disease assessed with 42 days prior to registration.

_____ f. Patients must have a unilateral or bilateral bone marrow biopsy performed within 42 days prior to registration.

SWOG Patient No. _____

Patient Initials (L, F, M) _____

_____ g. Patients must have a diagnostic quality CT scan of the chest/abdomen and pelvis AND baseline FDG-PET scan (see Section 7.4) performed within 28 days prior to registration. Combined PET/CT scans are required for this study, and older "stand-alone" FDG-PET scans are not adequate for entry to this study. Low resolution "localization" CT scans performed as part of a combined PET/CT scan are not adequate for enrollment or response determination on this protocol. However, if the CT scan of a PET/CT hybrid is performed with both oral and IV contrast with contrast enhancement in the arterial and/or portal venous phase, is at least a 2-slice CT, is acquired with at least 80 mAs and CT scans are obtained with contiguous sections, with a maximum of 5 mm slice thickness, then the pre-treatment and any post-therapy PET/CT scan alone will suffice for patients enrolled on this trial.

_____ h. Patients must not have received prior chemotherapy, radiation, or antibody therapy for lymphoma.

_____ i. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.4).

_____ j. Serum erythrocyte sedimentation rate (ESR), LDH, hemoglobin, albumin, WBC, and lymphocytes must be measured within 28 days prior to registration.

_____ k. Serum estradiol (women only), testosterone (men only), FSH and LH (both men and women) levels must be drawn within 60 days prior to registration, to obtain baseline values.

_____ l. Patients with a history of hypertension or cardiac symptoms must have a MUGA scan or an echocardiogram (ECHO) with no significant abnormalities and a cardiac ejection fraction ≥ 45% within 42 days prior to registration.

_____ m. Patients must not be sero-positive for Hepatitis B (Hepatitis B surface antigen positive or anti-hepatitis B core antigen positive) or sero-positive for Hepatitis C (anti-Hepatitis C antibody positive). However, patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).

_____ n. Patient HIV status must be known prior to registration. HIV-positive patients must not have multi-drug resistant HIV infection, CD4 counts < 150/mcL or other concurrent AIDS-defining conditions. HIV-positive patients are eligible if they have CD4 counts ≥ 150/mcL at the time of enrollment OR if they had a documented CD4 count > 250 at any time within 8 months prior to HL diagnosis, but will be analyzed separately in an independent cohort.

_____ o. Patients must not have significant lung disease with abnormal lung function tests (DLCO > 25% below predicted after correction for hemoglobin) unless it is attributable to lymphoma. Patients must not be requiring continuous supplemental oxygen therapy.

_____ p. Patients must not have had prior solid organ transplantation.

SWOG Patient No. _____

Patient s Initials (L, F, M) _____

_____ q. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease-free for 5 years.

_____ r. Patients must not be pregnant or nursing due to the potential for congenital abnormalities, and the potential of this regimen to harm nursing infants. Women/men of reproductive potential must have agreed to use an effective contraceptive method. 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.

_____ s. All patients must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

_____ t. At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base.

5.2 SECOND REGISTRATION

_____ a. Patients must have completed 2 cycles of ABVD with no evidence of disease progression.

_____ b. Baseline and interim PET/CT scans must have been submitted promptly for centralized review to the CALGB Imaging Core Laboratory (CALGB ICL) as outlined in Sections 7.5, 15.2, 15.3 and 18.2.

_____ c. Patients must be planning to begin either continued ABVD or BEACOPP (escalated dose for HIV-negative patients, standard for HIV-positive patients) within 10 days after the interim PET/CT (see Sections 7.6-7.8) is done.

6.0 STRATIFICATION FACTORS

For Registration Step 1: Is the patient HIV positive? Yes vs. No

For Registration Step 2: Based on centralized review, is the patient PET-positive after 2 cycles of ABVD? Yes vs. No

7.0 TREATMENT PLAN

For treatment or dose modification related questions:

SWOG institutions: Please contact Dr. Press at press@u.washington.edu (Phone: 206/667-1872) or Dr. Friedberg at jonathan_friedberg@urmc.rochester.edu (Phone: 585/273-4150).

ECOG institutions: Dr. John Sweetenham at sweetej@ccf.org (Phone: 216/445-6707) or Dr. Andrew Evens at a-evens@norhwestern.edu (Phone: 312/695-4537)

CALGB institutions: Please contact Dr. Nancy Bartlett at nbartlett@im.wustl.edu (Phone: 314/362-5654) or Dr. Ann LaCasce at alacasce@partners.org (Phone: 650/723-5535).

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 Manuals" under the "Visitors" menu and choose Policy 38).

7.1 Good Medical Practice

The following pre-study tests are recommended within 28 days prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests/assessments that could impact patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Chair prior to registering. If an individual test is considered to be unnecessary, the rationale for not conducting the test must be documented in the medical record.

a. Platelets > 100,000 cells/mcL; ANC > 1,000 cells/mcL

b. Bilirubin ≤ 2 x ULN (unless from Gilberts syndrome or bile duct obstruction due to HL)

c. Creatinine ≤ 2 x ULN

d. Urinalysis, uric acid, and transaminases, should be performed as baseline prestudy tests to assess potential treatment-related toxicities. These tests are not required for eligibility.

e. Neck CT scan (advisable in patients with cervical disease). If performed at baseline, however, a neck CT scan MUST be repeated at completion of therapy (if initially abnormal).

f. Fertility consultation recommended. See ASCO Guidelines on fertility preservation. *(51)*

7.2 Initial ABVD Regimen for All Patients

NOTE: All questions regarding treatment or dose modifications should be directed to the Study Chairs. All patients will begin treatment with two cycles of ABVD chemotherapy. ABVD will be administered according to the standard dosing regimen as summarized in the table below (each cycle is 28 days):

Agent	Dose	Route	Days	Schedule
Doxorubicin	25 mg/m^2	IV	Day 1, 15	Every 28 days for 2 cycles
Bleomycin	10 units/m^2	IV	Day 1, 15	Every 28 days for 2 cycles
Vinblastine	6 mg/m^2	IV	Day 1, 15	Every 28 days for 2 cycles
Dacarbazine	375 mg/m^2	IV	Day 1, 15	Every 28 days for 2 cycles

All drugs will be given at full dose and on schedule in patients receiving ABVD, with no dose delays or dose reductions unless there are serious active infections or other significant complications since recent studies have indicated that dose attenuation, treatment delays and growth factor utilization may impair optimal treatment outcome. *(13,14)*

A full body FDG-PET/CT scan must be performed after 2 cycles of ABVD. This will be performed between 7 and 10 days after the second dose of ABVD chemotherapy in Cycle 2. Scan data must be submitted electronically in DICOM format immediately to the CALGB Imaging Core Laboratory (CALGB ICL) for real-time centralized review to determine if therapy with ABVD should be continued or whether dose-intensification to BEACOPP-escalated is justified (see Sections 15.2, 15.3 and Appendix 18.2).

7.3 ABVD Concomitant Medications

a. Use of Colony Stimulating Factors (CSF) for patients receiving ABVD: Growth factors, including G-CSF, GM-CSF, and Neulasta should be avoided during ABVD therapy since their use has been associated with diminished survival of HL patients treated with this regimen. *(13,14)* (Growth factor use is necessary on the more intense BEACOPP regimen, however.) However, growth factors may be used if patients develop neutropenic infections. Colony Stimulating Factors (CSF) should be administered only in accordance with published ASCO guidelines. Use of CSF under these conditions will be at the discretion of the treating investigator, but must be recorded on the **S0816** Treatment Form.

b. Prophylactic antibiotic therapy (e.g. levofloxacin) to prevent febrile neutropenia is at the discretion of the treating physician. Some authorities recommend, that patients receive pneumocystis prophylaxis during all ABVD therapy (e.g., Bactrim DS on Mondays, Wednesdays, and Fridays or Dapsone 50 mg orally twice daily for subjects allergic to Bactrim) as well as prophylaxis for oral thrush (e.g, fluconazole 100 mg daily or oral nystatin). Pneumocystis prophylaxis is strongly recommended for HIV-positive patients receiving either ABVD or BEACOPP.

c. Highly active anti-retroviral therapy (HAART) for HIV-positive patients receiving ABVD: In general, HIV-positive patients who are on a stable HAART regimen should continue HAART while receiving chemotherapy. However, for patients who are newly diagnosed with HIV, it is preferable to defer initiation of HAART until after chemotherapy is completed. HAART regimens containing zidovudine and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (Rayataz™) can cause a physiologically unimportant hyper-

bilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one. If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

7.4 FDG-PET/CT Imaging

a. This study requires FDG-PET/CT imaging at diagnosis, after two cycles of ABVD chemotherapy, and at the conclusion of chemotherapy. FDG-PET imaging will be used to assess the adequacy of ABVD chemotherapy for each individual patient and to determine whether treatment should be escalated due to a suboptimal response to two cycles of ABVD.

b. Combined PET/CT scans are required for this study and older "stand-alone" FDG-PET scans are not adequate for entry to this study. However, it should be noted that low resolution "localization" CT scans performed as part of combined PET/CT scans are NOT adequate for tumor measurements or response determinations and that high resolution, diagnostic quality CT scans must also be performed at study entry and at completion of therapy for all patients. If the CT scan of a PET/CT hybrid is performed with both oral and IV contrast with contrast enhancement in the arterial and/or portal venous phase, is at least a 2-slice CT, is acquired with at least 80 mAs and CT scans are obtained with contiguous sections (with a maximum of 5 mm slice thickness), then the pre-treatment and any post-therapy PET/CT scan alone will suffice for patients enrolled on this trial.

7.5 Centralized Review of PET/CT scans at the CALGB Imaging Core Laboratory

a. To ensure the highest standards and consistency between different centers, all FDG-PET/CT scans (baseline, interim, and end of treatment PET/CT scans) must be submitted to the CALGB Imaging Core Laboratory at Ohio State University for centralized review (see Sections 15.2, 15.3 and Appendix 18.2). Response determinations and treatment decisions (e.g. continuation of ABVD or switch to BEACOPP) must be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians. The crucial FDG-PET scan conducted after the 2nd cycle of ABVD should be performed on Day 22-25 of Cycle 2 (i.e. 7-10 days after the Day 15 doses of ABVD during Cycle 2). The second PET/CT scan should be scheduled at the start of Cycle 2 of treatment to ensure appropriate timing of response scans.

b. Centralized review will be performed by a member of a team of PET/CT readers. There will be one adjudicator, Dr. Nathan Hall, in the CALGB Core Lab, for cases where major discrepancies exist between local site and central PET interpretation. He will also function as a primary PET/CT reader for cases where immediate interpretation is needed (e.g. time window too short for response by other PET expert readers outside the core lab, technical problems with online review of data by other experts, etc.) If an immediate review is needed, please call the CALGB imaging core lab directly at 614/293-9151. All scans will be submitted to the CALGB Imaging Core Laboratory. The CALGB Imaging Core Laboratory will transmit the scans to the expert reviewers for response determination and then will transmit the results to the SWOG Statistical Center and to the site's primary contact with 72 hours of image receipt (not including weekends) (see Sections 15.2, 15.3 and Appendix 18.2).

The central PET/CT expert review will only focus on the assessment of Hodgkin lymphoma disease sites. This central expert review will NOT provide a comprehensive assessment of the entire PET/CT study and will thus NOT record incidental findings and abnormalities unrelated to Hodgkin lymphoma. Centralized PET/CT is done for the purpose of this trial; it does NOT relieve local PET/CT readers of their responsibility to issue a comprehensive PET/CT report.

c. Cycle 3 of chemotherapy must not be administered until the results of the second PET/CT scan are available. Determination of FDG-PET positivity or negativity will be performed using a 5 point scoring system (Section 18.2) based on guidelines established by an international PET harmonization conference convened in London in May 2007 (Section 18.2). According to these guidelines, scans will be judged to be positive if lesions are more hypermetabolic than the liver by visual, qualitative inspection. Borderline metabolism in a lesion will be considered negative as determined by the international harmonization conference and in concordance with the policies of Gallamini and Hutchinson whose studies established the value of early interim FDG-PET imaging. *(33, 36-38)*

d. Absolute and relative standard uptake values (SUVs) will be recorded for research purposes but MUST NOT be used to determine scan positivity because of inter-institution variations in scan performance and the acknowledged lack of standardization for SUV values. Details of submission of PET/CT scans to the CALGB Imaging Core Laboratory for centralized review and on the performance and interpretation of PET/CT scans are listed in Sections 15.2, 15.3 and Appendix 18.2.

7.6 Continued ABVD Regimen* (for PET negative patients only)

After the initial 2 cycles of ABVD, if FDG-PET imaging indicates that patient disease is PET negative, then patients will continue treatment with four additional cycles of ABVD chemotherapy (a total of 6 cycles). ABVD will be administered according to the standard dosing regimen as summarized in the table below (each cycle is 28 days):

Agent	Dose	Route	Schedule	Re-Treatment Interval
Doxorubicin	25 mg/m^2	IV	Day 1, 15	Every 28 days for 4 cycles
Bleomycin	10 units/m^2	IV	Day 1, 15	Every 28 days for 4 cycles
Vinblastine	6 mg/m^2	IV	Day 1, 15	Every 28 days for 4 cycles
Dacarbazine	375 mg/m^2	IV	Day 1, 15	Every 28 days for 4 cycles

* See also Section 7.3.

