The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

SWOG S0925: A randomized phase 2 study of androgen deprivation combined with cixutumumab versus androgen deprivation alone in patients with new metastatic hormone-sensitive prostate cancer

Yu, et al

DOI: 10.1200/JCO.2014.59.4127

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Distribution Date: February 15, 2014
CTEP Submission Date: January 30, 2014

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

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Chairs: Drs. E.Y. Yu and C.S. Higano.

REVISION #4

Study Chair: Evan Y. Yu, M.D.
Phone number: 206/288-7595
E-mail: evanyu@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 above-referenced study has been revised as follows:

1. **Page 1, Face page**: The following changes have been made to this page:
   - The version date of the protocol and the model consent form has been updated (*Note: No updates have been made to the model consent form aside from repagination).*
   - The page has been reorganized so that the contact information for all **S0925** co-Study Chairs is now listed on page 1 and the table of contents on pages 2-3.

- The heading "Study Coordinators" has been changed to "Study *Chairs*". The change from "Study Coordinators" to "Study *Chairs*" was also made throughout the protocol in Section 7.1 (page 29), Section 8.4b (page 36), and Section 8.6 (page 37).
- The clinicaltrials.gov identifier (NCT number) has been added below the study title.
- The address for the SWOG Statistical Center has been changed from "1100 Fairview Avenue North, MP-557" to "1100 Fairview Avenue North, *M3-C102*".

2. **Page 11 (Section 3.2b); Page 37 (Section 8.6); Pages 57-63 (Section 16.1):** References to the "Adverse Event Expedited Reporting System (AdEERS)" have been changed to "CTEP Adverse Event Reporting System (CTEP-AERS)" throughout the protocol.

3. **Page 31, Section 7.6, CTEP Requirements:** Form numbers have been removed from this section.

4. **Pages 38-40, Section 9.0, Study Calendar**: The following changes have been made to this section:

   - Follow Up After Progression: Follow-up assessments after disease progression are no longer required, thus the 'follow up after progression' column has been removed.
   - Footnotes: The "π" footnote has been revised to include the following instructions regarding activities following disease progression: "*After disease progression, follow-up for survival status will continue to be assessed every 6 months for the first two years and then annually for up to 5 years after registration or until death."*

5. **Pages 49-50, Section 14.4, Data Submission Overview and Timepoints**: The following changes have been made to these pages:
   - Section 14.4a-h: Form numbers have been removed.
   - Section 14.4f: Because PSA testing is not required for follow-up testing after disease progression, the instruction "*if disease has not progressed*" has been added next to the **S0925** Prostate Specific Antigen Reporting Form.

6. **Page 57, Section 16.0, Ethical and Regulatory Considerations**: The following new section regarding the confidentiality of this study has been added:

   "*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."

7. **Page 57, Section 16.1c, Adverse Event Reporting Requirements**: The first sentence of the second paragraph as been revised as follows:

   Original: "In the rare event when internet connectivity is disrupted a 24-hour notification is made to NCI by telephone at 310-897-7497."

   New: "In the rare event when internet connectivity is disrupted, a 24-hour notification ~~is~~ *must be* made to *the* NCI by telephone at ~~310-~~*301*-897-7497."

8. **Page 61, Section 16.1h, Reporting Secondary Malignancy, including AML/ALL/MDS**: The following clarification note regarding when to report a secondary malignancy has been added to this section:

"Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified."

9. **Pages 62-63, Section 16.1i, Reporting Pregnancy, Fetal Death, and Death Neonatal**: A new section regarding when to report pregnancy, fetal death, or death neonatal has been added. As a consequence, repagination of subsequent pages was necessary.

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
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swog.org

January 15, 2014

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug IMC-A12. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S0925 Genitourinary	Dec. 10, 2013 AE #1563579 FU Dec. 19, 2013 AE #1453331 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

December 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	Nov. 1, 2013 AE #1563579

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

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November 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following study:	Reports:	
S0925 Genitourinary	Oct. 22, 2013	AE #1658527 FU
	Oct. 29, 2013	AE #1453331

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

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November 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	Oct. 22, 2013 AE #1787705 FU

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

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September 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:
S0925 Genitourinary	Aug. 12, 2013 AE #1658527 Aug. 13, 2013 AE #1787705

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

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August 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	June 28, 2013 AE #1522228 FU

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

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swog.org

July 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	June 21, 2013 AE #1037753

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

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swog.org

June 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	May 24, 2013 AE #1522228

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

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swog.org

May 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	Apr. 16, 2013 AE #1226320 FU

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

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swog.org

April 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
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MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug IMC-A12. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0925 Genitourinary	Mar. 21, 2013 AE #1226320

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

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swog.org

February 15, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug IMC-A12. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0925 Genitourinary	Jan. 30, 2013 AE #1365330 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
Brian Zeller

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swog.org

February 1, 2013

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0925 Genitourinary	Jan. 7, 2013	AE #1365330
	Jan. 8, 2013	AE #1418370

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

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swog.org

December 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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MEMORANDUM

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	Nov. 27, 2012 AE #1423836 FU

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

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December 1, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following study:	Reports:	
S0925 Genitourinary	Nov. 21, 2012	AE #1386661 FU
	Nov. 21, 2012	AE #1633719 FU

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

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Distribution Date: December 1, 2012
CTEP Submission Date: October 29, 2012

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swog.org

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

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and C.S. Higano.

REVISION #3

Study Coordinator: Evan Y. Yu, M.D.
Phone number: 206/288-1152
E-mail: evanyu@u.washington.edu

IRB Review Requirements

( ) Full board review required. Reason:
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REVISION #3

Sites must suspend accrual of new patients until the local IRB approves the revised consent form.

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

SWOG considers that the Model Consent Form changes represent a **minor alteration** in risk-benefit ratio. Therefore, the site must suspend accrual of new patients until the local IRB approves the revised consent form. (Patients are considered on study if they have already signed a consent form as of today [the date of SWOG's distribution of the October 20, 2010 FDA Drug Communication]. Such patients may be registered to the study.)

However, this revision may undergo **expedited** review at the discretion of the local IRB chair.

Patients who have completed treatment with or are currently receiving Lupron (leuprolide acetate) or Zoladex (goserelin acetate), and patients who have signed a consent form but have not yet started treatment, **must** be informed of these changes. The manner by 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.

This revision has been prepared in response to the October 20, 2010 FDA Drug Communication regarding ongoing safety review of GnRH agonists. The associated safety announcement is attached.

The above-referenced study has been revised as follows:

1. **Face Page, Page 1:** The version date of the protocol has been updated.

2. **Sections 3.3-3.4, Pages 15-22:** The following changes were implemented in these sections:

   - The goserelin acetate (Zoladex®) and leuprolide acetate (Lupron®) drug information sections have been replaced with updated descriptions.
   - A new paragraph describing the FDA Communication (distributed 20 Oct 2010) regarding the risk of diabetes and cardiovascular disease associated with LHRH agonists is included in the "adverse effects" portion of both of these sections.

3. **Section 5.2i, page 26**: The reference to "…Sections 5.5, 5.7, 5.8" has been changed to "…Sections *5.1e, 5.2g, and 5.2h*".

4. **Section 5.3o, page 27:** The following editorial change has been made: The sentence "Patients must have a HgA1c ≤ 7 AND fasting glucose…" has been changed to "Patients must have a *hemoglobin A1c* (HgA1c) ≤ *7%* AND fasting glucose…"

5. **Section 7.6, page 31**: The reference to Section 14.5 has been changed to Section *14.4b*.

6. **Section 8.3c, page 34**: The reference to Section 7.8c (in the second paragraph) has been changed to Section *7.8d*.

7. **Section 8.6, page 37**: The reference to Section 16.0 has been changed to Section *16.1*.

8. **Section 9.0, page 40**: The following footnotes to the study calendar have been revised:

   - The bolded note (at the top of the page), "Forms are found in Section 18.0" has been changed to "*Refer to Master Form instructions in Section 14.2*".
   - Я: The reference to "Section 5.16" has been changed to "Section *5.3p*".
   - †: The reference to "Section 5.4" has been changed to "Section *5.1d*".

9. **Section 14.2, page 48**: Instructions regarding submission of master forms have been revised as follows:

   "Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data

Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports)."

Has been changed to:

"*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*."

10. **Sections 14.4g & 14.4h, page 50**: The reference to Section 14.8 has been changed to Section *14.4e*.

11. **Model Informed Consent, "What side effects or risks…", page 9:** Because of the 20 Oct 2010 FDA safety communication (now described in Sections 3.3 and 3.4 of the protocol), "development of diabetes," "heart attack," and "stroke" have been added in a new list of rare but serious risks.

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 calendars into MS Word and removal of the consent form as Section 18.0.

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
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FDA U.S. Food and Drug Administration

Drugs

FDA Drug Safety Communication: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases

Safety Announcement

[10-20-2010] The U.S. Food and Drug Administration (FDA) has notified the manufacturers of the Gonadotropin Releasing Hormone (GnRH) agonists of the need to add new safety information to the *Warnings and Precautions* section of the drug labels. This new information warns about increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) in men receiving these medications for the treatment of prostate cancer. FDA's notification to manufacturers of GnRH agonists to add this safety information is based on the Agency's review of several published studies[1-7], described in the Agency's Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[1], issued in May 2010.

GnRH agonists are approved to treat the symptoms (palliative treatment) of advanced prostate cancer. The benefits of GnRH agonist use for earlier stages of prostate cancer that have not spread (non-metastatic prostate cancer) have not been established.

Although the risk for diabetes and cardiovascular diseases appears to be low in men receiving GnRH agonists for prostate cancer, it is important for healthcare professionals to evaluate patients for risk factors for these diseases. Healthcare professionals should always carefully weigh the benefits and risks of using GnRH agonists before determining appropriate treatment for prostate cancer.

Patients who are receiving treatment with GnRH agonists should undergo periodic monitoring of blood glucose and/or glycosylated hemoglobin (HbA1c). Increased blood glucose levels may represent development of diabetes or worsening of blood glucose control in patients with diabetes. Healthcare professionals should also monitor patients for signs and symptoms suggestive of development of cardiovascular disease and manage according to current clinical practice.

Additional Information for Patients

- GnRH agonists are sold as the brand names – Lupron, Zoladex, Trelstar, Viadur, and Eligard.
- Before receiving GnRH agonists, tell your healthcare professional if you have diabetes, heart disease, a previous heart attack or stroke, or any cardiovascular risk factors like high blood pressure, high cholesterol, or cigarette smoking.
- If you have any concerns about receiving these medicines, talk to your healthcare professional.
- Report any side effects from the use of GnRH agonists to the FDA MedWatch program, using the information in the "Contact Us" box at the bottom of the page.

Additional Information for Healthcare Professionals

- Most of the studies reviewed by FDA reported small, but statistically significant increased risks of diabetes and/or cardiovascular events in patients receiving GnRH agonists.
- Carefully weigh the known benefits and risks of GnRH agonists when determining appropriate treatment for prostate cancer.
- Monitor blood glucose and/or glycosylated hemoglobin periodically in patients receiving GnRH agonists.
- Monitor patients for signs and symptoms suggestive of development of cardiovascular disease.
- Ensure that cardiovascular risk factors such as cigarette smoking, high blood pressure, high cholesterol, high blood sugar, and being overweight are managed according to current clinical practice.
- Report adverse events involving GnRH agonists to the FDA MedWatch program using the information in the

"Contact Us" box at the bottom of this page.

Data Summary

FDA's decision to notify sponsors that new safety information be added regarding increased risk of diabetes and certain cardiovascular diseases to the *Warnings and Precautions* section of the drug labels for GnRH agonists is based on the Agency's review of several published studies[1-7] and a Science Advisory[8] described in the Agency's May 2010 Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[2].

References

1. Keating NL, O'Malley JO, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2006;24:4448-4456.
2. Keating NL, O'Malley JO, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of Veterans with prostate cancer. *J Natl Cancer Inst*. 2010;102:39-46.
3. Tsai HK, D'Amico AV, Sadetsky N, Chen M-H, Carroll PR. Androgen deprivation therapy for localized prostate cancer and the risk of cardiovascular mortality. *J Natl Cancer Inst*. 2007;99:1516-1524.
4. Saigal CS, Gore JL, Krupski TL, Hanley J, Schonlau M, Litwin MS, and the Urologic Diseases in America project. Androgen deprivation therapy increases cardiovascular morbidity in men with prostate cancer. *Cancer*. 2007;110:493-500.
5. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelson A, et al. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the population-based PCBaSe Sweden. *J Clin Oncol*. 2010;28:3448-56.
6. Alibhai SMH, Duong-Hua M, Sutradhar R, Fleshner NE, Warde P, Cheung AM, et al. Impact of androgen deprivation therapy on cardiovascular disease and diabetes. *J Clin Oncol*. 2009;27:3452-3458.
7. Efstathiou JA, Bae K, Shipley WU, Hanks GE, Pilepich MV, Sandler HM, Smith MR. Cardiovascular mortality after androgen deprivation therapy for locally advanced prostate cancer: RTOG 85-31. *J Clin Oncol*. 2008;27:92-99.
8. Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, Keating NL, et al on behalf of the American Heart Association Council on Clinical Cardiology and Council on Epidemiology and Prevention, the American Cancer Society, and the American Urological Association. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation*. 2010;121:833-840.