7.7 BEACOPP$_{escalated}$ regimen (only for patients who are both PET positive and HIV-negative)

a. BEACOPP$_{escalated}$ will only be administered to HIV-negative patients with HL who remain FDG-PET positive after two cycles of ABVD. The regimen will be administered as described by the German Hodgkin Disease Study Group as described below:

It is recommended that the first cycle of BEACOPP$_{escalated}$ be administered in the hospital, due to its dose intensity. Doxorubicin is given at 35 mg/m^2 IV on Day 1, Cyclophosphamide at 1,250 mg/m^2 IV on Day 1, Etoposide at 200 mg/m^2 IV on Days 1, 2, and 3, Procarbazine at 100 mg/m^2 PO on Days 1-7, Prednisone at 40 mg/m^2 on Days 1-14, Bleomycin at 10 Units/m^2 on Day 8, and Vincristine 1.4 mg/m^2 (capped at a maximum of 2 mg) on Day 8. Filgrastim (G-CSF) is given at a dose of 5 mcg/kg/day from Day 8-14 SubQ (see Section 7.7b.2). Mesna is given as described in Section 7.7b.3. The maximum upper limit for the

calculation of chemotherapy dosages is fixed at a body surface of 2.1 m^2 even if the calculated body surface exceeds this. Cycles are repeated every 21 days provided the leukocytes have recovered to 2,500/mcL and the platelets to 80,000/mcL with a rising trend (after reaching the nadir). If these values are not attained, then a treatment postponement and dose reduction strategy will be put into effect (see Section 8.3a).

Agent	Dose	Route	Schedule	Re-Treatment Interval
Etoposide	200 mg/m^2	IV	Day 1,2,3	Every 21 days for 6 cycles
Doxorubicin	35 mg/m^2	IV	Day 1	Every 21 days for 6 cycles
Cyclophosphamide	1,250 mg/m^2	IV	Day 1	Every 21 days for 6 cycles
Procarbazine	100 mg/m^2	PO	Days 1-7	Every 21 days for 6 cycles
Prednisone	40 mg/m^2	PO	Days 1-14	Every 21 days for 6 cycles
Bleomycin	10 Units/m^2	IV	Day 8	Every 21 days for 6 cycles
Vincristine	1.4 mg/m^2 (2 mg max)	IV	Day 8	Every 21 days for 6 cycles
Filgrastim (G-CSF)	5 mcg/kg/day	SubQ	Days 8-14	Every 21 days for 6 cycles

b. Supportive Therapy for $BEACOPP_{escalated}$

1. IV Fluids: Oral or IV fluid intake in excess of 2.5 L daily is required during therapy.

2. Administration of G-CSF: Due to the high dose intensity of $BEACOPP_{escalated}$, administration of filgrastim (G-CSF) is mandatory in every cycle from Day 8 of the cycle. G-CSF should be discontinued when, after reaching the nadir, the leukocyte count has remained over 1,000/mm^3 on 3 successive days. At least 48 hours should transpire after discontinuation of G-CSF before the next cycle of $BEACOPP_{escalated}$ is administered.

3. Prophylaxis of hemorrhagic cystitis. The German Hodgkin Disease Study Group recommends treatment with mesna on Day 1 of each cycle for patients receiving $BEACOPP_{escalated.}$ On the other hand, several U.S. investigators have given $BEACOPP_{escalated}$ successfully without mesna without encountering hemorrhagic cystitis.

   If mesna is administered for the prophylaxis of cyclophosphamide-induced hemorrhagic cystitis, it is recommended that one of the two schedules below is used. Mesna may be given on a fractionated dosing schedule of three bolus intravenous injections or a single bolus injection followed by two oral administrations of mesna tablets as outlined below. Mesna may be given as intravenous bolus injections in a dosage equal to 20% of the cyclophosphamide dosage (w/w) at the time of cyclophosphamide administration and 4 and 8 hours after each dose of cyclophosphamide. The total daily dose of mesna is 60% of the cyclophosphamide dose. The recommended dosing schedule is outlined below:

	0 Hours	4 Hours	8 Hours
Cyclophosphamide	1,250 mg/m^2	---	---
Mesna Injection	240 mg/m^2	240 mg/m^2	240 mg/m^2

Alternatively, mesna can be given as an intravenous bolus injection equal to 20% of the cyclophosphamide dosage (w/w) at the time of cyclophosphamide administration followed by mesna tablets given orally in a dosage equal to 40% of the cyclophosphamide dose 2 and 6 hours after each dose of cyclophosphamide. The total daily dose of mesna is 100% of the cyclophosphamide dose, as indicated below. The recommended dosing schedule is outlined below:

	0 Hours	2 Hours	6 Hours
Cyclophosphamide	1,250 mg/m^2	---	---
Mesna Injection	240 mg/m^2	---	---
Mesna Tablets	---	480 mg/m^2	480 mg/m^2

Patients who vomit within two hours of taking oral mesna should repeat the dose or receive intravenous mesna. The dosing schedule should be repeated on each day that cyclophosphamide is administered. When the dosage of cyclophosphamide is adjusted (either increased or decreased), the ratio of mesna to cyclophosphamide should be maintained.

4. Antibiotic prophylaxis with Bactrim, is obligatory on Days 8-15 of each cycle. Dapsone (50 mg orally twice daily) may be substituted for Pneumocystis prophylaxis in subjects allergic to Bactrim.

5. Antiemetic therapy should include 5-HT3 receptor antagonists (e.g. ondansetron, granisetron).

6. Erythrocyte and platelet transfusions may be administered as necessary at the discretion of the treating physician.

7.8 BEACOPP$_{standard}$ regimen

a. BEACOPP$_{standard}$ will be administered to HIV-positive patients with HL who are FDG-PET positive after two cycles of ABVD. The regimen will be administered as described by the German Hodgkin Disease Study Group as described below:

Agent	Dose	Route	Days	Schedule
Etoposide	100 mg/m^2	IV	Day 1,2,3	Every 21 days for 6 cycles
Doxorubicin	25 mg/m^2	IV	Day 1	Every 21 days for 6 cycles
Cyclophosphamide	650 mg/m^2	IV	Day 1	Every 21 days for 6 cycles
Procarbazine	100 mg/m^2	PO	Days 1-7	Every 21 days for 6 cycles
Prednisone	40 mg/m^2	PO	Days 1-14	Every 21 days for 6 cycles
Bleomycin	10 Units/m^2	IV	Day 8	Every 21 days for 6 cycles
Vincristine	1.4 mg/m^2 (2 mg max)	IV	Day 8	Every 21 days for 6 cycles

b. Cycles will be repeated on Day 22 if leukocyte count is above 2.0 x 10^9/L and platelet count is above 50 x 10^9/L. *(52)* No dose reduction will be performed if delays of leukocyte or platelet recover are less than one week. Otherwise dose reductions will be undertaken as described in Section 8.4.

c. Adequate ingestion of fluids (i.v./oral) of at least 2.5 liters/day for Days 1-7 must be assured for patients on BEACOPP regimens. It is the responsibility of the treating physician to monitor the hydration of this regimen.

d. Erythrocyte and platelet transfusions will be administered as necessary at the discretion of the treating physician.

7.9 Supportive care measures for HIV-positive patients

a. HAART (highly active anti-retroviral therapy): In general, HIV-positive patients who are on a stable HAART regimen should continue HAART while receiving chemotherapy. However, for patients who are newly diagnosed with HIV, it is preferable to defer starting HAART until after chemotherapy is completed. HAART regimens containing zidovudine and stavudine should be avoided during chemotherapy due to concerns for overlapping toxicity with chemotherapy. In addition, the protease inhibitor atazanavir (Rayataz™) can cause a physiologically unimportant hyperbilirubinemia; however, in the setting of chemotherapy, some experts suggest switching that drug for another equally effective one. If HAART is withheld during chemotherapy, it should be resumed promptly after conclusion of the last cycle of chemotherapy.

b. Bactrim (one double strength tablet twice daily three days per week) should be given for Pneumocystis and Toxoplasmosis prophylaxis to HIV-positive patients receiving chemotherapy. Dapsone (50 mg orally twice daily), atovaquone, or aerosolized pentamidine may be substituted for Pneumocystis prophylaxis in subjects allergic to Bactrim. Pneumocystis prophylaxis should be continued until the CD4 cells are over 200/mcL.

c. Fluconazole, 100 mg daily, should be given for antifungal prophylaxis for patients on BEACOPP regimens. Itraconazole, 200 mg daily, should be substituted for fluconazole for histoplasmosis prophylaxis if the CD4 count falls below 150/mcL and if the patient lives in an endemic area.

d. Azithromycin, 1,200 mg PO, once weekly, should be given for prophylaxis against Mycobacterium avium complex if the CD4 count falls below 50/mcL.

e. CD4 counts and HIV viral load will be measured each cycle for HIV-positive patients.

f. Administration of granulocyte growth factors (filgrastim, pegfilgrastim, sargramostim) is recommended in HIV+ patients getting $BEACOPP_{standard}$ (e.g. 5 mcg/kg subcutaneously of filgrastim daily) until the leukocyte count has recovered to > 1 x 10^9/L.

7.10 Disease Evaluation Off Treatment

a. 6-8 weeks after the last cycle of chemotherapy:

1. Physical examination

2. Laboratory tests including full blood count, serum electrolytes, urea, creatinine, serum bilirubin, liver transaminases, alkaline phosphatase, lactate dehydrogenase.

3. Contrast enhanced CT scan of chest, abdomen and pelvis (+ neck, if performed at baseline).

4. FDG-PET/CT scan: Patients that are removed from protocol treatment must receive a PET/CT scan before starting subsequent therapy. All FDG-PET/CT scans must be centrally reviewed by the CALGB Imaging Core Laboratory as specified in Section 7.5.

5. Bone marrow biopsy (if initially involved with lymphoma).

b. Follow Up

1. Clinic visit with physical examination at Days 276 and 365, then every 6 months for Years 2-5, then annually until Year 7.

2. Follow-up tests at each time point will be the same as those listed above in Section 7.10a except:

a) FSH, LH and estradiol or testosterone levels will be drawn once per year.

b) Contrast-enhanced CT Scans will only be done every 6 months in Year 2 and annually in Years 3-5. CT scans are not required after Year 5. No PET/CT scans are required after the "end of treatment" scan.

7.11 Criteria for Removal from Protocol Treatment

a. Documented progression of disease as defined in Section 10.2d.

b. Development of unacceptable toxicity, as defined in Section 8.0.

c. Treatment delay of over 4 weeks.

d. Completion of protocol treatment.

e. The patient may withdraw from the study at any time for any reason.

7.12 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.13 Follow-Up Period

All patients will be followed for a maximum of seven years from registration or until death whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS

8.1 Two different versions of the NCI Common Terminology Criteria for Averse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 will be utilized for SAE reporting only. The CTCAE Version 4.0 is identified and located at the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE Version.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 3.0 for routine toxicity reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0.

8.2 ABVD Dose Modifications (applies to all cycles)

a. Hematologic Toxicity: Although it is common practice in the United States to attenuate doses, administer growth factors, or delay treatment due to cytopenias alone, recent studies have shown that this policy is unneccessary and inadvisable for patients receiving ABVD and results in suboptimal treatment outcomes. *(13,14)* Patients should receive full doses of ABVD on schedule on Days 1 and 15 of each 28 day cycle without treatment delays, unless neutropenic fever or documented infections are present. In nearly all cases, counts will recover despite administration of the next course of full dose chemotherapy administered on time. *(13,14)*

If febrile neutropenia occurs, then prophylaxis with antibacterial therapy is recommended for the subsequent cycle (e.g., levofloxacin 500 mg PO daily, Days 4-13 and Days 18-27). Continued anti-bacterial antibiotic use thereafter is at the discretion of the treating physician. In addition, abbreviated G-CSF may be considered (e.g., G-CSF Days 5 to 10 and/or Days 18-23 of each cycle).

If a second febrile neutropenia episode occurs, then a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle (in addition to above antibiotic and G-CSF supportive care measures). Re-escalation is at the discretion of the treating physician. If a third episode occurs, please contact the Study Chair.

b. Transfusions. Erythrocyte and platelet transfusions will be administered as necessary at the discretion of the treating physician.

c. Severe infection (NCI CTC Version 3.0, Grade 3 or 4) due to chemotherapy-related neutropenia requires a decrease in the doses of vinblastine and doxorubicin to 75% of the last dose received for the next cycle. Re-escalation is at the discretion of the treating physician.

d. Impaired Hepatic Function: All patients with bilirubin ≤ 2 x the upper limit of normal (ULN) will receive a full initial dose of doxorubicin and vinblastine. If the bilirubin rises to > 2 x ULN (but ≤ 5 x ULN), the doxorubicin and vinblastine doses must be reduced by 50% of last dose received to avoid undue hepatic toxicity. Full doses should be given once the bilirubin is ≤ 2 x ULN. If the bilirubin rises to

> 5 x ULN, doxorubicin and vinblastine should be discontinued for that cycle. If hepatic function has not recovered to ≤ 2 x ULN by the time the next cycle is due, then remove patient from protocol treatment. In cases of obstruction of the biliary duct by a tumor mass, a biliary drainage stent should be placed prior to chemotherapy.