Related Information

- FDA Drug Safety Communication: Ongoing Safety Review of GnRH Agonists and possible increased risk of diabetes and certain cardiovascular diseases[3]
  5/3/2010
- FDA Drug Safety Podcast for Healthcare Professionals: Update to Ongoing Safety Review of GnRH Agonists and Notification to Manufacturers of GnRH Agonists to Add New Safety Information to Labeling Regarding Increased Risk of Diabetes and Certain Cardiovascular Diseases[4]
  10/20/2010
- Gonadotropin-Releasing Hormone (GnRH) Agonists Information[5]

Contact Us

- **Report a Serious Problem**
- 1-800-332-1088
- 1-800-FDA-0178 Fax

MedWatch Online[6]

Regular Mail: Use postage-paid FDA Form 3500[7]

Mail to: MedWatch 5600 Fishers Lane

Rockville , MD 20857

Links on this page:

1. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209842.htm
2. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209842.htm
3. /Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm209842.htm
4. /Drugs/DrugSafety/DrugSafetyPodcasts/ucm230464.htm
5. /Drugs/DrugSafety/InformationbyDrugClass/ucm209848.htm
6. https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm
7. http://www.fda.gov/downloads/Safety/MedWatch/DownloadForms/UCM082725.pdf

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Distribution Date: November 15, 2012
E-mailed Date: November 8, 2012

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

FROM: Gilbert R. Carrizales, M.S., Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and C.S. Higano.

STATUS NOTICE

Study Coordinator: Evan Y. Yu, M.D.
Phone number: 206/288-7595
E-mail: evanyu@u.washington.edu

IRB Review Requirements

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- ( ) Study closure due to new risk information

(√) Expedited review allowed

( ) No review required

PERMANENT CLOSURE

The above-referenced study has met its accrual goal and will be permanently closed **effective December 1, 2012 at 11:59 p.m. PST**.

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
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swog.org

November 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

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This safety report pertains to the following study:	Report:
S0925 Genitourinary	Oct. 23, 2012 AE #1982512

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

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October 15, 2012

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FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

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S0925 Genitourinary	Sep. 20, 2012	AE #1423836
	Oct. 1, 2012	AE #1633719

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( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug IMC-A12. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:

S0925 Genitourinary

Report:

Sep. 14, 2012 AE #1386661

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

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
Jean Barce
Austin Hamm
Brian Zeller

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swog.org

September 15, 2012

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug IMC-A12. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following study:	Reports:
S0925 Genitourinary	Aug. 31, 2012 Mfr Rpt #IT201201007623 FU
	Aug. 31, 2012 Mfr Rpt #TR201205004612 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

June 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug IMC-A12. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following study:	Report:
S0925 Genitourinary	May 31, 2012 Mfr Rpt #IT201201007623 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Hongli Li, M.S.
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Brian Zeller

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Distribution Date: June 1, 2012
CTEP Submission Date: May 11, 2012

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swog.org

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

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and M.H.A. Hussain.

REVISION #2

Study Coordinator: Evan Y. Yu, M.D.
Phone number: 206/288-1152
E-mail: evanyu@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

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 receiving protocol treatment, and patients who sign a consent form prior to Institutional Review Board (IRB) approval and local implementation of the consent form changes, need not be informed of these changes unless required by the local IRB.

Face Page: "Southwest Oncology Group" has been replaced with "SWOG". The participants list was revised to delete "UCOP" as this program has been discontinued. The alternative names for IMC-A12 (A12, Cixutumumab) have been added under "Agents". Benjamin Ely is no longer with the Group. His name and contact information has been replaced with that for Hongli Li, M.S. The version date of the protocol has been updated.

Sections 1.5-1.7, page 3: The following statement has been added to each of these sections for clarification: "(If patient develops clinical progression or clear castration-resistant disease prior to Cycle 4, Day 1, <insert item> should be obtained earlier as the patient goes off protocol, before initiation of next line therapy.)"

Section 3.0, page 5: Information regarding Investigator's Brochures has been added to this section.

Section 3.2c, page 9a: The section regarding "How supplied" has been revised to include an additional vial concentration of 15 mg/mL. The text ", polyolefin, or polyvinyl chloride (PVC)" has been added to the section regarding preparation. A new sentence has been added at the end of this section to provide instructions if using pre-filled AVIVA.

Section 3.2d, pages 9a-10: The drug ordering section has been revised to delete the information regarding requesting drug by mail, to add faxing and e-mail instructions, and to emphasize that **beginning June 1, 2012 all sites must convert to ordering drug through the PMB's Online Agent Order Processing (OAOP) for PMB-supplied agents. The paper-based Clinical Drug Request Form, NIH Form 986, will no longer be accepted after this date.** The Drug Accountability section has been revised to reflect the Group's current standard language. Paragraphs have been added to address Drug Returns and Questions.

Section 4.0, page 12: Information has been added to this section to define severity of disease (minimal versus extensive).

Section 5.1, page 13: The "Note" regarding no formal biopsy report has been added to this section.

Section 5.2, page 13: This section has been revised to indicate that non-measurable disease must be assessed within 56 days instead of 42 days.

Section 5.5, page 13a: This section has been revised to clarify that patients must have had no more than 30 days of prior medical castration for metastatic prostate cancer. Prior androgen deprivation therapy is allowed if it was received with curative intent in the neoadjuvant, concurrent, and/or adjuvant fashion and at least 2 years have elapsed since completion of androgen deprivation therapy. The start date of medical castration is considered the day the patient first received an injection of a LHRH agonist, not an oral antiandrogen. This section has also been revised to clarify that the 30 day window begins from the date of receiving the LHRH agonist, not the oral antiandrogen. Text has been added to indicate that patients must not have received a bilateral orchiectomy or LHRH antagonists (i.e., Degarelix). However, if the patient was initiated on a LHRH antagonist within the 30 day window and is willing to switch to a LHRH agonist with bicalutamide, he may enroll in the late induction group. The last sentence "If this method of castration…" has been deleted. The text "LHRH agonist and/or anti-androgens" has been replaced with "androgen deprivation therapy" in the second paragraph of this section.

Section 5.6, page 14: The sentence "Once a patient has started…" has been added at the end of this section.

Section 5.7, page 14: The sentence regarding prior cytotoxic chemotherapy with curative intent in the neoadjuvant or adjuvant setting has been added to this section.

Section 5.10, page 14: The text “non-orchiectomy” has been replaced with “all major.”

Section 5.12, page 14 The text "(unless documented Gilbert's disease)" was added to this section.

Section 5.16, page 15: The text “should” has been replaced with “must” in the last sentence of this section.

Section 5.20, page 15: The sentence regarding concurrent bone targeting agents has been added to indicate that bone targeting agents that do not have effect on PSA (i.e., denosumab or zoledronic acid) are allowed.

Section 5.25, page 15: This section has been revised to include the Group’s current standard language regarding ensuring the current date of IRB approval within the OPEN registration process.

Section 7.1, page 16: This section has been revised to indicate that tests/assessments performed for Good Medical Practice are recommended, not required.

Section 7.3, pages 16-17: The text “androgen deprivation therapy” has been replaced with “protocol treatment” in the last sentence of the last paragraph on page 16. The bolded paragraph at the top of page 17 has been revised for clarification purposes. A sentence has been added to indicate that asymptomatic patients without pain may begin bicalutamide on the same day as the LHRH agonist. A second “NOTE” section has been added to Section 7.3a regarding monitoring for one hour after the first infusion of IMC-A12. The paragraph beginning “Cycle 1, Day 1 is designated…” was added to Section 7.3a. The paragraph beginning “Cycle 1, Day 1 is designated…” was added to Section 7.3b. The sentence “The PSA obtained prior to initiating any androgen deprivation therapy, including bicalutamide, should be used as the baseline PSA” was added to Section 7.3b.

Section 7.7, page 18: This section has been revised to reflect the Group’s current standard wording regarding recording drug compliance.

Section 7.8, page 18a: A new section 7.8b has been added to indicate that development of castration-resistant prostate cancer as determined by two serial rises in PSA while on treatment with castrate testosterone levels qualifies as criteria for removal from protocol treatment. The remainder of this section has been revised accordingly.

Sections 8.4b and 8.4c, pages 20 & 21: The heading of the second column of the table has been revised to reference the CTCAE Version 4.0. The first sentence of Section 8.4c has been revised to reference CTCAE 4.0 terminology.

Section 8.6, page 22: This section has been revised to reflect the Group’s current standard language regarding reporting toxicities.

Section 9.1 (Study Calendar), page 23: The text “Chest” has been removed from the line for “CT or MRI” under “X-Rays and Scans” as this was included inadvertently. The “Follow-Up After Progression” column has been revised to indicate that PSA, CT or MRI and bone scan should be obtained. The “√” footnote was added and the “√” symbol added to the Cycle 4, Week 13 Column for “Blood Specimens”. The “*” footnote was revised to indicate Good Medical Practice is recommended, not required. The text “with cancer-associated pain” was added to the “Ω” footnote.

Section 10.8, page 27: This section has been added to define PSA progression.

Section 11.1, page 27: The word "eligible" has been added to Section 11.1 to clarify that the accrual goal for this study is 180 eligible patients. The name "Southwest Oncology Group" has been replaced with "SWOG" in this section.

Section 11.5, page 28: The name "Southwest Oncology Group" has been replaced with "SWOG" in this section.

Section 13.0, pages 29-30: The name "Southwest Oncology Group" has been replaced with "SWOG" in this section.

Section 14.3a, page 31: The name "Southwest Oncology Group" has been replaced with "SWOG" in this section. The phone number for the SWOG Operations Office has been updated.

Section 14.5, page 32: The heading of this section has been revised to reflect that forms must be submitted within 7 days of completion of each cycle.

Section 15.0, page 33: The text "or at the time the patient develops clinical progression or clear castration-resistant disease should that occur prior to Cycle 4, Day 1" has been added at the end of this section.

Sections 15.3-15.4, page 34: These sections have been rewritten to correctly reflect the materials contained in the specimen kit and the amount of plasma to be obtained in the green and purple top tubes. A sentence has been added to the end of Section 15.4d regarding ensuring tubes are completely full for adequate processing of samples.

Section 15.6 & 15.7, pages 34-35: These sections have been revised to correct the amount of plasma to be obtained in the green and purple top tubes (4 mL and 6 mL respectively).

Section 15.9, page 36: Text within this section has been bolded for emphasis.

Section 16.0, page 37: The "Drug Accountability" section has been revised to reflect the Group's standard language.

Section 16.1, pages 38-42: The Adverse Event Reporting Section has been revised to reflect current reporting requirements.

Model Informed Consent, pages 47-51a, 54 and 57: The name "Southwest Oncology Group" has been replaced with "SWOG" throughout the model consent and instructions. The text "(also called cixutumumab)" was added to the drug name in the "Why is this study being done" section on page 49. The word "chest" was deleted from the CT or MRI bullet point on page 50. The text "and you have pain from your cancer" was added midway in both paragraphs describing treatment on page 51. The sentence "If you have no pain, you may start bicalutamide (Casodex) on the same day as leuprolide acetate (Lupron) or goserelin acetate (Zoladex)." has been added to both paragraphs describing treatment on page 51. The word "chest" was deleted from "chest/abdomen/pelvis" on page 51. The text "you have not already begun taking drugs to block hormone production prior to starting this study and" has been added to #2, Submission of specimens for study-specific testing on page 57.

Section 19.1, pages 76-77: This section has been updated to reflect the Group's current standard wording for determination of expedited adverse event reporting requirements.

Pages 3a, 5a, 10a, 13a, 18a, 42a and 51a have been added to the protocol to prevent extensive repagination.

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
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swog.org

May 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug IMC-A12. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	Apr. 6, 2012 Mfr Rpt #ES201101003224 FU
S0925 Genitourinary	Apr. 6, 2012 Mfr Rpt #TR201111006442 FU
	Apr. 6, 2012 Mfr Rpt #IT201202003593 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
Cathy M. Tangen, Dr.P.H.
Shannon McDonough, M.S.
Hongli Li, M.S.
Cathryn Rankin, M.S.
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swog.org

Distribution Date: March 15, 2012
E-mailed Date: March 6, 2012
CTEP Submission Date: February 24, 2012

TO: ALL SWOG MEMBER, CCOP, UCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and M.H.A. Hussain.