Bilirubin	Doxorubicin Dose	Vinblastine Dose
≤ 2 x ULN	100%	100%
> 2 - 5 x ULN	50% (of last dose received)	50% (of last dose received)
> 5 x ULN	0%	0%

e. Neuropathy: Patients experiencing Grade 3 vinblastine-neuropathy (e.g., obstipation, weakness) will have the dose of vinblastine reduced by 50% for all further cycles of ABVD. Patients experiencing Grade 4 vinblastine neuropathy will have this drug omitted from all future cycles of ABVD.

f. Bleomycin-induced pneumonitis or pulmonary fibrosis is not predictable and often difficult to diagnose clinically. Therefore a high resolution CT scan and pulmonary function testing should be performed at the slightest suspicion. Since there are no histological or clinical findings which are pathognomonic for bleomycin-induced pneumonitis, the diagnosis must be made on the basis of clinical, radiological and/or histological findings after excluding other differential diagnoses. If these studies suggest bleomycin toxicity, no further bleomycin should be administered. Later resumption of bleomycin administration is justified only if and when the suspicion of bleomycin-induced toxicity has proved unfounded.

8.3 Treatment Postponement and Dose Modifications for $BEACOPP_{escalated}$

a. Treatment with $BEACOPP_{escalated}$ should be postponed until the leukocyte count is > 2,500/mcl and the platelet count is > 80,000/mcl. The maximum treatment delay is 4 weeks. In principle, treatment is to be continued punctually and at full dosage provided that after passage through the nadir, the following conditions are filled:

1. In case these values are not attained on the day of planned continuation of treatment, then therapy is postponed and blood values tested again after 3, 7, 10 and 14 days. As soon as the critical values (see above) are reached, treatment is resumed in accordance with the schedule in Section 7.7.

2. Bleomycin and vincristine should be administered even if leukopenia is observed on Day 8. If non-hematological events (fever, infection or signs thereof, etc.) occur, Day 8 will be eliminated without substitution. After recovery the next cycle begins.

3. If serious unexpected Grade 3 or 4 non-hematological side-effects occur, treatment should be continued only when recovery to ≤ Grade 1 is complete. If no recovery occurs within 14 days, further administration should be made only after consultation with the trial coordinator. If a serious adverse event (SAE) occurs, further administration should likewise await consultation with the trial coordination center.

b. Dose reductions for $BEACOPP_{escalated}$

Dose reduction for escalated BEACOPP follows a predefined de-escalation scheme, which is based upon the occurrence of toxic events in the previous cycles. There will be no dose re-escalations.

The following are considered dose-reduction events on BEACOPP:

- Leukopenia: Grade 4 for more than 4 days (leukocytes < 1,000/mcL).
- Thrombocytopenia: Grade 4 on one or more days (platelets < 25,000/mcL);
- Infection: Grade 4;
- Other toxicity: Grade 4, e.g. mucositis;
- Postponement of treatment for more than 2 weeks due to inadequate recovery of blood values

2. Should one or more dose-reduction events occur in a given cycle, the dose in all following cycles will be reduced by one dose level. If any toxic event occurs in two successive cycles, the following cycle is administered at $BEACOPP_{standard}$ doses. Further possible reductions follow the dose reduction scheme for $BEACOPP_{standard}$. No reduction is made for treatment postponement of up to 2 weeks.

3. Dose levels for $BEACOPP_{escalated}$

Treatment always begins at Dose Level 1. The following levels are to be used for dose reductions as necessary. (Doses of bleomycin, vincristine, procarbazine and prednisone are not reduced.)

Dose Level 1	**Dose**	**Route**	**Schedule**
Cyclophosphamide	1,250 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	200 mg/m^2	IV	Days 1-3

Dose Level 0	**Dose**	**Route**	**Schedule**
Cyclophosphamide	1,150 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	175 mg/m^2	IV	Days 1-3

Dose Level -1	**Dose**	**Route**	**Schedule**
Cyclophosphamide	950 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	150 mg/m^2	IV	Days 1-3

Dose Level -2	**Dose**	**Route**	**Schedule**
Cyclophosphamide	800 mg/m^2	IV	Day 1
Doxorubicin	35 mg/m^2	IV	Day 1
Etoposide	125 mg/m^2	IV	Days 1-3

Dose Level -3	**Dose**	**Route**	**Schedule**
Cyclophosphamide	650 mg/m^2	IV	Day 1
Doxorubicin	25 mg/m^2	IV	Day 1
Etoposide	100 mg/m^2	IV	Days 1-3

* Dose Level -3 is the same as $BEACOPP_{standard}$

Examples of dose reduction for BEACOPP$_{escalated}$

1st Example

Cycle	1	2	3	4	5	6	7	8
Dose Level	1	1	1	**0**	0	0	0	0
Dose-Reduction Event	No	No	**Yes**	No	No	No	No	No

2nd Example

Cycle	1	2	3	4	5	6	7	8
Dose Level	1	1	1	**0**	0	**-1**	-1	**-2**
Dose-Reduction Event	No	No	**Yes**	No	**Yes**	No	**Yes**	No

3rd Example

Cycle	1	2	3	4	5	6	7	8
Dose Level	1	1	1	**0**	0	**-1**	**-3**	-3
Dose-Reduction Event	No	No	**Yes**	No	**Yes**	**Yes**	No	No

If toxic effects occur in two successive cycles, doses based on BEACOPP$_{standard}$ will be used for all subsequent cycles.

4. Intolerance

In case of drug-specific intolerance (e.g. vincristine neuropathy, procarbacine allergy), single drugs may be dropped from the regimen without substitution. The reason for a deviation from protocol should always be recorded on the corresponding treatment forms.

8.4 Treatment Postponement and Dose Modifications for BEACOPP$_{standard}$

Treatment Delay	Dose Modification
< 1 week*	No dose reduction.
1-2 weeks	25% dose reduction should be implemented for cyclophosphamide, doxorubicin, procarbazine and etoposide
> 2 weeks	50% dose reduction should be implemented for cyclophosphamide, doxorubicin, procarbazine and etoposide

* No dose reduction will be performed if delays of leukocyte or platelet recovery are less than one week. Otherwise dose reductions will follow the schema described by the German Hodgkin Disease Study Group. *(52)*

8.5 For treatment or dose modification related questions:

SWOG institutions: Please contact Dr. Press at press@u.washington.edu (Phone: 206/667-1872) or Dr. Friedberg at jonathan_friedberg@urmc.rochester.edu (Phone: 585/273-4150).

ECOG institutions: Dr. John Sweetenham at sweetej@ccf.org (Phone: 216/445-6707) or Dr. Andrew Evens at a-evens@norhwestern.edu (Phone: 312/695-4537)

CALGB institutions: Please contact Dr. Nancy Bartlett at nbartlett@im.wustl.edu (Phone: 314/362-5654) or Dr. Ann LaCasce at alacasce@partners.org (Phone: 650/723-5535).

8.6 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 AdEERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

9.1 Study Calendar: Workup and Initial Therapy for All Patients

		Cycle 1		Cycle 2		Interim PET/CT ¢
REQUIRED STUDIES	**PRE STUDY**	**Day 1**	**Day 15**	**Day 29**	**Day 43**	**Day 53**
PHYSICAL						
History & Physical Exam	X			X		
Weight & Performance Status	X			X		
Tumor Assessment	X			X		
Toxicity Notation		X	X	X	X	
LABORATORY						
CBC, Platelets & Differential	X ß		X	X	X	
Serum Creatinine	X ß		X	X	X	
Electrolytes	X		X	X	X	
Bilirubin	X ß					
FSH, LH, and estradiol or testosterone level	X					
Urinalysis	X ß					
Uric acid	X ß					
AST/ALT/Alk Phosphatase	X ß					
Fertility Consultation	X ß					
Absolute Lymphocyte Count	X					
Albumin	X					
LDH	X					
Erythrocyte Sedimentation Rate	X					
Hepatitis B & C Screening	X					
HIV Screening	X					
Bone marrow biopsy	X					
Pulmonary Function Tests (including DLCO)	X					
Materials for pathology review ¥	X					
HIV Viral Load (only if HIV+)	X			X		
CD4 Count (only if HIV+)	X			X		

Calendar 9.1 continued on next page. Click here for footnotes.

		Cycle 1		Cycle 2		Interim PET/CT ¢
RESEARCH SPECIMENS						
Serum for Correlative Studies (10 cc) &	X					X
Tissue (paraffin block or slides) for correlative studies ¥ &	X					
X-RAYS AND SCANS						
Chest CT (Diagnostic Quality with Contrast) (See Section 5.1g)	X					X
CT scan: abdomen, pelvis (Diagnostic Quality, with Contrast)	X					X
FDG-PET/CT scan Δ	X					X
Transmit DICOM files to the CALGB Imaging Core Laboratory Δ	X					X
ECHO or MUGA ∑	X					
EKG	X					
CT Scan: neck *	X ß					
TREATMENT (See Section 7.2) π √						
Doxorubicin		X	X	X	X	
Bleomycin		X	X	X	X	
Vinblastine		X	X	X	X	
Dacarbazine		X	X	X	X	

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Data submission guidelines may be found in Section 14.0.

The same scanning technique as baseline must be used to allow uniformity of results.

¢ It is critical that Cycle 3 of chemotherapy not be administered until the results of the centralized Day 53 PET scan review are available. Selection of therapy regimen for Cycle 3 must be based on the centralized review of the PET scan, not local review.

¥ See Section 12.0.

& See Section 15.0.

π Patients with progressive disease at any time will be removed from protocol treatment.

√ Patients removed from protocol treatment for any reason will be evaluated at that time by repeating CBC with platelets, LDH, creatinine, liver enzymes, CT of chest, abdomen and pelvis, and all pre-treatment scans to evaluate disease.

ß Results of these tests do not determine eligibility but are recommended prior to registration in accordance with Good Medical Practice (see Section 7.1).

∑ Required if clinically indicated (see Section 5.1l).

Δ See Sections 15.2, 15.3 and 18.2.

* Advisable in patients with cervical disease. If performed at baseline, however, a neck CT scan must be repeated at completion

9.2 Study Calendar Continuation of ABVD Therapy for Patients who are PET-negative after 2 cycles of ABVD

									Restaging α	Follow-up	Follow-up*
	Cycle 3 ¢		Cycle 4		Cycle 5		Cycle 6				
REQUIRED STUDIES	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**
	57	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**197**	**276**	**365**
PHYSICAL											
History & Physical Exam	X		X		X		X		X	X	X
Weight & Performance Status	X		X		X		X		X	X	X
Tumor Assessment	X		X		X		X		X	X	X
Toxicity Notation	X	X	X	X	X	X	X	X	X	X	X
LABORATORY											
CBC, Platelets & Differential	X	X	X	X	X	X	X	X	X	X	X
Electrolytes and Serum Creatinine	X	X	X	X	X	X	X	X	X	X	X
Liver Function Tests	X		X		X		X		X	X	X
LDH											X
Uric acid											X
Alkaline phosphatase											X
FSH, LH, and estradiol or testosterone level									X		X
HIV Viral Load (only if HIV+)	X		X		X		X		X	X	X
CD4 Count (only if HIV+)	X		X		X		X		X	X	X
Bone marrow biopsy (only if positive at baseline)									X		
RESEARCH SPECIMENS (see Section 15.0)											
Serum for Correlative Studies (10 cc)									X		

Calendar continued on next page. Click here for footnotes.

									Restaging α	Follow-up	Follow-up*
	Cycle 3 ¢		Cycle 4		Cycle 5		Cycle 6				
REQUIRED STUDIES	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**
	57	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**197**	**276**	**365**
X-RAYS AND SCANS											
Chest CT (Diagnostic Quality with Contrast) (See Section 5.1g)									X		X
CT scan: abdomen, pelvis (Diagnostic Quality w/ Contrast)									X		X
FDG-PET/CT scan Δ									X		
Transmit DICOM files to the CALGB Imaging Core Laboratory Δ									X		
TREATMENT (See Section 7.6) π √											
Doxorubicin	X	X	X	X	X	X	X	X			
Bleomycin	X	X	X	X	X	X	X	X			
Vinblastine	X	X	X	X	X	X	X	X			
Dacarbazine	X	X	X	X	X	X	X	X			

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Data submission guidelines may be found in Section 14.0.

Footnotes for Calendar 9.2.

¢ It is critical that Cycle 3 of chemotherapy not be administered until the results of the centralized Day 53 PET scan review are available. Selection of therapy regimen for Cycle 3 must be based on the centralized review of the PET scan, not local review.

π Patients with progressive disease at any time will be removed from protocol treatment.

√ Patients removed from protocol treatment for any reason will be evaluated at that time by repeating CBC with platelets, LDH, creatinine, liver enzymes, CT of chest, abdomen and pelvis, and all pre-treatment scans to evaluate disease.

* Follow-up evaluations will occur at Days 276 and 365, then every 6 months for Years 2-5, then annually, until Year 7. For patients who have not progressed, follow-up tests at each time point will be the same as those listed at Day 365 except hormone levels will only be done once per year and CT Scans will only be done every 6 months in Year 2 and annually in Years 3-5. CT scans are not required after Year 5. For patients who have progressed, only hormone levels will be done annually until Year 7, other follow-up tests and CT scans are not required, and patients will be followed for survival.