REVISION #1

Study Coordinator: Evan Y. Yu, M.D.
Phone number: 206/288-1152
E-mail: evanyu@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

Sites must suspend accrual of new patients until the local IRB approves the revised consent form.

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

The SWOG considers that the Model Consent Form changes represent a **minor alteration** in risk-benefit ratio. Therefore, the site must suspend accrual of new patients until the local IRB approves the revised consent form. (Patients are considered on study if they have already signed a consent form as of today [March 6, 2012]. Such patients may be registered to the study.)

However, this revision may undergo **expedited** review at the discretion of the local IRB chair.

Patients currently receiving IMC-A12 (cixutumumab), and patients who have signed a consent form but not yet started treatment, **must** be informed of these changes. The manner by 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.

This revision has been prepared in response to a RRA from Dr. Helen Chen (helen.chen@nih.gov; 301/496-1196). The associated Action Letter is attached.

The study referenced above has been revised as follows:

Title Page: The version date has been updated.

Section 3.2b, pages 7-9a: The CAEPR for IMC-A12 (cixutumumab) has been updated from Version 2.1 (March 15, 2010) to Version 2.2 (December 19, 2011). Page 9a was added to prevent extensive repagination. The changes to the CAEPR are outlined below.

- The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.

- Added New Risk:
  - Less Likely: Blurred vision; Dehydration; Musculoskeletal and connective tissue disorder - Other (muscle spasms)

  - Also Reported on Cixutumumab Trials But with the Relationship to Cixutumumab Still Undetermined: Abdominal distension; Acidosis; Acute coronary syndrome; Agitation; Alopecia; Ataxia; Atrial fibrillation; Atrial flutter; Blood and lymphatic system disorders - Other (pure red cell aplasia); Bone pain; CPK increased; Cardiac arrest; Cardiac disorders - Other (right atrial thrombus); Cardiac troponin I increased; Chest wall pain; Cholesterol high; Cognitive disturbance; Colitis; Colonic perforation; Confusion; Cough; Death NOS; Depressed level of consciousness; Depression; Dry eye; Dry skin; Dysesthesia; Dyspepsia; Epistaxis; Esophageal pain; Esophageal stenosis; Esophageal ulcer; Eye disorders - Other (blindness); Eye disorders - Other (central chorioretinopathy); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual disturbance, visual field defect, visual impairment); Febrile neutropenia; Gastrointestinal disorders - Other (feces discolored); Gastrointestinal disorders - Other (lip ulceration); Gastrointestinal disorders - Other (pneumoperitoneum); Generalized muscle weakness; Headache; Hot flashes; Hypercalcemia; Hyperhidrosis; Hyperkalemia; Hypertension; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Hypotension; Hypoxia; Intracranial hemorrhage; Ischemia cerebrovascular; Laryngeal hemorrhage; Laryngeal mucositis; Leukoencephalopathy; Lipase increased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Nail loss; Neck pain; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Palmar-plantar erythrodysesthesia syndrome; Palpitations; Pancreatitis; Paresthesia; Pleural effusion; Pneumothorax; Postnasal drip; Psychosis; Purpura; Renal and urinary

disorders - Other (chromaturia); Renal and urinary disorders - Other (nocturia); Renal and urinary disorders - Other (polyuria); Respiratory failure; seizure; Sinus bradycardia; Skin ulceration; Somnolence; Sore throat; Syncope; Thromboembolic event; Tinnitus; Tremor; Typhlitis; Urinary incontinence; Vaginal obstruction; Vascular access complication; Wound complication

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Hyperglycemia
  - Changed to Less Likely from Reported But Undetermined: Myalgia
  - Changed to Rare But Serious from Reported But Undetermined: Renal and urinary disorders - Other (renal failure)

- Provided Further Clarification:
  - Infections and infestations - Other (infection NOS), Lung infection, and Paronychia are now reported as Infection and footnote #3 added.

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Dehydration; Diarrhea

- Deleted Risk:
  - Also Reported on Cixutumumab Trials But with the Relationship to Cixutumumab Still Undetermined: Back pain; Extrapyramidal disorder; Tumor pain

Model Informed Consent, pages 52-53: The risk profile has been modified.

- Added New Risk:
  - Less Likely: Blurred vision; Dehydration; Muscle spasms
  - Less Likely: Muscle pain
  - Rare Bit Serious: Kidney Failure

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Increased blood sugar level

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

cc: PROTOCOL & INFORMATION OFFICE
Cathy M. Tangen, Dr.P.H.
Jean Barce
Austin Hamm
Brian Zeller

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **March 5, 2012**

FROM: Helen Chen, MD, Associate Branch Chief, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for Cixutumumab (IMC-A12, NSC 742460)

TO: Investigators for CTEP-supported Studies Involving Cixutumumab (IMC-A12, NSC 742460)

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

CTEP has also reviewed the informed consent documents (ICDs) for all active trials with cixutumumab. Most ICDs already contained information similar to that in the Comprehensive Adverse Events and Potential Risks (CAEPR) list update; however, some ICDs did not contain this information. In all cases, the protocol documents will need to be amended to include the CAEPR update and modified ICD wording, but active trials with ICDs that already contained similar risk language will **NOT** be required to suspend enrollment of new subjects until a revised ICD is reviewed and approved by the IRB.

CTEP has listed all the active trials below, and noted which trials will or will not be required to suspend new enrollment once the CTEP-approved amendment and the Action Letter are distributed, along with the rationale for this designation. In addition, the amendment may be reviewed by the Institutional Review Board (IRB) of record under an expedited review procedure if the IRB chairperson (or another experienced IRB member designated to conduct expedited review by the chairperson) concurs with CTEP assessment that the protocol changes are minor.

ACTIVE trials that WILL NOT be required to suspend enrollment at the time the CTEP-approved amendment and Action Letter are distributed:

- **8121, 8129, 8147, 8155, 8354, 8832, ADVL0813, ARST08P1, E2208, and E3508**
- Rationale: When changes in an ICD are the same or extremely similar to risks already included in the previous ICD, it is not necessary to suspend enrollment of new subjects. The trials listed above already include risk information in their ICDs that is similar to the new information in the CAEPR update:

a) Blurred vision is a further specification of the ocular risks flashing lights and floaters, risks that were previously included in the cixutumumab CAEPR.
b) Dehydration is often a consequence of diarrhea and vomiting, risks that were previously included in the cixutumumab CAEPR.
c) Renal failure was already communicated to patients as a risk associated with drugs given in combination with cixutumumab (or otherwise communicated as a risk in the ICD).
d) Myalgia and/or muscle spasms (which is a further specification of myalgia) was already communicated to patients as risks associated with drugs given in combination with cixutumumab (or otherwise communicated as risks in the ICD).

ACTIVE trials that WILL BE required to suspend enrollment at the time the CTEP-approved amendment and Action Letter are distributed:

- **8131, 8269, 8347, 8792, N0733, and S0925**

- Rationale: Since renal failure, myalgia, and muscle spasms were not already included in ICDs of these studies, enrollment of new subjects will need to be suspended at the time the CTEP-approved amendment and Action Letter are distributed until the IRB of record reviews and approves the amendment.

In response to the new/modified risk information CTEP is requiring that all trials with cixutumumab be amended to reflect this new information. Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on March 19, 2012** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Helen Chen (helen.chen@nih.gov; 301-496-1196). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since cixutumumab is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the IRB Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/Correspondence/nci200870929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised CAEPR list (Attachment 1) and ICD risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

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

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

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

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

2) Revision of the Protocol CAEPR:
   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.2, December 19, 2011): ___
   Page Number(s): ____

   - The Agent Specific Adverse Event List (ASAEL) is now termed the Specific Protocol Exceptions to Expedited Reporting (SPEER) and includes grades for adverse events found on the SPEER that are used to determine if expedited reporting is required.

   - Added New Risk:
     - Less Likely: Blurred vision; Dehydration; Musculoskeletal and connective tissue disorder - Other (muscle spasms)

     - Also Reported on Cixutumumab Trials But with the Relationship to Cixutumumab Still Undetermined: Abdominal distension; Acidosis; Acute coronary syndrome; Agitation; Alopecia; Ataxia; Atrial fibrillation; Atrial flutter; Blood and lymphatic system disorders - Other (pure red cell aplasia); Bone pain; CPK increased; Cardiac arrest; Cardiac disorders - Other (right atrial thrombus); Cardiac troponin I increased; Chest wall pain; Cholesterol high; Cognitive disturbance; Colitis; Colonic perforation; Confusion; Cough; Death NOS; Depressed level of consciousness; Depression; Dry eye; Dry skin; Dysesthesia; Dyspepsia; Epistaxis; Esophageal pain; Esophageal stenosis; Esophageal ulcer; Eye disorders - Other (blindness); Eye disorders - Other (central chorioretinopathy); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual disturbance, visual field defect, visual impairment); Febrile neutropenia; Gastrointestinal disorders - Other (feces discolored); Gastrointestinal disorders - Other (lip ulceration); Gastrointestinal disorders - Other (pneumoperitoneum); Generalized muscle weakness; Headache; Hot flashes; Hypercalcemia; Hyperhidrosis; Hyperkalemia; Hypertension; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Hypotension; Hypoxia; Intracranial hemorrhage; Ischemia cerebrovascular; Laryngeal hemorrhage; Laryngeal mucositis; Leukoencephalopathy; Lipase increased; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Nail loss; Neck pain; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Palmar-plantar erythrodysesthesia syndrome; Palpitations; Pancreatitis; Paresthesia; Pleural effusion; Pneumothorax; Postnasal drip; Psychosis; Purpura; Renal and urinary disorders - Other (chromaturia); Renal and urinary disorders - Other (nocturia); Renal and urinary disorders - Other (polyuria); Respiratory failure; Seizure; Sinus bradycardia; Skin ulceration; Somnolence; Sore

throat; Syncope; Thromboembolic event; Tinnitus; Tremor; Typhlitis; Urinary incontinence; Vaginal obstruction; Vascular access complication; Wound complication

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Hyperglycemia
  - Changed to Less Likely from Reported But Undetermined: Myalgia
  - Changed to Rare But Serious from Reported But Undetermined: Renal and urinary disorders - Other (renal failure)

- Provided Further Clarification:
  - Infections and infestations - Other (infection NOS), Lung infection, and Paronychia are now reported as Infection and footnote #3 added.

- Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:
  - Added: Dehydration; Diarrhea

- Deleted Risk:
  - Also Reported on Cixutumumab Trials But with the Relationship to Cixutumumab Still Undetermined: Back pain; Extrapyramidal disorder; Tumor pain

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.2 and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.1. If your trial contains an older CAEPR version (i.e., does **NOT** currently contain CAEPR Version 2.1), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as Specified Below:

The terminology for CTEP's suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

- Added New Risk:
  - Less Likely: Blurred vision; Dehydration; Muscle spasms

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Increased blood sugar level
  - Changed to Less Likely from Reported But Undetermined: Muscle pain
  - Changed to Rare But Serious from Reported But Undetermined: Kidney failure

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

Action Letter

Attachment 1: Revised Cixutumumab CAEPR – Version 2.2, December 19, 2011

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cixutumumab (IMC-A12, NSC 742460)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via AdEERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 470 patients.* Below is the CAEPR for cixutumumab (IMC-A12).