Δ See Sections 15.2, 15.3 and 18.2.

α Disease evaluation should be performed 6-8 weeks after the last chemotherapy treatment (see Section 7.10).

9.3 Study Calendar Continuation of Therapy for Patients who are PET-positive after 2 cycles of ABVD: Switch to BEACOPP

							Restaging α	Follow-up	Follow-up*
	Cycle 3 ¢	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8			
REQUIRED STUDIES	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**	**Day**
	57	**78**	**99**	**120**	**141**	**162**	**211**	**276**	**365**
PHYSICAL									
History & Physical Exam	X	X	X	X	X	X	X	X	X
Weight & Performance Status	X	X	X	X	X	X	X	X	X
Tumor Assessment	X	X	X	X	X	X	X	X	X
Toxicity Notation	X	X	X	X	X	X	X	X	X
LABORATORY #									
CBC, Platelets & Differential	X	X	X	X	X	X	X	X	X
Electrolytes and Serum Creatinine	X	X	X	X	X	X	X	X	X
Liver Function Tests	X	X	X	X	X	X	X	X	X
LDH									X
Uric acid									X
Alkaline Phosphatase									X
FSH, LH, and estradiol or testosterone level							X		X
HIV Viral Load (only if HIV+)	X	X	X	X	X	X	X	X	X
CD4 Count (only if HIV+)	X	X	X	X	X	X	X	X	X
Bone marrow biopsy (only if positive at baseline)							X		
RESEARCH SPECIMENS (see Section 15.0)									
Serum for Correlative Studies (10 cc)							X		

Calendar continued on next page. Click here for footnotes.

REQUIRED STUDIES	Cycle 3 ¢ Day 57	Cycle 4 Day 78	Cycle 5 Day 99	Cycle 6 Day 120	Cycle 7 Day 141	Cycle 8 Day 162	Restaging α Day 211	Follow-up Day 276	Follow-up* Day 365
X-RAYS AND SCANS									
Chest CT (Diagnostic Quality with Contrast)							X		X
CT scan: abdomen, pelvis (Diagnostic Quality, with Contrast) (See Section 5.1g)							X		X
FDG-PET/CT scan Δ							X		
Transmit DICOM files to the CALGB Imaging Core Laboratory Δ							X		
TREATMENT (See Section 7.7 or 7.8) π √									
BEACOPP Chemotherapy§£	X	X	X	X	X	X			
Prophylactic antibiotics per Sections 8.3 & 8.4	X	X	X	X	X	X	X		

NOTE: Forms are found on the protocol abstract page of the SWOG website (www.swog.org). Data submission guidelines may be found in Section 14.0.

Footnotes for Calendar 9.3

¢ It is critical that Cycle 3 of chemotherapy not be administered until the results of the centralized Day 53 PET scan review are available. Selection of therapy regimen for Cycle 3 must be based on the centralized review of the PET scan, not local review

§ Patients who are HIV-negative and PET-positive after 2 cycles of ABVD will switch to $BEACOPP_{escalated}$ as described in Section 7.7. It is recommended that the first cycle of BEACOPP-escalated be administered in the hospital. Note that it is recommended that complete blood counts be checked twice weekly during $BEACOPP_{escalated}$ (or $BEACOPP_{standard}$). See Section 8.3 for more detailed monitoring instructions.

£ Patients who are HIV-positive and PET-positive after 2 cycles of ABVD will switch to $BEACOPP_{standard}$ as described in Section 7.8.

π Patients with progressive disease at any time will be removed from protocol treatment.

√ Patients removed from protocol treatment for any reason will be evaluated at that time by repeating CBC with platelets, LDH, creatinine, liver enzymes, CT of chest, abdomen and pelvis, and all pre-treatment scans to evaluate disease.

* Follow-up evaluations will occur at Days 276 and 365, then every 6 months for Years 2-5, then annually, until Year 7. For patients who have not progressed, follow-up tests at each time point will be the same as those listed at Day 365 except hormone levels will only be done once per year and CT Scans will only be done every 6 months in Year 2 and annually in Years 3-5. CT scans are not required after Year 5. For patients who have progressed, only hormone levels will be done annually until Year 7, other follow-up tests and CT scans are not required, and patients will be followed for survival.

It is recommended that leukocytes, hematocrit and platelets be measured twice weekly and body temperature monitored daily. At the end of each cycle, the following additional examinations are recommended: leukocytes, electrolytes, creatinine, glucose, uric acid, bilirubicin, AST, and ALT.

Δ See Sections 15.2, 15.3 and 18.2.

α Disease evaluation should be performed 6-8 weeks after the last chemotherapy treatment (see Section 7.10).

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of Lesions

a. Measurable Disease: Lesions that can be accurately measured in two dimensions by CT, MRI, plain x-ray, or other conventional technique and have a greatest transverse diameter of 1 cm or greater; or palpable lesions with both diameters 2 cm or greater. Splenomegaly alone is not sufficient to qualify as measurable disease. Note: PET scans are insufficient for evaluation of measurable disease.

b. Non-measurable Disease: All other lesions including unidimensional lesions, lesions too small to be considered measurable, pleural or pericardial effusion, ascites, bone disease, leptomeningeal disease, lymphangitis, pulmonitis, abdominal masses not confirmed or followed by CT or disease documented only by PET imaging or indirect evidence (e.g., lab values).

10.2 Objective Disease Status

Objective status is to be recorded at each evaluation according to the 2007 revised Cheson et al. criteria. *(53)* All measurable lesions up to a maximum of 6 lesions (largest) should be identified as target lesions at baseline. If there are more than 6 measurable lesions the remaining will be identified as non-target lesions and included as non-measurable disease. The 6 lesions should be selected according to the following features: they should be from disparate regions of the body as possible and they should include mediastinal and retroperitoneal areas of disease if these sites have measurable lesions. Measurements must be provided for target lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

a. Complete Response (CR): Complete disappearance of all measurable and non-measurable disease with the exception of the following. In patients with a positive PET scan before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative. If the PET scan was negative before therapy, all nodal masses > 1.5 cm in greatest transverse diameter (GTD) at baseline must 1have regressed to ≤ 1.5 cm in GTD and all nodal masses > 1 cm and ≤ 1.5 cm in GTD and > 1 cm in their short axis before treatment must have regressed to ≤ 1 cm in their short axis. No new lymphoma lesions should be visible on PET scan or by any other imaging studies. The spleen and/or liver, if considered enlarged at baseline based on physical examination or imaging study (other than PET), must have regressed in size and must not be palpable. If bone marrow was positive at baseline, it must be negative based on biopsy and aspirate at same site. Normalization of markers (e.g., LDH) definitely assignable to NHL. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline.

b. Partial Response (PR): Applies to patients with at least one lesion that does not qualify for a CR. For patients with measurable disease, ≥ 50% decrease in the sum of the product of the diameters (SPD) of up to six dominant lesions identified at baseline. No new lesions and no increase in the size of the liver, spleen, or other nodes. Splenic and hepatic nodules must have regressed by ≥ 50% in SPD. In patients with a positive PET scan before therapy, PET should be positive in at least one previously involved site. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline. Note: Patients who meet all other criteria, but have new lesions observed on PET scan only (i.e., not confirmed on CT or other imaging studies), are considered partial responders.

c. Stable Disease (SD): Does not qualify for CR, PR, or Relapsed/Progressive Disease. Tumor measurements must be obtained by an imaging modality other than PET. Persistent abnormalities seen on CT scans must be FDG-avid on PET scans. All disease must be assessed using the same technique as baseline.

d. Relapsed Disease (after CR)/Progressive Disease (after PR, SD): At least 50% increase in the SPD of target measurable nodal lesions over the smallest sum observed (over baseline if no decrease during therapy), or ≥ 50% increase in the GTD of any node > 1 cm in shortest axis, or ≥ 50% increase in the SPD of other target measurable lesions (e.g., splenic or hepatic nodules) over the smallest sum observed. Appearance of any new bone marrow involvement. Appearance of any new lesion > 1.5 cm in longest axis, or ≥ 50% increase in GTD of any previously involved node with a diameter ≤ 1 cm in the short axis such that its longest axis is now > 1.5 cm. Lymph nodes should be considered abnormal for relapse or progressive disease only if the long axis is > 1.5 cm, or if both the long and short axes are > 1 cm. In patients with a positive PET scan before therapy, lesions should be PET positive. Tumor measurements must be obtained by an imaging modality other than PET. All disease must be assessed using the same technique as baseline. Note: Appearance of any new lesion on PET alone (not confirmed by CT or other imaging modality) is NOT considered relapse/progression.

10.3 Best Response:

a. CR: One objective status of CR documented before relapse.

b. PR: One objective status of PR documented before progression but not qualifying as a CR.

c. Stable: At least one objective status of stable disease documented at least 6 weeks after registration, not qualifying as anything else above.

d. Increasing Disease: Objective status of progression within 12 weeks of registration not qualifying as anything else above.

e. Inadequate assessment, response unknown: Progression greater than 12 weeks after registration and no other response category applies.

10.4 Performance Status

Patients will be graded according to the Zubrod performance status scale:

GRADE

0 Fully active; able to carry on all pre-disease activities 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 all self-care but unable to carry out any work activities; up and about more than 50% of waking hours.

3 Capable of only 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.

10.5 Progression-Free Survival

From date of registration to date of first observation of progressive disease (as defined in 10.2d), or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

10.6 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive and are censored at date of last contact.

11.0 STATISTICAL CONSIDERATIONS

11.1 Primary Objective

This study employs these co-primary objectives: 1) to estimate the 2-year PFS rate in HIV-negative patients with advanced stage Hodgkin lymphoma treated with response-adapted therapy; 2) to estimate the 2-year PFS rate in the subset of these patients who are FDG-PET-positive after 2 cycles of ABVD and are subsequently treated with escalated dose BEACOPP. The error rates for the testing associated with the two objectives are split equally between the two hypotheses. Since the hypothesis within FDG-PET-positive patients is nested within the hypothesis for all HIV-negative patients, testing each hypothesis at the 1-sided 0.037 level results in an overall 1-sided level of 0.05 (determined via simulation studies).

11.2 Accrual Goals

We plan to accrue until 60 eligible patients in the FDG-PET-positive subgroup are enrolled. Under the assumption that 25% of patients are FDG-PET-positive after 2 cycles of ABVD this leads to a sample size of 240 eligible HIV-negative patients. If the PET-positive rate is 20%, then the total sample size will be increased to 300 eligible HIV-negative patients. At the time of the protocol revision to increase the accrual goal from 40 to 60 eligible PET-positive patients, the observed PET-positive rate was approximately 22%, which would lead to a total sample size of 278 eligible HIV-negative patients. Assuming an ineligibility rate of 7%, the total accrual is estimated to be 300 HIV-negative patients.

Two hundred seventy-eight eligible HIV-negative patients is sufficient to estimate the 2-year PFS rate (given complete follow-up) to within 6% (95% confidence interval). In the entire HIV-negative cohort, we will test the historical 2-year PFS estimate of 70% against an alternative hypothesis of 78%. We would consider an observed 2-year PFS estimate of 75% or greater to indicate further investigation of this risk-adapted therapy is warranted, provided other factors such as toxicity appear favorable. This hypothesis test has 89% power. Note that under the original accrual target, this hypothesis test would have had 75% power. Also note that if the fraction of FDG-PET positive patients declines, this would yield a larger overall sample size and therefore increased precision in the PFS estimates.

We assume a FDG-PET-positive rate of 22%, and historical 2-year PFS rates of 30% for FDG-PET-positive patients and 81% for FDG-PET-negative patients, giving the overall 2-year PFS rate of 70% on standard ABVD cited above. Although this assumes dramatically worse outcomes among FDG-PET-positive patients, this estimate of the

difference between FDG-PET-positive and FDG-PET negative patients is actually more conservative than that reported in the literature. *(38)* With 60 patients in the FDG-PET-positive group, we will be able to estimate the 2 year PFS rate in this subgroup (given complete follow-up) to within 13% (95% confidence interval). In the FDG-PET-positive subgroup, we will test this 2-year PFS estimate of 30% against an alternative hypothesis of 48%. We would consider an observed 2-year PFS estimate of 42% or greater to indicate further investigation of this therapy is warranted, provided other factors such as toxicity appear favorable. Under these assumptions, this hypothesis has 87% power. Note that, under the original accrual target, this hypothesis test would have had 70% power.

With 278 total HIV-negative patients (assuming approximately 22% patients are FDG-PET-positive), we will also be able to estimate the overall rates of response, toxicity, and PET positivity to within 6% (95% confidence interval). Any toxicity occurring with at least 5% probability is likely to be seen at least once (> 99% chance). If the fraction of FDG-PET-positive patients declines, this would yield a larger overall sample size and therefore increased precision in the response and toxicity estimates.

We will also conduct an exploratory study in a cohort of HIV+ HL patients receiving response-adapted therapy exactly as proposed for the HIV-negative cohort except that $BEACOPP_{standard}$ will be used for patients who are PET-positive after 2 cycles of ABVD rather than $BEACOPP_{escalated}$. This cohort will be analyzed separately from the HIV-negative cohort, using descriptive statistics. If we accrue 30 HIV+ patients, we will be able to estimate the 2-year PFS to within 19%.