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

Version 2.2, December 19, 2011[1]

Adverse Events with Possible Relationship to Cixutumumab (IMC-A12) (CTCAE 4.0 Term) [n= 470]			Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
EAR AND LABYRINTH DISORDERS			
	Hearing impaired[2]		
EYE DISORDERS			
	Blurred vision		
	Flashing lights		
	Floaters		
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
	Platelet count decreased		
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***

	Dehydration		***Dehydration (Gr 3)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal failure)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***

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

[2]Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

[3]Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on Cixutumumab (IMC-A12) trials but with the relationship to Cixutumumab (IMC-A12) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pure red cell aplasia); Febrile neutropenia;
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (right atrial thrombus); Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
EYE DISORDERS - Dry eye; Eye disorders - Other (blindness); Eye disorders - Other (central chorioretinopathy); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual disturbance, visual field defect, visual impairment)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Colitis; Colonic perforation; Constipation; Dry mouth; Dyspepsia; Esophageal pain; Esophageal stenosis; Esophageal ulcer; Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (feces discolored); Gastrointestinal disorders - Other (lip ulceration); Gastrointestinal disorders - Other (pneumoperitoneum); Mucositis oral; Pancreatitis; Typhlitis; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infection[3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Vascular access complication; Wound complication
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased; Neutrophil count decreased; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (polydipsia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Paresthesia; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Proteinuria; Renal and urinary disorders - Other (chromaturia); Renal and urinary disorders - Other (nocturia); Renal and urinary disorders - Other (polyuria); Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Laryngeal hemorrhage; Laryngeal mucositis; Pleural effusion; Pneumonitis; Pneumothorax; Postnasal drip; Respiratory failure; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Cixutumumab (IMC-A12) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

Action Letter

Attachment 2: Revised ICD section(s) for Cixutumumab

Please note that the terminology for CTEP's suggested lay terms may change periodically. The risk profile represents CAEPR risks in lay terms in a one-to-one mapping. It is provided as a guide and its use is completely optional; however, all risks listed in the current CAEPR must be reflected in the informed consent document. Expanding or condensing similar terms is acceptable. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

Risk Profile for Cixutumumab (CAEPR Version 2.2, December 19, 2011)

Likely:

- Fatigue or tiredness
- Increased blood sugar level

Less Likely:

- Lack of enough red blood cells (anemia)
- Hearing loss
- Blurred vision
- Seeing flashing lights
- Seeing spots before the eyes (floaters)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of blood cell that helps to clot blood (platelet)
- Weight loss
- Loss of appetite
- Dehydration (when your body does not have as much water and fluid as it should)
- Muscle spasms
- Muscle pain
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Stuffy or runny nose, sneezing
- Itching
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives

Rare But Serious:

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.
- Kidney failure

Action Letter

Attachment 3: Action Letter GENERAL INSTRUCTIONS

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

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

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

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

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

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If you have chosen to reformat and/or reword the risk profile in any way, please state, "The risk profile has been modified" in the cover memo.

Specific Instructions on Amendment Preparation Based on Protocol Status:

A. Trials with a current CTEP status of **"Active"**
   - Review and follow **ALL** the instructions outlined in this Action Letter.
   - The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
   - **ONLY for those trials listed on page 2 of this letter:** Suspend accrual of new patients until the IRB of record has reviewed and approved a CTEP-approved amendment created in response to this Action Letter.

Action Letter

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

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

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

If your trial is under a CTEP-held IND:
- Review and follow **ALL** the instructions outlined in this RRA.
- The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).

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

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

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swog.org

February 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety report has been posted regarding an adverse event that occurred in association with the drug IMC-A12. Please access this safety report via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	Jan. 25, 2012 AE #1152836

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

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

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
Cathy M. Tangen, Dr.P.H.
Bryan Goldman, M.S.
Holly Gundacker, M.S.
Cathryn Rankin, M.S.
Jean Barce
Stephanie Edwards
Austin Hamm
Christine McLeod
Rodney Sutter
Brian Zeller

SWOG
Leading cancer research. Together.

January 15, 2012

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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- ( ) Initial activation (should your institution choose to participate)
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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	
S0925 Genitourinary	Dec. 13, 2011 AE #1808095 FU Dec. 14, 2011 AE #1557427 Dec. 23, 2011 AE #1562608 FU

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

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

cc: PROTOCOL & INFORMATION OFFICE
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swog.org

December 1, 2011

TO: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug IMC-A12. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	Nov. 4, 2011 AE #1808095
S0925 Genitourinary	Nov. 10, 2011 AE #1804247

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

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

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
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November 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	Oct. 6, 2011 Mfr Rpt #1804247

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

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cc: PROTOCOL & INFORMATION OFFICE
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September 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	Aug. 25, 2011 Mfr Rpt #US201009007950

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

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September 1, 2011

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MEMORANDUM

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MEMORANDUM

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	Aug. 19, 2011 AE #1558000 FU

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

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August 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

IRB Review Requirements

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	July 22, 2011 AE #1558000

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

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August 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	July 7, 2011	AE #1271335
S0925 Genitourinary	July 15, 2011	AE #1278880

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

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July 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	June 17, 2011 AE #1278880
S0925 Genitourinary	June 21, 2011 AE #1271335
	June 23, 2011 AE #1471674

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

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July 1, 2011

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MEMORANDUM

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	June 8, 2011 AE #1116728

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

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June 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	May 25, 2011 AE #1471674
S0925 Genitourinary	June 1, 2011 AE #1116728
	June 1, 2011 AE #1413345

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

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June 1, 2011

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	May 13, 2011 AE #1413345
S0925 Genitourinary	May 16, 2011 AE #1003674

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

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May 15, 2011

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FROM: SWOG Operations Office

RE: IND Safety Report for IMC-A12

MEMORANDUM

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This safety report pertains to the following studies:	Report:
S0727 Gastrointestinal **S0925** Genitourinary	Apr. 27, 2011 AE #1980460

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

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May 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	Mar. 23, 2011 AE #1603948
S0925 Genitourinary	Apr. 11, 2011 AE #1743915
	Apr. 14, 2011 AE #1582750

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April 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The following new safety reports have been posted regarding adverse events that occurred in association with the drug IMC-A12. Please access these safety reports via the study's abstract page or the safety report link on the SWOG website (https://swog.org/safetyreports/safetyreports.asp).

These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal	Mar. 16, 2011 AE #1021986
S0925 Genitourinary	Mar. 22, 2011 AE #1710129

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

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

cc: PROTOCOL & INFORMATION OFFICE
Jacqueline K. Benedetti, Ph.D.
Cathy M. Tangen, Dr.P.H.
Benjamin W. Ely, M.S.
Bryan Goldman, M.S.
Holly Gundacker, M.S.
Cathryn Rankin, M.S.
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April 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following studies:	Reports:
S0727 Gastrointestinal **S0925** Genitourinary	Mar. 2, 2011 AE #1050692 Mar. 7, 2011 AE #1340642 Mar. 8, 2011 AE #1173887 Mar. 11, 2011 AE #1582750 Mar. 17, 2011 Mfr Rpt #ES201101003224 Mar. 21, 2011 AE #1598089

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swog.org

March 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	Feb. 9, 2011	AE #1040146
S0925 Genitourinary	Feb. 9, 2011	AE #1537201
	Feb. 14, 2011	AE #1003674

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

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swog.org

February 15, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	Dec. 27, 2010	AE #1409011
S0925 Genitourinary	Dec. 27, 2010	AE #1585911
	Feb. 2, 2011	AE #1603948

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

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February 1, 2011

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FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	Jan. 7, 2011	AE #1021986
S0925 Genitourinary	Jan. 10, 2011	AE #1423593
	Jan. 13, 2011	AE #1173887

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

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January 15, 2011

TO: ALL SWOG, CCOP, UCOP AND AFFILIATE MEDICAL ONCOLOGISTS

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

IRB Review Requirements

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	Dec. 14, 2010	AE #1565962
S0925 Genitourinary	Dec. 23, 2010	AE #1340642
	Dec. 23, 2010	AE #1926485

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

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swog.org

January 1, 2011

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

FROM: SWOG Operations Office

RE: IND Safety Reports for IMC-A12

MEMORANDUM

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MEMORANDUM

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These safety reports pertain to the following studies:	Reports:	
S0727 Gastrointestinal	Nov. 29, 2010	AE #1537201
S0925 Genitourinary	Dec. 6, 2010	AE #1598089
	Dec. 7, 2010	AE #1398066

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

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December 15, 2010

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TO: ALL SWOG MEMBER, CCOP, UCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and M.H.A. Hussain.

STATUS NOTICE

Study Coordinator: Evan Y. Yu, M.D.
Phone number: 206/288-1152
E-mail: evanyu@u.washington.edu

IRB Review Requirements

(√) Full board review required. Reason:
- (√) Initial activation (should your institution choose to participate)
- ( ) Increased risk to patient
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ACTIVATION

The study referenced above is now open for participation. The protocol is attached for your use.

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

cc: PROTOCOL & INFORMATION OFFICE
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December 15, 2010

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RE: IND Safety Reports for IMC-A12

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These safety reports pertain to the following study:	Reports:	
S0727 Gastrointestinal	Nov. 17, 2010	Mfr Rpt #US201008004837
S0925 Genitourinary	Nov. 23, 2010	Mfr Rpt #US201010003170

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

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Distributed to: MICHIGAN, PSOC, UTHSCSA, AND SOUTHERN NEVADA: December 9, 2010
CTEP Submission Date: November 30, 2010

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TO: PROTOCOL AND INFORMATION OFFICE

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0925**, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 versus Androgen Deprivation Alone for Patients with New Hormone-Sensitive Metastatic Prostate Cancer.

STATUS NOTICE

Study Coordinator: Evan Y. Yu, M.D.
Phone: 206/288-1152
E-mail: evanyu@u.washington.edu

IRB Review Requirements

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ACTIVATION AMENDMENT

The above-referenced protocol has been revised as follows. This revision is in response to Dr. Kem's September 9, 2010 notice regarding the concentration change for IMC-A12.

> **Section 3.1c, page 9:** The "How Supplied" section has been updated to indicate that IMC-A12 will be supplied by the DCTD/NCI as a 500 mg vial, and that each vial contains 10 mg/ml.

The above-referenced protocol has also been revised in response to a Request for Rapid Amendment from Dr. Helen Chen (chenh@ctep.nci.nih.gov; 301/496-1196). The related Action Letter is attached.

Sites that put the protocol through their IRB prior to activation must suspend accrual of new patients until the local IRB approves the revised consent form.

1. **Section 3.2b, pages 7-9**: The CAEPR for IMC-A12 has been updated as detailed below.

Added New Risk

- Less Likely: Hearing impaired
- Reported on IMC-A12 trials but with the relationship to IMC-A12 still undetermined: Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Sinus tachycardia; Vertigo; Constipation; Dry mouth; Gastrointestinal disorders – Other (eructation); Mucositis oral; Sudden death NOS; Infections and infestations – Other (infection NOS); Paronychia; Alkaline phosphatase increased; Creatinine increased; White blood cell decreased; Hyperuricemia; Metabolism and nutrition disorders – Other (polydipsia); Arthralgia; Back pain; Pain in extremity; Tumor pain; Extrapyramidal disorder; Proteinuria; Dyspnea; Pneumonitis; Flushing

Increase in Risk Attribution

- Changed to Likely from Less Likely: Fatigue
- Changed to Less Likely from Reported but Undetermined: Diarrhea; Dizziness

Provided further clarification

- Allergic reaction/hypersensitivity *(CTCAE version 3.0 language)* is now reported as two separate events: Allergic reaction (Less Likely) and Anaphylaxis (Rare but Serious).
- Vision – flashing lights/floaters *(CTCAE version 3.0 language)* is now reported as two separate events: Flashing Lights and Floaters (Less Likely).
- Hemorrhage, GI – Select *(CTCAE version 3.0 language)* is now only reported as Upper gastrointestinal hemorrhage.
- Infection with unknown ANC – Urinary tract NOS *(CTCAE version 3.0 language)* is now reported as part of Infections and infestations – Other (infection NOS).
- Neurology - Other (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) *(CTCAE version 3.0 language)* is now only reported as Reversible posterior leukoencephalopathy syndrome (RPLS).
- Cytokine release syndrome/acute infusion reaction *(CTCAE version 3.0 language)* is now reported as Infusion related reaction.
- Pancreatic endocrine: glucose intolerance (*CTCAE version 3.0 language)* is now reported as part of Hyperglycemia.

Deleted risk *(CTCAE version 3.0 language)*

- Reported on IMC-A12 trials but with the relationship to IMC-A12 still undetermined: Pain – Oral cavity

2. Model Consent Form, page 52: The heading of the IMC-A12 risks section has been reworded to match the CTEP-required language.

3. Model Consent Form, page 52: "Fatigue or tiredness" has been reworded to match the CTEP-required language and has been moved from the "less likely" category to the "likely" category. This change represents a minor increase in risk-benefit ratio.

4. Model Consent Form, pages 52-53: These risks have been added to the consent form: Hearing loss; Diarrhea; Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness). These additions represent a minor increase in risk-benefit ratio.

5. Model Consent Form, pages 52-53: These risks have been reworded to match the CTEP-required language. They do not represent any alteration in risk-benefit ratio.

   - Lack of enough red blood cells (anemia)
   - Seeing spots before the eyes (floaters)
   - Nausea or the urge to vomit
   - Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
   - Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
   - Increased blood sugar level
   - Stuffy or runny nose, sneezing
   - Itching
   - Acne
   - Skin rash with the presence of macules (flat discolored area) and papules (raised bump)

6. Model Consent Form, page 53: "Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness." has been reworded to match the CTEP-required language and has been moved from the "Less Likely" section to the "Rare but Serious" section. This change does not represent an increase in risk-benefit ratio.

   Institutions **must** update their local consent forms to include the changes to the Model Consent Form that are listed in item #3 and #4 above (the changes that represent an increase in risk-benefit ratio).

   Because these changes represent an increase in risk-benefit ratio, the site must suspend accrual of new patients until the local IRB approves the revised consent form. However, this revision may undergo **expedited** review at the discretion of the local IRB chair.