Estimate of Accrual Rate: Intergroup participation (SWOG, ECOG, CALGB): 120 patients/year. Note that this has been increased from the original estimate of 70 patients/year based on the observed accrual rate at the time of the protocol revision to increase the accrual goal.

11.3 Data and Safety Monitoring Committee

There is no formal data and safety monitoring committee for Phase II studies. 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

12.1 Pathology Review

All patients registered to this study will undergo pathology review. The purpose of this review is to verify the histologic diagnosis of classical Hodgkin lymphoma.

a. Pathology materials collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (https://swog.org/Members/ClinicalTrials/Specimens/Lymphpath.asp).

b. Failure to submit a registered patient's pathology materials for pathology will make the patient ineligible.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment).

13.2 Investigator/Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

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.

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 (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application and 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, 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. 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.

- 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.

13.6 CTSU Institutions

CTSU institutions (not aligned with SWOG): Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 18.1.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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.

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 by using the SWOG CRA Workbench. To access the CRA Workbench, go to the SWOG Web site (http://swog.org) and logon to the Members Area. After you have logged on, click on the *CRA Workbench* link to access the home page for CRA Workbench website. Next, click on the *Data Submission* link and follow the instructions. For new users, the link to a "Starter Kit" of help files may be found by clicking on the Starter Kit link at the Members' logon page.

To submit data via the web 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, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit 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 other difficulties with the CRA Workbench, please email *technicalquestion@crab.org*.

b. If you need to submit data that are not available for online data submission, the only alternative is via facsimile. Should the need for this occur, institutions may submit data via facsimile to 800/892-4007 or 206/342-1680 locally. Please do not use cover sheet for faxed data. Please make sure that each page of all faxed data includes the SWOG patient number, study ID, and patient initials.

c. Institutions participating through the Cancer Trials Support Unit (CTSU), please refer to Appendix 18.1.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF INITIAL REGISTRATION:

Submit a copy of the following:

a. **S0816** Prestudy Form

b. Lymphoma Baseline Tumor Assessment Form

c. Pathology report confirming histology.

d. Radiology report

b. WITHIN 28 DAYS OF REGISTRATION:

Submit histopathologic materials (H&E stained section, and paraffin block or 12 unstained paraffin slides) along with a copy of the pathology report to the SWOG Specimen Repository Solid Tumor, Myeloma and Lymphoma Division (see Section 12.1).

c. (FOR HIV-POSITIVE PATIENTS ONLY) AT PRESTUDY; AT THE BEGINNING OF EACH CYCLE OF TREATMENT; AT TIME OF RESTAGING AND FOLLOW-UP:

Submit the **S0816** CD4 and HIV Viral Load Reporting Form.

d. AT THE END OF EACH CYCLE OF TREATMENT:

Submit the **S0816** Treatment Form and the **S0816** Adverse Event Form.

e. AFTER BASELINE, INTERIM, AND END OF TREATMENT FDG-PET SCANNING:

Submit a copy of the interim and end of treatment radiology reports.

See Sections 15.2, 15.3 and 18.2 for instructions on submission of PET/CT data to the CALGB Imaging Core Laboratory.

f. AT BASELINE, AT TIME OF RESTAGING, DAY 365, THEN ANNUALLY UNTIL 7 YEARS AFTER REGISTRATION (for the first time submission include all measurements at prior timepoints):

Submit the Hormone Level Form

g. WITHIN 14 DAYS OF REMOVAL FROM PROTOCOL TREATMENT:

Submit the Off Treatment Notice.

h. THREE MONTHS AFTER OFF TREATMENT:

Submit the **S0816** Adverse Event Form

i. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit copies of the **S0816** Adverse Event Form, the **S0816** Treatment Form (if the patient was still on protocol treatment), and the Follow-Up Form documenting date, site, and method for determining progression/relapse

j. WITHIN 14 DAYS OF EACH DISEASE ASSESSMENT UNTIL PROGRESSION:

Submit the Lymphoma Follow-Up Tumor Assessment Form.

k. AFTER PROTOCOL TREATMENT: EVERY SIX MONTHS FOR YEARS 2-5 AND ANNUALLY THEREAFTER UNTIL 7 YEARS AFTER REGISTRATION:

Submit the Follow-Up Form.

l. WITHIN FOUR WEEKS OF KNOWLEDGE OF SUBSEQUENT MALIGNANCY:

Submit the Notice of Second Malignancy documenting date, site, and method for determining malignancy.

m. WITHIN FOUR WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 Correlative Studies and Banking

Specimens for correlative studies and banking (submitted to the SWOG Specimen Repository - Solid Tissue, Myeloma and Lymphoma Division, Lab #201) optional for patient:

a. With patient's consent specimens must be submitted at the following times (see Sections 9.1-9.3):

1. Serum: A 10 mL serum sample (red-top tube, Vacutainer®) for submission at study entry, after Cycle 2 of ABVD chemotherapy (at the time of interim response assessment with FDG-PET), and at the conclusion of chemotherapy (at the time of final response assessment). These specimens are being collected in order to correlate biomarker findings with tumor immunohistocytochemistry results and response assessments.

3. Tissue: A paraffin block (formalin-fixed paraffin-embedded) from the representative diagnostic section or 12 unstained paraffin slides at study entry. Note: If a paraffin block is unavailable or slides were previously submitted for pathology review (see Section 12.0), then only 12 additional slides for correlative studies should be submitted.

b. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/LymSpecimens.asp), or via the link on the **S0816** protocol abstract page on the SWOG website (www.swog.org).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.2 Instructions for Electronic Submission of Digital PET/CT Image Scans to AG Mednet

Response determinations and treatment decisions for this protocol will be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians.

SWOG and ECOG institutions must submit all FDG-PET/CT scans electronically via the AG Mednet service as described below and in Appendix 18.2. (Please note that while AG Mednet service is provided by SWOG, SWOG will not be responsible for the cost of the scans). Specific information about the imaging workflow and instructions can be found at http://www.agmednet.com.

Electronic Submission Set-up

All participating sites will be provided with an AG Mednet Desktop Agent. The Desktop Agent can be ordered online by filling out the Desktop Agent Order Form which can be found at http://www.agmednet.com/doc/DesktopAgentOrderForm. This form can also be accessed via the link on the protocol abstract page of the SWOG website (swog.org). AG Mednet will require the AG Mednet Desktop Agent Order Form to be faxed directly to AG Mednet at 617/674-8125 or submitted online at the link provided. After activating your desktop agent, sites will be able to submit images electronically, directly from a scanner or PACS, and also from a CD or file system.

NOTE: The person responsible for activating the desktop agent should be involved in submitting the scans as the desktop agent requires user specific log-in verification. All questions regarding AG Mednet agent use should be directed to 888.9AGMEDNET, and hit 2 for the support option.

Sites should contact AG Mednet at the time of IRB approval for AG Mednet enrollment to allow time for the Desktop Agent activation prior to patient registration. This contact is needed even if you are using AG Mednet for another SWOG trial.

Exam Submission Process

When submitting images, you will be required to follow the **S0816** Image Submission protocol, which includes completing the **S0816** Imaging Adjunctive Data Sheet (see Section 18.3) form and de-identifying the scan. First import the scan from a CD or file system, PACS, or directly from the scanner.
To allow for proper image comparison images should be imported in the following order:

1. head
2. cervical
3. thoracic
4. lumbar spine
5. pelvis
6. shoulders
7. sternum

Next, select the scan in your Desktop Agent work list, assign it to the **S0816** trial.

To complete the **S0816** Adjunctive Data Sheet, select the form under the tasks column. Instructions for the form will be sent to your site at the time you enroll with AG Mednet. The data from that adjunctive data sheet will be automatically integrated with the trial databases.

To de-identify the scan, select de-identification in the task list. The Agent will guide you through the proper blind encoding. If sites de-identify scans prior to importing, the AG Mednet Agent de-identification task will ensure the scan has been properly blind encoded.

The final task in your workflow after completing the **S0816** Adjunctive Data Sheet and de-identification is to upload the scan and associated information to SWOG. This can be completed by selecting upload scan in the task list.

Note: All questions regarding AG Mednet Agent use, **S0816** Adjunctive Data Sheets, de-identification or image submission through AG Mednet should be directed to 888.9AGMEDNET, and hit 2 for the support option.

15.3 Instructions for Electronic Submission of Digital PET/CT Images by CALGB FTP

Response determinations and treatment decisions for this protocol will be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians.

CALGB must submit their FDG-PET/CT scans via the CALGB Imaging Core Lab FTP Transfer site described below and Appendix 18.2. Submit scans and corresponding reports as follows:

At Baseline: submit within 24 hours after study entry for QA purposes:

PET/CT
Diagnostic CT with contrast (required if PET/CT not done with contrast)
S0816 Imaging Adjunctive Data Sheet (Appendix 18.3)
S0816 Imaging Site Personnel Form (Appendix 18.4)

After cycles of Primary Chemotherapy: submit within 24 hours upon image acquisition completion for central review to determine treatment decisions:

PET/CT
Diagnostic CT with contrast
Local Report
S0816 Imaging Adjunctive Data Sheet (Appendix 18.3)

After the completion of Chemotherapy submit within 72 hours upon image acquisition:
PET/CT
Diagnostic CT with contrast
Local Report
S0816 Imaging Adjunctive Data Sheet (Appendix 18.3)

The complete PET/CT and diagnostic CT images with contrast data outlined above should be transferred to the CALGB Imaging Core Laboratory in digital DICOM format electronically by CALGB FTP transfer. BMP files, JPG files or hard copies (films) are not acceptable. The raw data of the entire study should be saved until the Imaging Core Laboratory accepts the scan. De-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the SWOG patient ID number (e.g. 002121) and protocol number (e.g. **S0816**). The **S0816** Adjunctive Data Sheet should be faxed to the CALGB Imaging Core Laboratory at the same time as the FTP transfer. Send and email notification to inform the CALGB Imaging Core Laboratory at SWOG0816@imagingcorelab.com of the electronic data transfer, including SWOG number, registering institution name and contact information, date of study, and timepoint (i.e. baseline interim/C2D22-25, final/post-chemotherapy).

The CALGB Imaging Core Lab will notify sites of a protocol deviation/violation via the trial email SWOG0816@imagingcorelab.com if submitted scans from the site are not de-identified. The CALGB Imaging Core Lab will de-identify the received images using the CALGB Imaging Core Lab standard operating procedure (SOP) with trial protocol compliance before transmitting them to the expert reviewers. Sites that are unable to de-identify DICOM images or keep transmitting non-de-identified images to the CALGB Imaging Core Lab after violation notifications will be reported to the trial committee for an inclusion/exclusion decision.

Electronic Data Transfer Instructions

CALGB Imaging Core Lab FTP Transfer Instructions:

The de-identified digital images may be burned to a CD and/or transferred to a PC based system in which the FTP software is installed. Any FTP software can be used to initiate access to the secure FTP Server of the Imaging Core Lab. The standard FTP access information (host address, user account & password) will be provided separately through the specific trial e-mail SWOG0816@imagingcorelab.com, per the request by participating sites before their first data submission. The **S0816** Imaging Adjunctive Data Sheet and the **S0816** Imaging sire Personnel Form (at baseline) can be faxed to the CALGB Imaging Core Laboratory:

CALGB Imaging Core Laboratory
ATTN: **S0816**
FAX: 614/293-9275

Any questions concerning FTP transfer of PET/CT data diagnostic CT with contrast data, the **S0816** Imaging Adjunctive Data Sheet, and the **S0816** Imaging Site Personnel form can be directed to the CALGB Imaging Core Laboratory: CALGB Imaging Core Laboratory, Direct: 614/293-9151, FAX: 614/293-9275.

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).

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.

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 timelier monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. See also Appendix 18.5 for general and background information about expedited reporting.

b. Reporting Methods

This study requires that expedited adverse event reporting use the NCI's Adverse Event Expedited Reporting System (AdEERS). The NCI's guidelines for AdEERS can be found at
http://ctep.cancer.gov. An AdEERS report must be submitted to the SWOG Operations Office electronically via the AdEERS Web-based application located at http://ctep.cancer.gov.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via AdEERS.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1.

d. Other recipients of adverse event reports

The Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable must also be reported according to local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

e. Expedited reporting for commercial agents

Commercial reporting requirements are provided in Table 16.1. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1: Expedited reporting requirements for adverse events experienced by patients who have received commercial drugs on this study.

Attribution	**Grade 4**		**Grade 5[a]**	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**AdEERS**	**AdEERS**
Possible, Probable, Definite	**AdEERS**		**AdEERS**	**AdEERS**

AdEERS: Indicates an expedited report is to be submitted via **AdEERS** 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 AdEERS 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 by fax to 210/614-0006.

f. Reporting secondary AML/MDS/ALL

1. All cases of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following chemotherapy for cancer must be reported in AdEERS.

   i. In protocols using CTCAE Version 4.0 for SAE reporting, three options are available to describe treatment-related events:

   - Leukemia secondary to oncology chemotherapy
   - Myelodysplastic syndrome. NOTE: The only grading option for "Myelodysplastic syndrome" is Grade 4, life-threatening. If reporting MDS that is other than Grade 4, use “Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, (specify,__)” and insert MDS as the specify term.
   - Treatment related secondary malignancy

   ii. In protocols using CTCAE Version 3.0 for SAE reporting, the event(s) can be reported as “Secondary malignancy-Other (specify, ___)”. Report MDS as “Myelodysplasia,” in the BLOOD/BONE MARROW category.

   iii. Secondary malignancies <u>other than</u> AML/ALL/MDS that are related to protocol treatment must also be reported in AdEERS.

iv. Non-treatment related cases of AML/ALL/MDS must be reported as follows:

In protocols using CTCAE Version 4.0 for SAE reporting, report as "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other, specify"

In protocols using CTCAE Version 3.0 for SAE reporting, report MDS as "Myelodysplasia" and Leukemias as "Blood/Bone Marrow - Other (Specify, __)"

For more information see:
http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers.