In addition, between CTEP approval of the protocol referenced above and activation, the following editorial revisions have been made:

Face Page: "Activated December 15, 2010" has replaced the version date of December 11, 2009 in the upper right hand corner of the page. The Version Date of 11/30/10 has been added to the lower left hand corner of the page. The title has been revised to match the order of the arms. The phone and fax numbers for Dr. Yu have been revised. Dr. Celestia S. Higano has replaced Dr. Maha H.A. Hussain as the secondary Study Coordinator and the contact information has been updated accordingly. The page numbers listed in the Table of Contents have been revised to correctly reflect updated page numbers resulting from protocol additions detailed below. An end parenthesis has been added to the NSC number for Leuprolide Acetate (Lupron).

Schema, page 2: The subheadings of "Arm 1" and "Arm 2" have been added to the schema. The words "with" have been deleted from "LHRH Agonist" and the parentheses revised for clarity purposes.

Section 1.1, page 3: The text “an” has been corrected to “a” in two places.

Section 1.5, page 3: The text “IGF-1” has been replaced with “IGF-I” in two places to be consistent with the remainder of the protocol. The text “”our study” has been replaced with “protocol”. The text “consented” has been deleted and the text “who consent to specimen submission” has been added to the last sentence of this section for clarification.

Section 1.6, page 3: The text “our study” has been replaced with “protocol”. The text “consented” has been deleted and the text “who consent to specimen submission” has been added to the last sentence of this section for clarification.

Background, page 3: The word “a” has been deleted from the first line of the Background section.

Background, page 4: The text “IGF-1” has been replaced with “IGF-I” in two places in the second paragraph to be consistent with the remainder of the protocol.

Section 3.1, page 5: The NSC number for bicalutamide has been corrected to NSC #722665.

Section 4.0, page 12: The reference has been updated to refer to the AJCC Seventh Edition, 2010 rather than the AJCC Sixth Edition, 2002.

Section 5.0, page 13: The second paragraph has been revised to indicate that the Monday 2 weeks versus would be considered Day 14 rather than Day 28. The text “14,” has been added to the last sentence of this paragraph.

Section 5.2, page 13: The first sentence of this section has been broken into two sentences and the text “in all patients” added to the second sentence. The form number for the Baseline Tumor Assessment Form has been revised from Form #9570 to #49593.

Section 5.6, page 14: The text “specimen banking for future use (to include serum and peripheral blood mononuclear cells [PBMNC], CTC’s and microRNAs as” has been replaced with the text “the translational medicine studies.”

Sections 5.12 - 5.15, page 14: The word “institutional” has been added in front of each occurrence of upper limit of normal or ULN.

Section 5.14, page 14: The “C” in Coumadin is now in lower case.

Section 5.18, page 15: The reference to Section 10.4 has been corrected to Section 10.3.

Section 5.19, page 15: The text “AIDS” has been replaced with “HIV positivity”.

Section 5.21, page 15: The text “while on this protocol treatment” has been added.

Section 5.23, page 15: The text “while receiving treatment on this study and for at least three months after treatment ends” has been added to this section.

Section 6.0, page 16: The text “will be stratified by” has been replaced with will be randomized using a dynamic balancing algorithm (Pocock and Simon, 10975) with stratification based on”.

Section 7.0, page 16: The phone number for Dr. Yu has been revised. Dr. Celestia Higano’s name and contact information has replaced the information for Dr. Hussain.

Section 7.1, page 16: This section has been revised to be consistent with the Group's current standard language. Specifically, the word "must" replaced "should" in the first sentence. The word "affect" has replaced "impact on" in the second sentence. The sentence "If an individual test in considered to be unnecessary, the rational for not conducting the test must be documented in the medical record" has been added at the end of this paragraph.

Section 7.1b, page 16: This section has been expanded to clarify that lipid profile includes cholesterol, LDL, HDL and triglycerides.

Section 7.3, page 16: The word "a" has replaced "an" in two places in the first paragraph of this section.

Section 7.3, page 17: The first sentence of the first paragraph on this page has been bolded for emphasis.

Section 7.3a, page 17: The text "QD" has been moved over to line up with the "Days" column. The text "(See bolded note above)" has been added.

Section 7.3b, page 17: The text "(See bolded note above)" has been added.

Section 7.6, page 18: The reference to Section 14.6 has been corrected to Section 14.5.

Section 8.1, page 18: This section has been revised to reflect that this study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 versus the "Active" version.

Section 8.3, page 19: The sentence "The need for the use of G-CSF is not anticipated" has been added to Section 8.3a. The text "to $\leq$ Grade 1" has been added to the final sentence of Section 8.3b. The section number "1" has been deleted from Section 8.3b since there is no "2". The parenthetical heading for abnormal liver function tests has been corrected to reference "SGPT/ALT" rather than "PT".

Section 8.5, page 22: The phone number for Dr. Yu has been revised. Dr. Celestia Higano's name and contact information has replaced the information for Dr. Hussain.

Section 9.0, page 23: The title has been updated to be consistent with the title change noted above. The section "Suggested Laboratory" has been collapsed into the "Laboratory" section. "Completion of 7th Cycle" has been deleted from the Week 29 heading. A "s" was added to "method" in the "≠" footnote. The "§" footnote has been added and a cross-reference to the "Disease Assessment" and "PSA" lines underneath the Week 29 column. The cross-reference in the "я" has been corrected from Section 5.15 to 5.16. The "Φ" footnote was added underneath the table and a cross-reference to it on the line for testosterone. The star footnote has been added underneath the table and a cross reference to it on the lines for testosterone and lipid profile. A sentence was added to the "Ω" footnote. The parenthetical statement has been added to the "¶" footnote. A footnote has been added to indicate that fasting serum glucose must be obtained during treatment for all patients on Arm 1.

Sections 10.1 and 10.2, pages 24-26: These sections have been replaced with the Group's standard language for RECIST criteria.

Section 11.2, page 27: The word "an" has been replaced with "a" in two places in the first paragraph of this section. The parenthesis around "0.65/0.45" has been replaced with brackets in the last sentence of the second paragraph of this section.

Section 11.4, page 28: A new section 11.4 has been added regarding the analysis of translational medicine endpoints and the remainder of Section 11.0 renumbered accordingly.

Section 13.1, page 29: This section has been revised to indicate that patients must be registered within 10 working days versus 5 working days prior to planned start of treatment. This is to allow time for the shipping and receipt of the prestudy specimen collection kit.

Section 13.3a, page 30: This section has been revised to be consistent with the Group's standard language. Specifically the text "at https://open.ctsu.org, or from the OPEN tab on" has replaced the word "from ; the text "side of the" has been inserted between "members' and "web"; the words "web" and "site" have been combined to "website"; and the text "at https://www.ctsu.org," has replaced "OPEN tab".

Section 13.3d, page 30: This section has been revised to be consistent with the Group's standard language. Specifically the text "OPEN tab on the" and "side of the" has been added to the first sentence of this section. The text "at https://www.ctsu.org or at https://open.ctsu.org" has replaced "OPEN tab or within the OPEN URL".

Section 14.4, page 31: The form number for the Baseline Tumor Assessment Form has been updated from Form #9570 to Form #49593 to reflect the correct version of the form.

Section 14.6, page 32: The heading of this section has been revised to more specifically indicate "At Week 29 For All Patients Who Have Not Progressed" instead of "After Seven Cycles of Protocol Treatment". The form number for the Baseline Tumor Assessment Form has been updated from Form #9570 to Form #49593 to reflect the correct version of the form.

Section 14.8, page 32: The form number for the Off Treatment Notice has been updated from Form #28829 to Form #52393 to reflect the correct version of the form.

Section 14.9, page 32: The text "Submit copies of the" and the period have been deleted from this section.

Section 14.10, page 32: The form number for the Off Treatment Notice has been updated from Form #28829 to Form #52393 to reflect the correct version of the form. The form number for the Follow-Up Tumor Assessment Form has been updated from Form #34962 to Form #24225 to reflect the correct version of the form.

Sections 14.10 & 14.11, page 32: The instructions in these sections have been re-written for clarity purposes.

Section 15.0, pages 33-36: This section has been re-written to include the Group's standard specimen submission instructions and language regarding the Specimen Tracking System. This section has also been expanded to provide additional information regarding obtaining, handling and submitting specimens for this study.

Section 16.1e, page 39: This section has been revised to delete the text "(s)" and add the text "Arm 1 of" in the third sentence of this section. The prefix of the Operations Office's phone number has been revised.

Section 16.1f, page 41: The prefix of the Operations Office's phone number has been revised in subsection 1. The text "For study arm(s) [applicable study arm(s)]," has been deleted from subsection 2 and the word "the" capitalized.

Section 16.1g and Table 16.2, pages 41 & 42: The prefix of the Operations Office's phone number has been revised.

Section 16.1h, page 42: The address for the Southwest Oncology Group has been revised to reflect the current address for the Group's Operations Office.

Section 18.1, page 46: The word "authors" has been capitalized.

Section 18.2, page 46: The following forms have been updated to reflect the Group's current standard forms: the Baseline Tumor Assessment Form (from Form #9570 to #49593), the Follow Up Tumor Assessment Form (from Form #34962 to #24225); and the Off Treatment Form (from Form #28829 to #52393). Form dates have been deleted from this section.

Informed Consent Model: "DCT" has been revised to correctly reference "DCTD" on page 47. The readability statistics have been added to page 47. The title has been updated on page 49 to be consistent with the title change noted above. The text "in terms of PSA results" has been added to the last sentence of the "Why is this study being done" section on page 49. The word "people" has been replaced with "men" in the "How many people will take part in the study" section on page 49. Under the "What will happen …Before you begin" section on page 50, text has been added to the blood test bullet to add cholesterol and triglycerides and indicate that sugar level will be done after fasting. The word "low" has been replaced with "lower than normal" in the LVEF bullet in this same section. Under "During the study" on page 50, the word "Fasting" has been added in two places. The word "any" has been replaced with the more correct "either" in the second paragraph on page 51. The sentence "If you have not received hormone therapy before, you will take bicalutamide (Casodex) for seven days before receiving leuprolide acetate (Lupron) or goserelin acetate (Zoladex)" has been added for clarification in both the third and fourth paragraphs on page 51. The text "for at least 4 weeks" has been replaced with "every six months for the first two years and then once a year for a maximum of five years from the time you began the study". The text "IMC-A12" has been replaced with "drugs" in the second paragraph of the "Can I stop being in the study" section on page 52. The third paragraph of the "What side effects…" section on page 52 has been revised to include the text "the", "treatment" and "those that are". On page 53 under "Likely", breast tenderness and excessive development of the breast in the male have been separated into two bullet points. On page 54 under the "Will my medical information be kept private" section, the text "the Pharmaceutical Collaborator" has been replaced with "ImClone Systems, Inc." On page 56, under "What are my rights …" a paragraph has been added to include the Group's standard language regarding a Data Safety and Monitoring Board. The parenthetical text "(about 2 ½ tablespoons)" and "separately from other tests" have been added to the third sentence of sub-point #2 on page 57. The text "and tissue" has been deleted from sub point #2 on page 57 as it was included erroneously. The word "blood" has been replaced with "specimens" in the bolded question of sub-point #2 on page 57. Sub-point 3 on pages 57-59 regarding banking of specimens has been deleted as it is not anticipated that there will be any leftover specimens to bank once the translational medicine studies have been performed. The Specimen Consent Supplemental Sheets (pages 61-62) have been deleted from the protocol.

Section 19.3, page 80: The typographical error in the title has been corrected from "IGT" to "IGF".

Enclosed please find a complete copy of the study. Please replace any previous copies with the version dated November 30, 2010.

PC/jis
Enclosure/file copy

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

Action Letter

DATE: **May 21, 2010**

FROM: Helen Chen, MD, Associate Branch Chief, IDB, CTEP, DCTD, NCI
James Zwiebel, MD, Branch Chief, IDB, CTEP, DCTD, NCI
Meg Mooney, MD, Branch Chief, CIB, CTEP, DCTD, NCI

SUBJECT: **CONFIDENTIAL COMMUNICATION** – Action Letter for IMC-A12 (HuMAb IGF-1R, NSC 742460, IND 100947)

TO: Investigators for CTEP-supported Studies Involving IMC-A12 (NSC 742460)

The purpose of this Action Letter is to alert patients and investigators in studies conducted by the Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI), of new and/or modified risk information associated with IMC-A12, and to request all trials with IMC-A12 be amended to reflect these changes. You are receiving this letter because you are conducting a CTEP-sponsored trial that includes IMC-A12. See the accompanying list of CTEP trials with IMC-A12.