2. The following supporting documentation must also be submitted within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

Submit the Report and documentation to:

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.

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18.0 APPENDIX

18.1 Cancer Trials Support Unit (CTSU) Participation Procedures

18.2 FDG-PET Imaging Methods

18.3 **S0816** Imaging Adjunctive Data Sheet

18.4 Imaging Site Personnel Form

18.5 Determination of Expedited Adverse Event Reporting Requirements

18.1 Cancer Trials Support Unit (CTSU) Participation Procedures

This procedure applies to all non-SWOG cooperative groups and AMC participants.

Registration/Randomization

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. 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 (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the members' section of the CTSU website or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. EST.

Each CTSU 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 enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the members' section of the CTSU website at www.ctsu.org

All forms and documents associated with this study can be downloaded from the **S0816** web page on the members' section of the CTSU website (www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Requirements for S0816 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Prestudy requirements for patient enrollment on S0816:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations performed.

CTSU Procedures for Patient Enrollment

All site staff (Lead Group and CTSU Sites) will use OPEN to enroll patients to this study. OPEN can be accessed at (https://open.ctsu.org) or from the CTSU member's web site OPEN tab.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.

- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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.

- To perform registrations, the site user must have been assigned 'Registrar' role on the relevant Group or CTSU roster.

- To perform registrations on protocols for which you are a member of the Lead Group, you must have an equivalent Registrar role on the Lead Group Roster. Role assignments are handled through Groups in which you are a member.

- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) 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.

Further instructional information is provided on the CTSU member's web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patients must be registered prior to initiation of treatment (no more than five working days prior to planned start of treatment.)

Data Submission and Reconciliation

1. All case report forms (CRFs) associated with this study must be downloaded from the **S0816** web page located on the members' section of the CTSU website (www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. The preferred method of sending data is via fax at 800/892-4007, (large volumes of data may be sent via post, see contacts table for mailing address). Do NOT include a cover sheet for faxed data.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please fax query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. When faxing data, include the query sheet that was originally sent from SWOG.

4. Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP-IAM account contact information current. This will ensure timely communication between the clinical site and the SWOG data center.

Special Materials or Substudies

1. All specimens submitted for this study must be entered and tracked using the SWOG on-line Specimen Tracking System, as specified in protocol Sections 12.0 and 15.0.

2. You can also access the Tracking System from the members' section of the CTSU website. Go to the **S0816** protocol page and click on the link provided under the Case Report Forms header.

3. Pathology Review
   - Collect, prepare, and submit specimens as outlined in protocol Section 12.0.
   - Do not send specimens, supporting clinical reports, or transmittals to the CTSU.

4. Specimen Submission
   - Submit serum for biomarker testing as outlined in Section 15.1.
   - Submit tissue for biomarker testing as outlined in Section 15.1.

Serious Adverse (AE) Reporting (Section 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the members' section of the CTSU website (www.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the **S0816** web page.

3. Do not send adverse event reports to the CTSU.

4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

Drug Procurement (Section 3.0)

Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 3.0 of the protocol.

Commercial agents: Bleomycin, Cyclophosphamide, Dacarbazine, Doxorubicin, Etoposide, Prednisone, Procarbazine, Vinblastine, and Vincristine
- These drugs are commercially available and will not be supplied free of charge.

Regulatory and Monitoring

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. (e.g., NSABP members may only request credit for protocols pertaining to breast or colorectal cancers). Registrations to protocols for other disease sites may still take place through CTSU without receiving credit for your NSABP activities. Per capita reimbursement will be issued directly from CTSU.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the members' section of the CTSU website.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the privacy rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release protected health information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data Update System (CDUS) 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. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDUS data collected from the study-specific case report forms.

18.2 FDG-PET Imaging Methods

FDG-PET/CT scans with ^{18}Fluorine- fluorodeoxyglucose (FDG) will be performed at baseline, after 2 cycles of ABVD chemotherapy, and at completion of chemotherapy.

Response determinations and treatment decisions for this protocol will be based on the centralized review of the FDG-PET scan and NOT on scan assessments by local physicians.

Baseline PET/CT scan:
All patients should have a pre-treatment FDG-PET/CT scan as a baseline to compare with subsequent scans to assess response. This should be performed not more than 28 days before registration. The baseline scan must be submitted within 24 hours upon image acquisition to the CALGB Imaging Core Laboratory at study entry to assure that the submitted scan is of adequate quality for review before treatment decisions are required. The Imaging Core Laboratory will confirm the receipt of the baseline scan data to the site within 24 hours and send a Quality Check Report within 1-3 business days. If the baseline scan data is non-compliant, as determined by one of the PET/CT expert readers and a member of the CALGB core laboratory, the submitting site will be notified of this decision and will be asked to rectify all non-compliant issues when the interim response scan is obtained. Non-compliant baseline scans will not disqualify patient participation in this trial, because it is only the interim scan that determines patient management. However, compliance with study requirements is strongly encouraged for the baseline scan. The Imaging Core Laboratory will notify the SWOG Statistical center and the sites primary contact of this decision, point out the specific issues of non-compliance, and advise the participating site regarding how to rectify this when the interim scan is obtained.

Interim Response PET/CT scan:
To assess the response to the first two cycles of ABVD chemotherapy, an interim PET/CT scan will be performed on Day 22-25 of Cycle 2 of ABVD chemotherapy (i.e. 7-10 days after the Day 15 administration of the ABVD drugs). Scan data must be submitted within 24 hours upon image acquisition to the CALGB Imaging Core Laboratory for real-time centralized review to determine if therapy with ABVD should be continued or whether dose-intensification to BEACOPP-escalated is justified. This second PET/CT scan should have been scheduled at the time of starting Cycle 2 of ABVD treatment, to ensure appropriate timing and availability of response scans. The CALGB Imaging Core Laboratory will send a reminder email to the site 3 days before the patient scan. The PET/CT images need to be electronically uploaded to the CALGB Imaging Core Laboratory on the day of examination (no later than 24 hours after scanning) via either CALGB FTP data transfer or AG Mednet service (see Section 15.2 and 15.3 for submission instructions). The CALGB Imaging Core Laboratory will transmit the scans to the expert reviewers for response determination and then will transmit the results to the SWOG statistical center and to the sites primary contact via an email from the SWOG0816@imagingcorelab.com email address within 72 hours of image receipt (not including weekends or holidays).

Please see the table below delineating the acceptable days in which the Cycle 2 PET/CT scan can be scheduled. Depending on what day of the week the **second** cycle of ABVD was started, the table indicates the days in which the post-cycle 2 PET/CT has to be completed. The days in which scans can be completed appear shaded. Scans must be schedule according to this table in order to provide CALGB Imaging Core Laboratory the PET/CT images to perform a central review and return findings in sufficient time to begin Day 1 of the determined treatment. This table is based on a 72-hour turn around from the time of image receipt at the CALGB Imaging Core Laboratory.

		SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	SU	M	T	W	TH	F	SA	*SU*	*M*	*TU*	*W*	*TH*	*F*	*SA*
Cycle 2 start day	**Sunday**	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	**24**	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*	*7*
	Monday		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*	*6*
	Tuesday			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	24	25	26	27	28	*1*	*2*	*3*	*4*	*5*
	Wednesday				1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	24	25	26	27	28	*1*	*2*	*3*	*4*
	Thursday					1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	24	25	26	27	28	*1*	*2*	*3*
	Friday						1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	23	**24**	**25**	26	27	28	*1*	*2*
	Saturday							1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	**22**	**23**	**24**	**25**	26	27	28	*1*

Final Response Assessment scan:
To assess the final response after completion of all therapy, patients should have repeat whole body PET/CT scans and diagnostic quality, contrast-enhanced CT scans of the chest, abdomen, and pelvis (and neck, if done at baseline), between 6 and 8 weeks after completion of the last dose of chemotherapy. The final response scan must be submitted within 72 hours upon image acquisition to the CALGB Imaging Core Laboratory. The CALGB Imaging Core Laboratory will transmit the scan data to the SWOG Statistical Center.

Scanning Facilities

- Only full-ring dedicated PET/CT scanners are acceptable. The CT of the PET/CT is used for attenuation correction of PET data and anatomic localization. CT settings should follow institutional guidelines (usually 120-140kV, at least 60mA).

- A documented daily quality control procedure must be in place and records kept.

- Scans must be sent by electronic data transfer via either FTP or AG Mednet service to the CALGB Imaging Core Laboratory. For further information on transfer of imaging data to the CALGB Imaging Core Laboratory, see the Central Review portion of this Appendix (Appendix 18.2).

Scanning Protocol

Patient preparation
Non-diabetic patients should fast for at least 4 hours prior to the scan. Plain (unflavored water) should be taken during the period of fasting and the uptake period to ensure good hydration.

Diabetic patients should ideally be given a morning appointment. They should take their usual antidiabetic medication (oral or insulin) and eat a light meal (lighter than they normally would) on that morning. The time interval between that morning meal and PET/CT scan should be approximately 3-4 hours.

Blood glucose of all patients should be measured on arrival and consideration given to rescheduling when the blood glucose level is higher than 200 mg/dl. Insulin should not be administered to reduce glucose level when the blood glucose is > 200 mg/dl at the time of arrival in the PET clinic.

Oral diazepam may be given if desired to reduce brown fat uptake one hour prior to tracer injection.

Oral diluted contrast (e.g., Gastografin or 2% barium sulfate) may be administered, according to institutional guidelines. Intravenous contrast may also be administered, provided this is done in a technique that avoids deterioration of the CT images by streak artifacts from high-concentration iv. contrast bolus.

Detailed scanning protocol

1. Administer 260 - 555 MBq (7-15mCi) ^{18}F- FDG
2. Emission part of the scan should start no earlier than 60 and no later than 80 minutes after injection.
3. The exact same period of uptake must be used for staging and response scans – within 15 minutes.
4. Perform attenuation corrected 'half-body' PET-CT scan to cover the area from the base of the skull to mid-thigh. This should be done with the arms above the head.
5. Perform a separate head and neck scan, with arms down, ONLY IF this is the only site of disease.
6. Attenuation correction of PET emission data will be based on the low dose CT from the PET/CT.
7. It is critical that follow-up PET/CT scans be performed in an identical way to the baseline scan, with the same PET/CT scanner, same scan direction (skull to thighs or thighs the skull), and consistent arm positioning (arms up or arms down).

Acquisition should be performed using the institution's standard protocol, i.e. with regard to time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc. Images should be reconstructed using OSEM or a similar iterative reconstruction algorithm. Both attenuation-corrected and non attenuation-corrected images should be reconstructed. The proposed data acquisition/reconstruction protocol (including details of all the parameters above) must be agreed with the core lab prior to the start of the study.

Information to be recorded and transferred for each patient:
For each patient, study data acquisition information and patient information must be recorded on the **S0816** Imaging Adjunctive Data Sheet (see Appendix 18.3) and submitted to the CALGB Imaging Core Laboratory. Image data must be transferred to the CALGB Imaging Core Laboratory at the same time as the completed **S0816** Imaging Adjunctive Data Sheet (see below). For further information on transfer of imaging data to the CALGB Imaging Core laboratory, see the Central Review portion of this Appendix (Appendix 18.2).

The following image files are required:

- Attenuation corrected half body images (skull base to mid thigh)
- Non-attenuation corrected half body images
- Half body CT scan
- Attenuation corrected view of head and neck (if performed)
- Non-attenuation corrected view of head and neck (if performed)
- Head and neck CT scan (if performed)
  Projection images (MIPs) are not required

See Sections 15.2 and 15.3 image submission instructions for central review.

WebEx Conferences and Training

The CALGB Imaging Core Lab enables Internet based Visual & Virtual conferences that allow the simultaneous display of images (desktop presentations/desktop applications such as PowerPoint) and mutual communication between participating sites and the core lab in a secure manner (SSL-encoded). The Imaging Core Lab will setup WebEx meetings for problem shooting, site training and important issue brainstorming upon necessary.

Initial Analysis of the first 10 patients and Monthly Monitoring Calls

The CALGB Imaging Core Lab database will track all information of site accrual, patient accrual, study compliance/non-compliance and will release a monthly report to the SWOG trial committee. After the first 10 patients have completed baseline and interim scans and these scans have been graded by the expert readers, a phone conference will be held among PET expert readers. Using WebEx, the expert readers will jointly assess these first 10 cases to assure interobserver agreement. In addition, monthly phone conferences will be held among PET expert readers to monitor study progress, address any issues with data transfer, online access to the core lab, scan interpretation, feed-back from core lab or local sites etc. The leader of the PET expert team (H. Schoder), or his designee, will be available to answer immediate questions from the core lab or other expert readers on a daily basis.

Reporting

PET scans will be reviewed and scored by a member of a team of expert PET/CT readers who are blinded to the patient's clinical status. There will be one reviewer, Dr. Nathan Hall, who will provide backup PET/CT reviewing services within the CALGB Imaging Core Laboratory (see Section 7.5b). Visual interpretation will be used. A local report may also be issued but it is the score from the CALGB Imaging Core Laboratory that will be used to determine subsequent treatment for trial purposes.

The PET response scans will be scored with reference to sites of presumed lymphomatous involvement on the PET staging scan

Negative
1 no uptake
2 uptake ≤ mediastinum
3 uptake > mediastinum but ≤ liver
Positive
4 uptake > liver in some sites even if uptake ≤ liver or mediastinum at other sites
5 uptake > liver in over 90% of sites or development of new uptake consistent with progressive disease

For the purpose of this study, scores 1, 2, 3 with uptake in sites abnormal on the staging scan equal or less than liver uptake will be regarded as 'negative' for disease and scores 4, 5 with uptake greater than liver will be regarded as 'positive' for disease. A separate analysis will be performed on patients with a score of 3 whose scan findings are analogous to the concept of 'minimal residual disease' (MRD) referred to in earlier

published data on the use of PET in lymphoma. However for the purposes of treatment, patients with a score of 3 on the interim PET scan will be regarded as negative for disease.

Standard uptake values (SUVs) will be used to quantify tracer uptake, and response to therapy will be determined by the change in SUV for scans acquired before and after therapy. The change in SUV will be correlated with actual prognosis to test the possibility of defining "quantitative response categories" which may have prognostic value. SUV numbers will be used in a post hoc analysis and the most appropriate measure to be used will be determined. The use of SUVmax and variations of SUVmax will be used in this analysis.

SUVs will be measured either by using a volumetric region of interest (ROI) that clearly encompasses a given lesion (carefully avoiding areas of higher normal activity in the vicinity, such as kidneys or bladder), or with a circular ROI. If a circular ROI is used, this needs to be done in several slices to assure that the recorded SUV is indeed the highest SUV within a given lesion. SUV max will be reported, normalized to body weight. A total of 6 lesions will be measured in this protocol.

Radiation Dosimetry

The whole body dose for FDG is about 0.10 rad/mCi, and the effective dose equivalent about 0.10 rem/mCi (0.03 mSv/MBq). For the suggested activity range of 7-15 mCi, the effective dose equivalent will be 0.7-1.5 rem (7.8 – 16.6 mSv). (ARSAC Notes for Guidance 2006). The target organ is the urinary bladder wall, which will receive 0.22 rad/mCi with a realistic one hour voiding interval (ICRP Publication 53). The dose from a low dose (140 kV, 80mA) CT as part of a PET/CT is about 0.9 rad (rem) or 9 mSv (Wu et al. Eur J Nucl Med Mol Imaging 31:38-43, 2004).

SUV Analysis

The study will rely on visual interpretation only. However data will be collected for post hoc analysis to determine whether visual interpretation can be refined and semi-quantitative measures used to subgroup patients further into 'tighter' quantitative response categories which may have prognostic value. A scheme for analysis of semi-quantitative data is suggested below.

The 'hottest' lesions at staging will be chosen for SUV analysis but if subsequently the response scan shows residual activity at sites different from the 'hottest' lesions at staging, these sites will be used as the index lesions instead. Uptake in up to 6 lesions will be documented. The maximum SUV within the lesion will be calculated using decay corrected administered dose and body weight. The maximum SUV will be selected using a region of interest placed on the axial PET slice with the highest uptake. The maximum CT diameter of the mass will be recorded on the axial slice with the greatest CT diameter. Note the PET and CT axial slices may not match as the maximum SUV may occur within the lesion in a different axial plane to the maximum size on CT. If this occurs and the entire lesion shows at least some degree of FDG uptake, the maximum CT diameter in transaxial dimension should be recorded. However, if only a section of a large residual mass shows residual FDG uptake on the interim scan, then the CT diameter should be measured on the slice where that residual FDG uptake occurs.

18.3 **S0816** Imaging Adjunctive Data Sheet

S0816 protocol requires PET scans to start at [60-80] min post FDG injection. This exact same period of uptake must be used consistently for follow-ups (no more than 15 min difference from the baseline)

1. SWOG Patient ID: _____ Patient Initials: _____
2. Institution/Affiliate: _____SWOG Institution ID: _____
3. Date of PET/CT Scan (MM/DD/YYYY) _____/_____/_____

   Time Period of the study (Mark the time period on the left side and provide required date on the right side):
   - __ Baseline (**≤ 28 days** before registration) Date of Registration: _____/_____/_____
   - __ Interim (**C2D22-25** of ABVD chemo) Date of C2D1: ____/____/____
   - __ Final (**30-60 days** after the last dose of chemo) Date of the last dose of chemo: ____/____/____
4. Patient had been fasting for ____**hours;** Patient blood glucose level was ____ **mg/dL** or ____ **mmol/L**
5. Patient weight prior to dosing _____**kg** / _____**lbs;** Patient height _____ **cm** / _____**ft** _____ **in**.
6. Location of injection side (Circle one):
   Right / **Left** Antecubital **Right** / **Left** Wrist **Other**, specify: _____
7. Effective FDG Dose injected:
   ____ **mCi** / ____ **MBq** at the Time of Injection: ____**hh**: _____**mm** (24 hour clock)
   Pre-injection FDG-Syringe Dose:
   ____ **mCi** / ____ **MBq** at the Time of Pre-Calibration: ____**hh**: _____**mm** (24 hour clock)
   Post-injection Residual Dose assay:
   ____ **mCi** / ____ **MBq** at the Time of Syringe Empty: ____**hh**: _____**mm** (24 hour clock)
8. **PET scan started at** _____ **minutes post FDG injection.**
9. CT of PET/CT: **kVp** _____ **mA** _____ or **mAs** _____
10. Was Oral contrast used during CT scan? **Yes** / **No** Was IV contrast used during CT scan? **Yes** / **No**
11. In the past 4 weeks, has the patient received colony stimulating factors? **No** / **Yes** (then mark all that apply):
    Filgrastim (Neupogen®) ___ Epoetin (Aranesp®, Epogen®, Procrit®) ___
    Pegfilgrastim(Neulasta®)___ Other _____
12. **Model** of the PET/CT scanner used for this study: _____
13. Was the PET imaging completed according to protocol? **Yes** / **No** If not, please explain:
    _____
14. Site treating physician:_____E-Mail: _____ Telephone: _____
15. Site Primary Contact:_____E-Mail: _____Telephone: _____
16. Completed by: _____Date of the form completed: _____/_____/_____

Reminder - This Form should be submitted to the CALGB Imaging Core Lab via:
Email: SWOG0816@imagingcorelab.com **Fax**: 614-293-9275
FTP: Contact Imaging Core Lab at the trial email
Mail: CALGB Imaging Core Lab, The Ohio State University, 395 W. 12th. Ave., Rm 414, Columbus, OH 43210

18.4 **SWOG-0816** Imaging Site Personnel Form

Responsible CRA Contact Complete Address E-mail Phone Number Fax Number	**Radiology Department Contact** Complete Address E-mail Phone Number Fax Number

Please provide the information requested above. Provide the middle initial for individuals who commonly use them. Also, please add or correct the degree/title as necessary. This information will be retained by the CALGB Imaging Core Laboratory.

Once completed, you may **fax this form to:**

CALGB Imaging Core Laboratory
ATTN: **S0816**
FAX: 614/293-9275

Call the Imaging Core Laboratory at 614-293-2788 with any questions. Thank you for your assistance.

18.5 Determination of Expedited Adverse Event Reporting Requirements

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. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps ***to determine if an adverse event is to be reported in an expedited manner*** (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

When a study includes both investigational and commercial agents, the following rules apply.

Concurrent *administration*: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Sequential administration: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting. Expected events are those that have been previously identified as resulting from administration of the agent and are listed in one of the following:

- The current NCI SPEER (Specific Protocol Exceptions to Expedited Reporting) for treatments using agents provided under an NCI-held IND, or an equivalent listing for treatments using agents provided under a Non-CTEP-held IND; located in Section 3.0 of the protocol.
- For treatments using commercial agents, the current CAEPR (Comprehensive Adverse Event and Potential Risks), ASAEL (Agent Specific Adverse Event List), or other list of expected toxicities located in Section 3.0 of the protocol, or the drug package insert.
- Exception to Expedited reporting located in Section 16.1f of the protocol.

An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

Informed Consent Model for S0816

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

- This model informed consent form has been reviewed by the DCT/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 Southwest Oncology Group 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 Southwest Oncology Group Operations Office.

Readability Statistics:	
Flesch Reading Ease	56.3 (targeted above 55)
Flesch-Kincaid Grade Level	9.4 (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 Principal Investigator of a cancer treatment trial is a physician. If this model is used for a trial in which the Principal 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.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035* 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.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. 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/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at *http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035* 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.

S0816, "A Phase II Trial of Response-Adapted Therapy of Stage III-IV Hodgkin Lymphoma using Early Interim FDG-PET Imaging"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have a kind of cancer called Hodgkin lymphoma that is considered "aggressive".

Why is this study being done?

This study is investigational and is being done to find out if it is possible to use early periodic PET scans to identify those patients who are not responding to a combination of standard chemotherapy called "ABVD" (the drugs doxorubicin, bleomycin, vinblastine and dacarbazine). This approach would allow an earlier switch to a more intensive combination chemotherapy called "BEACOPP" (the drugs bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone). We would like to find out if the experimental treatment of switching from ABVD to BEACOPP using periodic PET scanning will improve the chances that your Hodgkin lymphoma will be cured. We also want to compare what kind of side effects this experimental treatment can cause and how often they occur.

Researchers would also like to do laboratory testing on blood and tissue samples in order to find out as much as possible about Hodgkin lymphoma and how this treatment might affect the disease. Some of your tissue must be submitted for this study for testing in order to confirm your Hodgkin lymphoma. *(3/29/10)* **If any tissue is left over, you may choose to allow this tissue to be kept for research purposes. You will have the option to submit blood samples for research purposes only. This will be explained later in this consent form.** *(last two sentences added 3/29/10)*

How many people will take part in the study?

About 300 people will take part in this study. *(7/14/11)*

What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if

you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Medical History and Physical Exam
- Weight and Performance Status
- Disease Assessment including a PET/CT scan and a CT scan of the chest, abdomen, pelvis, and neck.
- Routine laboratory urine and blood tests (to measure your kidney and liver function), including virus testing for Hepatitis B, Hepatitis C, and human immunodeficiency virus (HIV)
- Electrocardiogram (EKG) and (if necessary) a MUGA scan or echocardiogram to monitor your heart function. These tests provide a graphic outline of the heart's activity and are used to determine if any heart disease is present.
- Lung function test to measure how well the lungs are working.
- You will also have your bone marrow examined (called "bone marrow aspiration and biopsy") at the start of this study. Your skin over your hipbone will be numbed by a shot of local anesthetic (lidocaine) given just under your skin. A needle will be inserted through the numbed skin and into the hipbone. The bone marrow will be removed by using suction and a twisting motion of the needle. You may have minor discomfort, and minor infection is also possible. Sometimes allergic reactions to the anesthetic may occur. These are regular tests for many patients with lymphoma. The bone marrow will be looked at to find out if any lymphoma cells are present, and to determine the status of normal blood cells.
- Your initial biopsy sample will be sent to our pathology laboratory to confirm your diagnosis.

During the study…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine laboratory blood tests (to measure your kidney and liver function): Before each cycle of treatment, at follow up visits, and at your doctor's discretion.
- CD4 and HIV viral load counts (*for HIV positive patients only)*: At each cycle
- Bone marrow biopsy (*if initially involved with lymphoma):* At one month after the last cycle of chemotherapy
- Disease Assessment (including full body PET/CT scans, CT scans of the chest, abdomen, pelvis, and neck [if performed at baseline]): After Cycle 2 of ABVD chemotherapy AND 6-8 weeks after the last cycle of chemotherapy

- Once you are registered to the study, you will begin treatment with a combination of chemotherapy drugs called "ABVD." The drug combination includes: doxorubicin bleomycin, vinblastine and dacarbazine. These drugs will be given to you through a needle in your vein over about one hour on Days 1 and 15 of a 28 day cycle. You will initially be given 2 cycles of this drug combination.

- Standard medications will be used to help prevent side effects, such as nausea, fevers, and allergic reactions. Stool softeners will be given to prevent constipation. These medications do not require a prescription, and are commonly used during ABVD therapy. In certain cases, your physician may suggest a medication to help your body produce red blood cells or white blood cells. In all cases, your physician will provide detailed instructions and information regarding these treatments.