In response to the new/modified risk information CTEP is requiring that all trials with IMC-A12 be amended to reflect this new information. **Please note that the addition of 'Hearing impaired' was done at the request of the FDA for all antibodies targeting the IGF-1 receptor. In the FDA letter, it was stated that "Adverse reactions of middle to high range sensorineural hearing loss has been reported in both healthy volunteers and patients with malignancies who received as little as one dose of antibody". FDA deemed that this information is relevant to all anti-IGF-1R antibodies.** Detailed description of the new/modified risk(s) as well as detailed instructions regarding amendment requirements are described in this Action Letter. **Amendments are due to the Protocol and Information Office (PIO) at PIO@CTEP.NCI.NIH.GOV by 5 PM ET on June 4, 2010** or as required based on protocol status (see the *General Actions Required Based on Protocol Status* section). The cover letter for the submitted amendment should state that it is being submitted in response to an Action Letter from Dr. Helen Chen (chenh@ctep.nci.nih.gov; 301-496-1196). Failure to respond in a timely fashion may result in suspension of the Principal Investigator or permanent study closure.

After review of all the available data, CTEP believes that the new and/or modified risk information does **NOT** significantly alter the risk-benefit profile for patients in the study since IMC-A12 is already known to cause serious adverse events and this new risk information does not change the overall weight given to risks versus benefits for patients in the study. CTEP considers all the proposed protocol and informed consent changes for studies affected by this Action Letter to be minor. Therefore, under the provisions of Department of Health and Human Services regulations for the protection of human subjects at 45 CFR 46.110, a protocol amendment that includes this new information can undergo expedited review if the Institutional Review Board (IRB) Chair (or other experienced IRB member designated to conduct expedited review by the Chair) concurs that the changes are minor. Additional information from the Office of Human Research Protections (OHRP) regarding this process is available at: http://www.hhs.gov/ohrp/policy/correspond/NCI20080929.html.

The following section, *Specific Instruction*, includes background information on the risk(s), any risk mitigation strategies, and amendment requirements. The revised Comprehensive Adverse Events and Potential Risks (CAEPR) list (Attachment 1) and Informed Consent Document (ICD) risk information (Attachment 2) are also attached. Action Letter general instructions as well as instructions regarding amendment preparation (if a CTEP-approved amendment does not already accompany this Action Letter) are included in Attachment 3. **You MUST follow the instructions outlined in Attachment 3.**

Action Letter

SPECIFIC INSTRUCTION

Background

As part of Good Clinical Practice, CTEP reviews each CAEPR list on an annual basis. The review includes literature search, AdEERS submission review and comparison to the latest agent Investigator's Brochure. After review of all the available data CTEP has identified new and/or modified risk information associated with IMC-A12.

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

1) New protocol amendment/version date included on the title/cover page per Operations Office policy:

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

2) Revision of the protocol CAEPR:
   Protocol Section(s) for Insertion of Revised CAEPR (Version 2.1, March 15, 2010): ___
   Page Number(s): ____

   • The section below utilizes CTCAE version 4.0 language unless otherwise noted.

   - Added New Risk:
     - Less Likely: Hearing impaired
     - Reported on IMC-A12 trials but with the relationship to IMC-A12 still undetermined: Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Sinus tachycardia; Vertigo; Constipation; Dry mouth; Gastrointestinal disorders – Other (eructation); Mucositis oral; Sudden death NOS; Infections and infestations – Other (infection NOS); Paronychia; Alkaline phosphatase increased; Creatinine increased; White blood cell decreased; Hyperuricemia; Metabolism and nutrition disorders – Other (polydipsia); Arthralgia; Back pain; Pain in extremity; Tumor pain; Extrapyramidal disorder; Proteinuria; Dyspnea; Pneumonitis; Flushing

   - Increase in Risk Attribution:
     - Changed to Likely from Less Likely: Fatigue
     - Changed to Less Likely from Reported but Undetermined: Diarrhea; Dizziness

   - Provided further clarification:
     - Allergic reaction/hypersensitivity *(CTCAE version 3.0 language)* is now reported as two separate events: Allergic reaction (Less Likely) and Anaphylaxis (Rare but Serious).
     - Vision – flashing lights/floaters *(CTCAE version 3.0 language)* is now reported as two separate events: Flashing Lights and Floaters (Less Likely).
     - Hemorrhage, GI – Select *(CTCAE version 3.0 language)* is now only reported as Upper gastrointestinal hemorrhage.
     - Infection with unknown ANC – Urinary tract NOS *(CTCAE version 3.0 language)* is now reported as part of Infections and infestations – Other (infection NOS).
     - Neurology - Other (Leukoencephalopathy syndrome including reversible posterior leukoencephalopathy syndrome [RPLS]) *(CTCAE version 3.0 language)* is now only reported as Reversible posterior leukoencephalopathy syndrome (RPLS).

- Cytokine release syndrome/acute infusion reaction *(CTCAE version 3.0 language)* is now reported as Infusion related reaction.
- Pancreatic endocrine: glucose intolerance (*CTCAE version 3.0 language)* is now reported as part of Hyperglycemia.

- Deleted risk *(CTCAE version 3.0 language)*:
  - Reported on IMC-A12 trials but with the relationship to IMC-A12 still undetermined: Pain – Oral cavity

PLEASE NOTE: The specific detailed changes listed here compare the new revised CAEPR Version 2.1, and associated risk information for the Informed Consent Document (ICD), to the most recent CAEPR Version 2.0. If your trial contains an older CAEPR version, (i.e., does **NOT** currently contain CAEPR Version 2.0), you **MUST** include a description of any additional changes resulting from migration from the older CAEPR version.

3) Revision of the ICD as specified below:

The terminology for CTEP's suggested lay terms may change periodically. Therefore, to maintain consistency, it is strongly recommended that you cut and paste the **entire** Risk Profile found in Attachment 2 directly into your protocol.

- Added New Risk:
  - Less Likely: Hearing loss

- Increase in Risk Attribution:
  - Changed to Likely from Less Likely: Fatigue or tiredness
  - Changed to Less Likely from Reported but Undetermined: Diarrhea; Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)

PLEASE NOTE: The potential risks listed in the CAEPR whose relationship to IMC-A12 is still undetermined are not required by CTEP to be described in the ICD; however, they may be communicated to patients according to local IRB requirements.

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Attachment 1: Revised IMC-A12 CAEPR – Version 2.1, March 15, 2010

PLEASE NOTE: This CAEPR utilizes CTCAE 4.0 language. Migration from CTCAE version 3.0 to 4.0 terminology may result in additional or fewer total adverse events on the CAEPR. However, there is no new or modified risk information for this agent other than what is outlined under the *Specific Instruction* section of this Action Letter.

Comprehensive Adverse Events and Potential Risks list (CAEPR) for IMC-A12 (HuMAb IGF-1R, NSC 742460)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.info.nih.gov/protocolDevelopment/default.htm#adverse_events_adeers for further clarification. *Frequency is provided based on 206 patients.* Below is the CAEPR for IMC-A12 (HuMAb IGF-1R).

Version 2.1, March 15, 2010[1]

Adverse Events with Possible Relationship to IMC-A12 (HuMAb IGF-1R) (CTCAE 4.0 Term) [n= 206]			**EXPECTED AEs FOR ADEERS REPORTING Agent Specific Adverse Event List (ASAEL)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	***Expected***
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia***
EAR AND LABYRINTH DISORDERS			
	Hearing impaired[2]		
EYE DISORDERS			
	Flashing lights		
	Floaters		
GASTROINTESTINAL DISORDERS			
	Diarrhea		
	Nausea		***Nausea***
	Vomiting		***Vomiting***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue***
	Infusion related reaction		***Infusion related reaction***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction***
		Anaphylaxis	
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased***
	Platelet count decreased		
	Weight loss		***Weight loss***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia***
	Hyperglycemia		***Hyperglycemia***

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NERVOUS SYSTEM DISORDERS				
	Dizziness			
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
	Allergic rhinitis			***Allergic rhinitis***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
	Pruritus			***Pruritus***
	Rash acneiform			***Rash acneiform***
	Rash maculo-papular			***Rash maculo-papular***
	Urticaria			***Urticaria***

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

[2]Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

Also reported on IMC-A12 (HuMAb IGF-1R) trials but with the relationship to IMC-A12 (HuMAb IGF-1R) still undetermined:

CARDIAC DISORDERS - Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Vertigo
GASTROINTESTINAL DISORDERS - Abdominal pain; Constipation; Dry mouth; Gastrointestinal disorders - Other (eructation); Mucositis oral; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema limbs; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS – Infections and infestations - Other (infection NOS); Lung infection; Paronychia
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS – Hyperuricemia; Metabolism and nutrition disorders - Other (polydipsia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Dysgeusia; Extrapyramidal disorder; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome (RPLS)
RENAL AND URINARY DISORDERS – Proteinuria; Renal and urinary disorders - Other (renal failure)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS – Dyspnea; Pneumonitis
VASCULAR DISORDERS - Flushing

Note: IMC-A12 (HuMAb IGF-1R) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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Attachment 2: Revised ICD section(s) for IMC-A12

Please note that the terminology for CTEP's suggested lay terms may change periodically. Therefore, to maintain consistency, it is strongly recommended that you cut and paste the entire Risk Profile found in Attachment 2 directly into your protocol.

Risk Profile for IMC-A12 (CAEPR version 2.1, March 15, 2010)

Likely:

- Fatigue or tiredness

Less Likely:

- Lack of enough red blood cells (anemia)
- Hearing loss
- Seeing flashing lights
- Seeing spots before the eyes (floaters)
- Diarrhea
- Nausea or the urge to vomit
- Vomiting
- Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.
- Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.
- Decreased number of a type of white blood cell (lymphocyte)
- Decreased number of a type of blood cell that help to clot blood (platelet)
- Weight loss
- Loss of appetite
- Increased blood sugar level
- Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)
- Stuffy or runny nose, sneezing
- Itching
- Acne
- Skin rash with the presence of macules (flat discolored area) and papules (raised bump)
- Hives

Rare but Serious:

- Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.

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Attachment 3: Action Letter GENERAL INSTRUCTIONS

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

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

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

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

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

1. Instructions regarding the due date for an amendment and where to send it are included on the first page of this Action Letter. The Clinical Trials Operations Offices may use the *Detailed Description of Required Protocol Changes* section in this Action Letter as the template for their Change Memo; however, it is not required if an Operations Office prefers to use its own Change Memo.
2. If any of the NCI-required changes are not applicable for your trial (i.e., already appear in your protocol), note this in your Change Memo.
3. The ICD changes include CTEP's suggested lay terms for each adverse event identified in the CAEPR. You may substitute different lay terms for each concept if appropriate for your patient population. If substitute terminology for an adverse event is used, the Change Memo **MUST** specify these alterations.

Specific Instructions on Amendment Preparation Based on Protocol Status:

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

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

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

D. Trials with a status of **"Temporarily Closed to Accrual"**
- If Action Letter INCLUDES information that impacts patient care (e.g., new or adjusted dose modifications, new AE monitoring requirements) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
- If Action Letter does NOT INCLUDE information that impacts patient care – Follow instructions outlined for trials with a current status of "Approved" or "Temporarily Closed to Accrual and Treatment" (Section B of this attachment).

E. Trials with a current CTEP status of **"Closed to Accrual"**
- If Action Letter INCLUDES information that impacts patient care (e.g., new or adjusted dose modifications, new AE monitoring requirements) - An amendment is required. Review and follow **ALL** the instructions outlined in this Action Letter. The information provided in this memo outlines the **ONLY** changes that can be made in response to the Action Letter, except for changes that are consistent with CTEP's editorial and administrative update policy (http://ctep.cancer.gov/protocolDevelopment/docs/requestsubmissionpolicyfinal.pdf).
- If Action Letter does NOT INCLUDE information that impacts patient care -Amendment is typically NOT required.

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

Southwest
Oncology Group
A National Clinical Research Group

August 26, 2010

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP AND UCOP MEDICAL ONCOLOGISTS AND SURGEONS AT: MICHIGAN, PSOC, UTHSCSA, AND SOUTHERN NEVADA

FROM: Jennifer I. Scott, Protocol Coordinator

RE: **S0925**, " A Randomized Phase II Study of Combined Androgen Deprivation Versus Combined Androgen Deprivation with IMC-A12 for Patients with New Hormone Sensitive Metastatic Prostate Cancer." Study Coordinators: Drs. E.Y. Yu and M.H.A. Hussain.

MEMORANDUM

Study Coordinator: Evan Y. Yu, M.D.
Phone: 206/288-1152
E-mail: evanyu@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

This protocol is being distributed at this time for Institutional Review Board (IRB) review only. **Once drug is ready for shipment, institutions will be informed that the study is active for patient registrations.**

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

PC/js
Enclosure

cc: Cathy M. Tangen, Dr.P.H.
Benjamin W. Ely, M.S.
Bryan Goldman, M.S.
Jean Barce
Janice Leaman
Brian Zeller

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Activated December 15, 2010

SWOG

A RANDOMIZED PHASE II STUDY OF ANDROGEN DEPRIVATION COMBINED WITH IMC-A12 VERSUS ANDROGEN DEPRIVATION ALONE FOR PATIENTS WITH NEW HORMONE-SENSITIVE METASTATIC PROSTATE CANCER

NCT#01120236

PARTICIPANTS: ALL SWOG MEMBER, CCOP AND AFFILIATE MEDICAL ONCOLOGISTS AND SURGEONS

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AGENTS:

Supplied by CTEP:
IMC-A12 (A12, Cixutumumab) (NSC-742460)
(IND-100947)

Commercially Available:
Bicalutamide (Casodex™) (NSC-722665)
Goserelin Acetate (Zoladex) (NSC-606864)
Leuprolide Acetate (Lupron) (NSC-377526)

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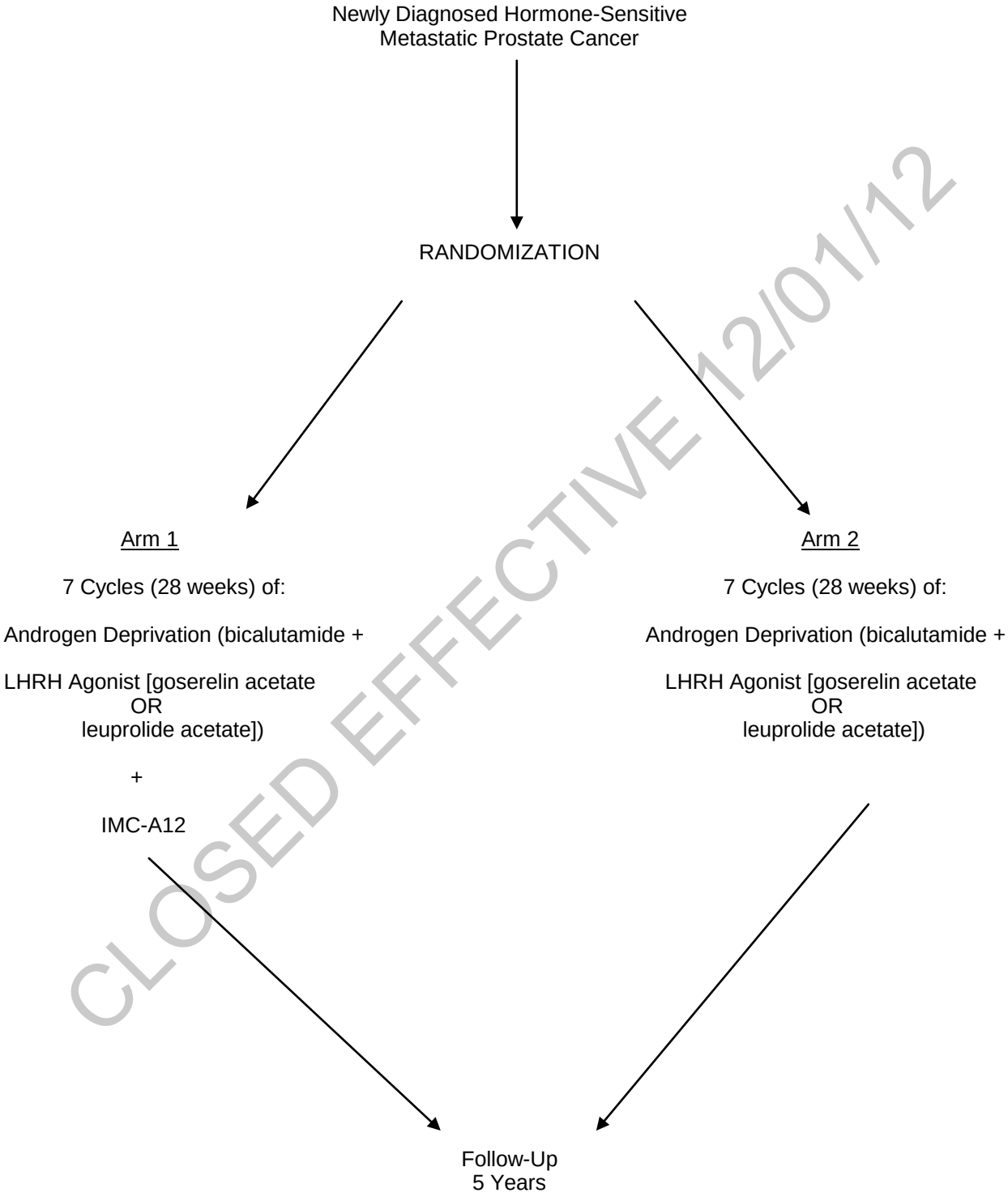
SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

The primary objective of this study is to compare the undetectable PSA rate (PSA < 0.2 ng/mL) after seven cycles (28 weeks) of protocol treatment between those randomized to a LHRH agonist and bicalutamide and those randomized to a LHRH agonist, bicalutamide and IMC-A12.

1.2 Secondary Endpoints

a. To assess the safety and tolerability of the combination of IMC-A12 with a LHRH agonist and bicalutamide.

b. To compare the proportion of men who do not achieve a PSA of < 4 ng/mL between the two groups.

c. To assess the accuracy of the prognostic model of undetectable PSA that was developed from **SWOG-9346** with the current trial data from each arm.

d. To assess serum samples and peripheral blood mononuclear cells (PBMNC) for pharmacodynamic activity with potential biomarkers for IMC-A12 (including, but not limited to: IGF-I, free IGF-I, IGF-II, IGFBP2, IGFBP3, Growth Hormone, insulin and C-peptide) obtained from optional blood specimens both before initiation of androgen deprivation therapy and twelve weeks after initiation of combined therapy. (If patient develops clinical progression or clear castration-resistant disease prior to Cycle 4, Day 1, these biomarkers should be obtained earlier as the patient goes off protocol, before initiation of next line therapy.) This analysis will be performed on the **FIRST 50 patients in each arm who consent to specimen submission** who start androgen deprivation therapy (ADT) on protocol.

e. To determine baseline pre-treatment circulating tumor cell (CTC) quantities and response to therapy (for those patients with detectable CTC levels ≥ 1) twelve weeks later. (If patient develops clinical progression or clear castration-resistant disease prior to Cycle 4, Day 1, CTCs should be obtained earlier as the patient goes off protocol, before initiation of next line therapy.) This analysis will be performed on the **FIRST 50 patients in each arm who consent to specimen submission** who start androgen deprivation therapy (ADT) on protocol. If ADT started within the 30 days prior to registration, the patient is not eligible for this analysis.

f. In the same subset of patients where CTC levels are obtained, determine baseline serum levels of microRNAs to include but not limited to mi-141 both before initiation of androgen deprivation therapy and twelve weeks after combined therapy. (If patient develops clinical progression or clear castration-resistant disease prior to Cycle 4, Day 1, these serum levels of micro RNAs should be obtained earlier as the patient goes off protocol, before initiation of next line therapy.)

2.0 BACKGROUND

M. Hussain and colleagues have recently reported, based on data from over 1,000 patients with new M1 prostate cancer undergoing androgen deprivation therapy (ADT) on **SWOG-9346**, that failure to achieve a PSA of ≤ 4 ng/mL after seven months of combined ADT is a very powerful negative predictor for survival. *(1)* The median overall survival for this group of patients was 20

months from the start of combined ADT (13 months from the end of the seven months of first hormonal therapy). This is to be contrasted with the 45% of the patients who achieved undetectable PSA levels (≤ 0.2 ng/mL) at month seven, whose median overall survival was 82 months from the start of combined ADT.

A large number of preclinical and clinical studies have implicated the IGF-IR and its ligands, IGF-I and IGF-II, in the development, maintenance, and progression of cancer. *(2-4)* IGF-I, IGF-II, and IGF-IR mediated signaling contribute to the development of prostate cancer. *(5)* The role of the IGF-IR axis in prostate carcinogenesis has been demonstrated in cell and animal models and in population-based studies. *(6)* IGF-I exerts mitogenic effects on prostate cancer cells in vitro. *(7)* Human prostate cancer tissues demonstrate enhanced IGF-IR expression. *(8)* Elevated levels of circulating IGF-I are associated both with an increased risk of developing prostate cancer and with the presence of metastatic disease. *(9)* Increased IGF-I and IGF-IR activity have been associated with progression to castration resistance both in vitro and in animal models. *(10, 11)* In prostate cancer models, IGF-IR signaling contributes to cell proliferation, tumor-stromal interactions, invasion, and metastasis. *(12-16)* Anti-IGF-IR antibodies, IGF-IR kinase inhibitors, and antisense oligonucleotides to IGF-IR inhibit prostate cancer growth in vitro and in vivo. *(17-19)*

Through screening of a Fab phage-display library, ImClone generated IMC-A12, a fully recombinant human monoclonal antibody (mAb) of the immunoglobulin G, subclass 1 (IgG_1) that specifically targets the human IGF-IR. *(20, 21)* IMC-A12 binds to the IGF-IR with high affinity ($4.11x10^{-11}$ M) and potently inhibits IGF-I and IGF-II ligand binding with an IC_{50} of 0.6 to 1 nM. IMC-A12 does not bind to or recognize the human insulin receptor. In addition to blockade of ligand binding, this antibody inhibits the IGF-IR pathway by effecting the internalization and degradation of IGF-IR, leading to a reduction in surface receptor density on treated cells. IMC-A12 also inhibits the proliferation and growth of a variety of human tumor cell lines, both in vitro and in vivo. *(20)*

The Pacific Northwest Prostate Cancer SPORE, and in particular Dr. Steve Plymate, has been integral in studying the interaction of the IGF-IR pathway and the androgen receptor (AR). Recent data from his group suggests that IGF-IR activity may stimulate nuclear translocation of AR, resulting in AR-mediated signaling in the absence of androgens. This signaling and associated growth are inhibited by anti-IGF-IR antibodies. *(22)* IMC-A12 significantly inhibits the growth of androgen-dependent LuCaP 35 and androgen-independent LuCaP35V prostate xenografts, by different mechanisms. In LuCaP 35 xenografts, IMC-A12 treatment induced tumor cell apoptosis or G1 cycle arrest. In LuCaP35V xenografts, IMC-A12 treatment induced tumor cell G2-M cycle arrest. *(21)* Additionally, in LuCaP 35 xenografts, IMC-A12 inhibition of IGF-IR enhances the effects of castration by significantly decreasing tumor size with associated decrease in AR signaling and nuclear localization. *(23)* This combined work by Plymate et al. emphasizes the potential for IMC-A12 to potentially be more effective in combination with ADT, with the potential for inducing apoptosis and improving tumor shrinkage. Recent studies from Plymate et al. also suggest additional growth inhibition when IMC-A12 is coadministered with docetaxel in prostate cancer models. *(24)*

Two Phase I studies were conducted to evaluate the safety and antitumor effects of IMC-A12 administered either weekly (CP13-0501) or every other week (CP13-0502) at doses ranging from 2 mg/kg through 27 mg/kg. Interim results on 24 patients with advanced cancer treated with weekly IMC-A12 (study CP13-0501) demonstrate that IMC-A12 has been well tolerated at doses of up to 10 mg/kg. *(25)* The most significant adverse event to date has been hyperglycemia, observed in four patients and considered a dose-limiting toxicity (Grade 3) in two patients. Other Grade 1/2 toxicities observed include infusion reaction, anemia, psoriasis, pruritus, rash, acne, arthralgia, dizziness, fatigue, and nephrotoxicity. *(26)* Only three patients experienced an adverse event (AE) ≥ Grade 3 that was considered to be possibly, probably, or definitely related to IMC-A12: two cases of hyperglycemia, one observed in the 3 mg/kg cohort, and the other in the 10 mg/kg cohort; and one case of fatigue, observed in the 6 mg/kg cohort.

A total of 16 patients have been enrolled in study CP13-0502, a Phase I dose-escalation trial of IMC-A12 administered every other week in advanced solid tumors: five patients at 6 mg/kg, nine patients at 10 mg/kg, and two patients at 15 mg/kg. This regimen has been well-tolerated at all dose levels. To date, only one adverse event of Grade ≥ 3 has been observed that was considered definitely, probably, or possibly related to IMC-A12 treatment (one episode of QTc prolongation in the 10 mg/kg cohort). Sufficient PK data has been obtained to establish a Phase II dose for every other week dosing. Accordingly, enrollment has been closed and no further dose escalation will occur. To date, two patients have experienced stable disease > 5 months and one continues treatment with IMC-A12. *(27)*

A Phase II study of men with asymptomatic metastatic castration-resistant prostate cancer with every other week dosing of IMC-A12 at 10 mg/kg has completed accrual. *(28)* Thirty-one patients have been treated with nine patients experiencing disease stabilization for ≥ 6 months (range 7.4-12.5 months). The most common AEs were fatigue (25.8%) and hyperglycemia (19.4%). Grade 3 hyperglycemia occurred in four patients but no patients required treatment discontinuation. One patient required insulin but remained on study. Other Grade 3 AEs were one case each of thrombocytopenia, hyperkalemia, fatigue, pneumonia (resulting in death), and Grade 4 leukoencephalopathy. An expansion cohort to this study has completed accrual of 10 patients treated with every 3-week IMC-A12 for additional PK assessments.