- After completing two cycles of ABVD chemotherapy, your disease will be studied to find out the size of your tumor and its exact location in your body using a full body PET/CT scan. The PET/CT scan will be sent to a centralized laboratory at Ohio State University ("the CALGB Imaging Core Laboratory") where a panel of three PET experts will review the PET/CT scans. If the three PET experts at the centralized laboratory decide that the PET/CT scan shows that your disease is inactive, then you will receive an additional 4 cycles of ABVD. If the PET experts determine that the PET scan shows that your disease is still active, then you will receive 6 cycles of BEACOPP chemotherapy as described below. If there is disagreement in the interpretation of the PET/CT scans between the local radiologist and the centralized laboratory, it will be the opinion of the three PET experts at the centralized laboratory that will determine which chemotherapy is recommended.

- "BEACOPP" is a combination of seven drugs:
  - Cyclophosphamide – given as an infusion in your veins on Day 1.
  - Doxorubicin – given as an infusion in your veins on Day 1.
  - Etoposide – given as an infusion in your veins on Days 1, 2 and 3.
  - Procarbazine – given as pills to be taken by mouth on Days 1 through 7.
  - Prednisone – given as pills to be taken by mouth on Days 1 through 14
  - Bleomycin – given as a short intravenous injection on Day 8.
  - Vincristine – given as a short intravenous infusion on Day 8.
- The BEACOPP therapy will be given on a 21-day cycle. If you are given BEACOPP therapy you will receive 6 cycles of this treatment. *(For HIV-positive patients: you will receive the same amount of treatment cycles, but the BEACOPP dosage will be less intense.)*

The following tests and procedures are being done to see how the study is affecting your body. Samples of your tumor tissue and blood are being requested for current scientific studies. At the end of this form you can indicate your preferences related to the use of any of these samples. Your participation in these studies is optional.

- Serum (for biomarker studies): a 10 milliliter sample of your blood (about 2-3 teaspoons) will be collected at prestudy (before starting treatment), after Cycle 2 of ABVD chemotherapy, and at the end of chemotherapy. These specimens will be used for biomarker testing to see if the protocol treatment is having any effect on your disease.
- Tissue (for biomarker testing): a sample of your tumor from the original biopsy will be removed and analyzed for biomarkers involved in your immune system to see if this predicts how well you will respond to the treatment.

How long will I be in the study?

Following the completion of this experimental study, your doctor will continue to follow your health status at Days 276 and 365 (one year), then every 6 months for Years 2-5, and then annually thereafter, for a maximum of 7 years from the time you entered the study. (*7/5/12*) The follow-up evaluation tests that are standard to cancer care will include a medical history, physical examination, and performance status.

The researcher may decide to take you off this study if your disease gets worse despite the treatment; the side effects of the treatment are too dangerous for you; new information about the treatment becomes available and this information suggests the treatment will be ineffective or unsafe for you. It is unlikely, but the study may be stopped early due to lack of funding.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the experimental treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after the completion of this experimental treatment. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to the ABVD combination chemotherapy (doxorubicin, bleomycin, vinblastine and dacarbazine) include:

Likely

- **Nausea/vomiting**
- **Tingling, numbness/weakness in the hands and feet**

-
- **Temporary hair loss**
- **Rash and/or skin changes: Patients may develop a rash, particularly on the hands and feet. Later, the skin on the palms and soles may peel. A variety of creams may lessen the symptoms significantly. Bleomycin may cause changes in skin color, which can be permanent, particularly in areas that are scratched.**
- **Achiness/fatigue/muscle pain**
- **Bone marrow suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, cells that line the mouth, stomach and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells) and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to anemia, an increased risk of bleeding and infection. Should these effects occur, they can be treated with blood products (transfusions), growth factors (drugs that stimulate the bone marrow) and antibiotics.**
- **Discolored urine: Discoloration of the urine may occur up to 48 hours after the doxorubicin is given. This is not harmful.**

Less Likely

- **Pain in the jaw bones, other bones and organ(s) that contain tumor**
- **Loss of appetite**
- **Facial flushing**
- **Abdominal pain**
- **Diarrhea**
- **Constipation: Severe constipation may occur requiring hospital admission. Stool softeners and laxatives may prevent this.**
- **Stomach/intestinal ulcers**
- **Abnormal liver function and kidney function tests**
- **EKG changes**
- **Itchy or swollen eyelids**
- **Watery eyes or "pinkeye"**
- **Malaise/weakness**
- **Temporary blindness**
- **Sensitivity to light: You should use a maximum protection sunscreen and avoid excess sun exposure as your skin will be more sensitive and may burn more easily than normal.**
- **Shortened breath, coughing**
- **Depression**
- **Dizziness**
- **Headache**
- **Inflammation of the vein at the injection site**
- **Rectal bleeding**

- **Chills/fever**
- **Soreness/ulcers in mouth and throat: Temporary irritation to the mouth and the lining of the gastrointestinal track may lead to mouth ulcers (similar to canker sores). Anesthetic medications may ease the mouth discomfort.**
- **Skin rash/redness/itching**
- **Swelling/redness of hands/feet**
- **Thickening nail beds**
- **Loosening of fingernails/toenails**

Rare, but serious

- **Pneumonia**
- **Lung damage: Permanent scarring (fibrosis) of the lungs may occur. Report any cough or shortness of breath to your doctor immediately.**
- **Pulmonary fibrosis**
- **Severe allergic reaction: A fast heart rate, wheezing, low blood pressure, sweating and face rash could occur within a few minutes of treatment. These reactions have generally been controlled with steroids or adrenaline. This reaction is rarely severe or fatal the first time the drug is given. The drugs will not be given again if you become allergic. You will be observed closely while the drugs are given, and medication for controlling an allergic reaction will be immediately available.**
- **Inflammation of the blood vessels**
- **Irregular heartbeat**
- **Heart failure: A small number of patients given doxorubicin over a period of months (at doses higher than those used in the protocol treatment) have developed shortness of breath and swollen ankles because of heart weakness. Report any of these symptoms to your doctor.**

Risks and side effects related to the BEACOPP combination chemotherapy (cyclophosphamide, doxorubicin, etoposide, procarbazine, prednisone, bleomycin, and vincristine) include:

Likely

- **Fatigue**
- **Malaise/weakness**
- **Loss of appetite**
- **Nausea/vomiting**
- **Tingling, numbness/weakness in the hands and feet**
- **Temporary hair loss**
- **Rash and/or skin changes: Patients may develop a rash, particularly on the hands and feet. Later, the skin on the palms and soles may peel. A variety of creams may lessen the symptoms significantly. Bleomycin may cause changes in skin color, which can be permanent, particularly in areas that are scratched.**
- **Achiness/fatigue/muscle pain**

- **Bone marrow suppression: The drugs used to kill cancer cells also kill some normal body cells, especially those that grow rapidly (blood cells, hair, cells that line the mouth, stomach and intestines). Blood cells are made in the bone marrow and are responsible for fighting infections (white blood cells), carrying oxygen (red blood cells) and causing blood to clot (platelets). A reduction in the number of these blood cells (marrow suppression) can lead to anemia, an increased risk of bleeding and infection. Should these effects occur, they can be treated with blood products (transfusions), growth factors (drugs that stimulate the bone marrow) and antibiotics.**
- **Discolored urine: Discoloration of the urine may occur up to 48 hours after the doxorubicin is given. This is not harmful.**
- **Infertility**

Less Likely

- **Chills/fever**
- **Infections**
- **Facial flushing**
- **Abdominal pain**
- **Diarrhea**
- **Constipation: Severe constipation may occur requiring hospital admission. Stool softeners and laxatives may prevent this.**
- **Stomach/intestinal ulcers**
- **Abnormal liver function and kidney function tests**
- **EKG changes**
- **Itchy or swollen eyelids**
- **Watery eyes or "pinkeye"**
- **Sensitivity to light: You should use a maximum protection sunscreen and avoid excess sun exposure as your skin will be more sensitive and may burn more easily than normal.**
- **Shortness of breath, coughing**
- **Depression**
- **Dizziness**
- **Headache**
- **Inflammation of the vein at an injection site**
- **Rectal bleeding**
- **Soreness/ulcers in mouth and throat: Temporary irritation to the mouth and the lining of the gastrointestinal track may lead to mouth ulcers (similar to canker sores). Anesthetic medications may ease the mouth discomfort.**
- **Skin rash/redness/itching**
- **Swelling/redness of hands/feet**
- **Thickening nail beds**
- **Loosening of fingernails/toenails**

Rare, but serious

- **Pneumonia**
- **Lung damage: Permanent scarring (fibrosis) of the lungs may occur. Report any cough or shortness of breath to your doctor immediately.**
- **Severe allergic reaction: A fast heart rate, wheezing, low blood pressure, sweating and face rash could occur within a few minutes of treatment. These reactions have generally been controlled with steroids or adrenaline. This reaction is rarely severe or fatal the first time the drug is given. The drugs will not be given again if you become allergic. You will be observed closely while the drugs are given, and medication for controlling an allergic reaction will be immediately available.**
- **Inflammation of the blood vessels**
- **Irregular heartbeat**
- **Heart failure: A small number of patients given doxorubicin over a period of months (at doses higher than those used in the protocol treatment) have developed shortness of breath and swollen ankles because of heart weakness. Report any of these symptoms to your doctor.**
- **Other types of cancer later in life, including leukemia and myelodysplasia (abnormal bone marrow cells that may lead to leukemia).**

Reproductive risks: You should not get pregnant or father a baby while on this study because the drugs in this study can affect an unborn baby. It is important you understand that you need to use birth control while on this study and for 6 months after the treatment stops. Check with your study doctor about what kind of birth control methods to use and how long to use them.

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope this experimental treatment of switching from ABVD to BEACOPP using periodic PET scanning will be more effective at treating the cancer compared to the usual treatment, there is no proof of this yet. We hope the information learned from this study will benefit other patients with Hodgkin lymphoma in the future. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:

- **Getting treatment or care for your cancer without being in a study**
- **Taking part in another study**
- **Getting no treatment**

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Your local Institutional Review Board (IRB)
- The National Cancer Institute (NCI);
- The Food and Drug Administration (FDA), involved in keeping research safe for people;
- The CALGB Imaging Core Laboratory (CALGB ICL): a central review center helping to review the PET/CT scan results to confirm your response to treatment.
- The Ohio State University Imaging Core Laboratory: a central review center helping to review the PET/CT scan results to confirm your response to treatment.
- (For SWOG and ECOG patients) A qualified representative of AG Mednet (the company providing image transfer of PET/CT scans)
- The Southwest Oncology Group
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials. *(added 6/21/10)*
- *(All AMC institutions must include the following:) The AIDS Malignancy Clinical Trials consortium (AMC) Operations Center (added 6/21/10)*

  [ALL AMC INSTITUTIONS MUST INCLUDE THE FOLLOWING LANGUAGE] (section added 6/21/10)

  To help protect your privacy, the AMC investigators have obtained a Certificate of Confidentiality from the National Institutes of Health. With this Certificate, the AMC researchers cannot be forced to disclose information that may identify you, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

  The Certificate cannot be used to resist a demand for information from personnel of the United States Government that is used for auditing or evaluation of Federally funded projects or for information that must be disclosed in order to meet the requirements of the federal Food and Drug Administration (FDA).

  You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

What are the costs of taking part in this study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

The cost of the PET scan after the second treatment cycle will be reimbursed by the study sponsors, up to a set amount for patients registered up to December 15, 2011. *(11/29/11)* Please discuss with the study doctor what the potential additional costs could be.

Administration of the drugs will be *(provided free of charge/charged in the usual way).* The parts of the research consisting of keeping research records and collecting and storing research specimens for both current and future studies will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be *(charged in the usual way/provided at a reduced rate). (local institutions must choose the option that best fits the hospital's situation)*

The doxorubicin, bleomycin, vinblastine, vincristine, dacarbazine, etoposide, cyclophosphamide, procarbazine, and prednisone are commercially available.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage . You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No

matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*
[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Please note: This following 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 a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

Occasionally, researchers working with the Southwest Oncology Group (SWOG) may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to 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**

Submission of specimens for study-specific testing

Blood Specimen for Biomarker Testing

I agree to submit a 10 milliliter samples of blood (about 2-3 teaspoons) at prestudy (before starting treatment), after Cycle 2 of ABVD chemotherapy, and at the end of chemotherapy for biomarker testing to see if the protocol treatment is having any effect on my disease. (*Since this is an experimental test [the significance of this test has not been proven] neither you nor your doctor will be given the results of this test.)*

Yes No

Tissue Specimen for Biomarker Testing

I agree to allow a portion of my <u>original tumor biopsy</u> to be submitted at prestudy for the analysis of biomarkers involved in my immune system to see if this predicts how well I will respond to the protocol treatment. (*Since this is an experimental test [the significance of this test has not been proven] neither you nor your doctor will be given the results of this test.)*

Yes No

<u>Consent for use of excess diagnostic tissue for research purposes</u>.

Should any tissue or blood remain from the biomarker studies that were discussed previously, we would like to store your specimens for future research studies. The remaining sections of the informed consent document apply to specimens for research purposes.

(address deleted 11/7/11)

Consent Form for Use of Specimens for Research

About Using Specimens for Research

We would like to keep some of the specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

Your specimens may be helpful for research whether you do or do not have cancer. The research that may be done with your specimens are not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens and will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, treat, or cure cancer.**

   Yes No

2. **My specimens may be kept for use in research to learn about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, a written withdrawal of consent should be submitted through your treating physician to the Southwest Oncology Group Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the treating physician.

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

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 the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, 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 the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group 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 the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group 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 the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group 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).