We believe that the biologic mechanism of IMC-A12 offers excellent rationale for combination with initial ADT. We plan to use the intermediate endpoint of undetectable PSA rate after seven cycles (28 weeks), and we hypothesize that if IMC-A12 can increase the percentage of patients with new M1 prostate cancer achieving undetectable PSA levels at 28 weeks of ADT it will be worthy of future Phase III testing.

Inclusion of Minorities:

This study was designed to include minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	0	7	7
Not Hispanic or Latino	0	173	173
Total Ethnic	0	180	180
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	0	2	2
Black or African American	0	32	32
Native Hawaiian or other Pacific Islander	0	1	1
White	0	144	144
Racial Category: Total of all Subjects*	0	180	180

3.0 DRUG INFORMATION

3.1 Bicalutamide (Casodex®) (NSC-722665)

Investigator's Brochures:

For information regarding Investigator's Brochures, please refer to SWOG Policy 15.

For this study, bicalutamide, goserelin acetate and leuprolide acetate are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

For this study, IMC-A12 is investigational and is being provided under an IND held by the National Cancer Institute. The Investigator Brochure(s) may be obtained by contacting the NCI's Pharmaceutical Management Branch (PMB) at 301/496-5725.

a. DESCRIPTION

Chemistry: Bicalutamide is a racemic mixture containing two enantiomers, (2RS)-4'-Cyano-3(4-fluorophenylsulphonyl)-2-hydroxy-2-methyl-3'-trifluoromethyl) propionanilide.

Bicalutamide is an active non-steriodal antiandrogen and its antiandrogen activity resides exclusively in the (-) or (R) enantiomer. Unlike flutamide, it is peripherally selective and does not cause a rise in serum LH or Testosterone in male rats and dogs. This peripheral selectivity may be because it penetrates poorly the CNS and Hypothalamus (the site of negative feedback of androgens). In humans, rises in LH, Testosterone and Estradiol concentrations were seen. These rises were not dose related. In 90%, testosterone levels remained within normal limits. There was no significant rise in mean serum FSH.

b. TOXICOLOGY

In rats, besides antiandrogenic changes, there was evidence of hepatocyte hypertrophy and basophilia. In dogs treated for 6 months, there was increased heart rate with decreased PR interval, transient decrease in circulating PMNs and increased plasma cholesterol. No cardiac pathology was found. In a mouse oncogenicity study, an increased incidence of hepatocellular carcinoma was observed in the top dose male group (75 mg/kg/day). The no effect dose level for hepatocellular carcinoma in this study was 15 mg/kg/day with steady state blood levels in excess of 10 µg/ml. The mechanism for this tumor formation is a non-genotoxic, phenobarbitone-type MFO induction and is not considered to represent a risk for humans. A two-year study in rats and female mice at similar doses did not show an increased incidence of hepatic tumors.

Bicalutamide has been given to over 3,500 men in 35 different clinical studies worldwide, in doses up to 600 mg daily. When bicalutamide is given in combination with an LHRH analog, the pharmacologic adverse event profile is dominated by the LHRH analog and includes hot flashes (53%), gynecomastia (9%) and breast pain (6%). Other adverse events reported regardless of causality included diarrhea (12%), constipation (22%), nausea (15%) and abdominal pain (11%). Other adverse were reported, such as fatigue (22%), pain (35%), back pain (25%), pelvic pain (21%), infection (18%), peripheral edema (13%), dyspnea (13%), nocturia (12%), hematuria (12%), anemia (11%), dizziness (10%). Bicalutamide has been associated with changes in liver function, although these are infrequent (7%) and rarely occur with jaundice. Many of these changes improved or resolved despite continuation of bicalutamide therapy. There have been no reports of fatal hepatotoxicity associated with bicalutamide therapy.

c. PHARMACOLOGY

Pharmacokinetics:

Animal studies: After oral single dose administration, absorption of the compound was slow with peak concentration occurring 3 - 12 hours and plateau between 2 and 48 hours. There was non-proportional increase in plasma levels with increasing doses. Elimination half life ranges from 17 - 28 hours in male rats, 21 - 29 hours in female rats and 5 - 7.5 days in dogs. 91 - 96% of bicalutamide is bound to plasma protein.

Human studies: After single doses, mean time for peak plasma concentration was 6 hours at 10 and 30 mg, but at 50 mg, it was 16 hours. Mean plasma elimination half lives after 12 weeks of 10, 30, 50, 100 mg/day was 7 - 10 days. This finding was consistent with single dose data. In patients given daily doses of 50 mg, mean plasma concentration was 10 ug/ml at 12 weeks. After single doses, there was linear increase with doses between 10 and 50 mg, but became non-linear at doses of 50 - 100 mg. At 100 mg, the oral bioavailability is reduced by 30% but plasma elimination half life is unchanged. Bicalutamide is extensively metabolized and metabolites are excreted by both the biliary and urinary system.

Formulation: Bicalutamide is prepared as round, film-coated green or white tablets containing standard recipients and 50 mg of the drug.

Storage and stability: All packages of bicalutamide should be stored securely in a dry place at room temperature.

Route of Administration: Bicalutamide is to be administered in tablet form as a once-daily oral dose. Patients should be instructed to take one tablet once daily.

Supplier: Bicalutamide 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.

3.2 IMC-A12 (HuMAb IGF-1R) (NSC-742460) (IND-100947)

a. DESCRIPTION

Other names: A12, cixutumumab, HuMAb IGF-1R

A fully human monoclonal antibody of IgG1/λ selectively binding human insulin like growth factor-I receptor (IGF-IR).

b. TOXICOLOGY

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Cixutumumab (IMC-A12, NSC 742460)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 470 patients.* Below is the CAEPR for cixutumumab (IMC-A12).

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

Version 2.2, December 19, 2011[1]

Adverse Events with Possible Relationship to Cixutumumab (IMC-A12) (CTCAE 4.0 Term) [n= 470]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
EAR AND LABYRINTH DISORDERS			
	Hearing impaired[2]		

EYE DISORDERS			
	Blurred vision		
	Flashing lights		
	Floaters		
GASTROINTESTINAL DISORDERS			
	Diarrhea		***Diarrhea (Gr 3)***
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Infusion related reaction		***Infusion related reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
	Allergic reaction		***Allergic reaction (Gr 2)***
		Anaphylaxis	
INVESTIGATIONS			
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 3)***
	Platelet count decreased		
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		***Dehydration (Gr 3)***
Hyperglycemia			***Hyperglycemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
RENAL AND URINARY DISORDERS			
		Renal and urinary disorders - Other (renal failure)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Allergic rhinitis		***Allergic rhinitis (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Pruritus		***Pruritus (Gr 2)***
	Rash acneiform		***Rash acneiform (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Urticaria		***Urticaria (Gr 2)***

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

2 Middle to high range sensorineural hearing loss has been reported in patients treated with monoclonal antibodies to Insulin-like Growth Factor-1 Receptor (IGF-1R).

3 Infection may include all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on Cixutumumab (IMC-A12) trials but with the relationship to Cixutumumab (IMC-A12) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pure red cell aplasia); Febrile neutropenia;
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Cardiac arrest; Cardiac disorders - Other (right atrial thrombus); Left ventricular systolic dysfunction (when used in combination with doxorubicin); Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo
EYE DISORDERS - Dry eye; Eye disorders - Other (blindness); Eye disorders - Other (central chorioretinopathy); Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual disturbance, visual field defect, visual impairment)
GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Colitis; Colonic perforation; Constipation; Dry mouth; Dyspepsia; Esophageal pain; Esophageal stenosis; Esophageal ulcer; Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (feces discolored); Gastrointestinal disorders - Other (lip ulceration); Gastrointestinal disorders - Other (pneumoperitoneum); Mucositis oral; Pancreatitis; Typhlitis; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema limbs; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Infection[3]
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Vascular access complication; Wound complication
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; Lipase increased; Neutrophil count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (polydipsia)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (groin pain); Musculoskeletal and connective tissue disorder - Other (pain in jaw); Neck pain; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage)
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Paresthesia; Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Somnolence; Syncope; Tremor
PSYCHIATRIC DISORDERS - Agitation; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Proteinuria; Renal and urinary disorders - Other (chromaturia); Renal and urinary disorders - Other (nocturia); Renal and urinary disorders - Other (polyuria); Urinary incontinence
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Vaginal obstruction
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Dyspnea; Epistaxis; Hypoxia; Laryngeal hemorrhage; Laryngeal mucositis;

Pleural effusion; Pneumonitis; Pneumothorax; Postnasal drip; Respiratory failure; Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Skin ulceration
VASCULAR DISORDERS - Flushing; Hot flashes; Hypertension; Hypotension; Thromboembolic event

Note: Cixutumumab (IMC-A12) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent

c. PHARMACOLOGY

How Supplied: ImClone Systems and Lilly supply cixutumumab and DCTD/NCI distributes it. Cixutumumab is available as a 10 mg/mL (500 mg/50mL) or 15 mg/mL (750 mg/50 mL) aqueous solution. Each single-use vial contains a sterile solution in citrate-based saline (10 mM sodium citrate, 100 mM sodium chloride, 100 mM glycine, and 0.01% Tween -80) and pH 6.5. The vials are Type I glass, stoppered with a Flurotec coated **latex-free** plus style stopper, and sealed with an aluminum flip-off seal cap. The solution is clear to slightly opalescent, colorless to pale yellow liquid, without visible particulates.

Preparation: Do not mix lot numbers when preparing the solution. Withdraw the calculated amount of IMC-A12 from the vial(s) and transfer it into ethylene vinyl acetate (EVA), polyolefin, or polyvinyl chloride (PVC) IV bag, or an evacuated glass bottle. If using a pre-filled AVIVA (non-PVC), withdraw an amount of 0.9% sodium chloride from the container equivalent to the volume of IMC-A12 dose.

IMC-A12 solution can be given undiluted if volume ≥ 250 mL. For doses with volumes less than 250 mL, dilute the IMC-A12 solution further to 250 mL of 0.9% NaCl, USP. Mix by gently inverting the solution bag. Do not shake.

Storage and Stability: Store the intact vials refrigerated at (2-8°C). Do Not Freeze. Shelf life surveillance of the intact vials is ongoing. Refrigerate the IMC-A12 prepared solutions at 2-8°C for up to 8 hours. Discard any remaining solution after 8 hours.

Administration: IMC-A12 solution is given intravenously over 1 hour via an in-line, 0.22 micron, protein-sparing filter. Following the infusion, flush the IV-line with normal saline. Monitor patients for hypersensitivity reactions during and following the IMC-A12 administration. If patients experience hypersensitivity reactions, slow or hold the infusion. (Refer to Sections 7.0 and 8.0 for specific administration rate, premedication, and supportive care guidelines).

d. SUPPLIER

IMC-A12 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. IMC-A12 is provided to the NCI under a Collaborative Agreement between Imclone Systems Incorporated and the DCTD, NCI.

Drug Ordering: NCI supplied agents may be requested by the Principal Investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from

PMB is obtained). The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Drug may be requested by completing a Clinical Drug Request Form (NIH-986) and faxing it to the Pharmaceutical Management Branch at 301/480-4612. For questions call 301/496-5725 or via e-mail at PMBAfterHours@mail.nih.gov, where a response will be sent within one business day.

Alternatively, active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Ordering Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password.

Beginning June 1, 2012, all sites must convert to agent order submission through the PMB's Online Agent Order Processing (OAOP) for PMB-supplied agents. The paper-based Clinical Drug Request Form, NIH Form 986, will no longer be accepted after this date.

Drug Returns: All unused drug supplies should be returned to the PMB. When it is necessary to return study drug (e.g. sealed vials remaining when expired vials are recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov).

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition and return of all drugs received from the PMB using the Drug Accountability Record Form available on the NCI home page (http://ctep.cancer.gov).

Questions about drug orders, transfers, returns or accountability should be addressed to the PMB by calling 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time by emailing PMBAfterHours@mail.nih.gov anytime.

3.3 Goserelin acetate implant (Zoladex®) (NSC-606864)

a. PHARMACOLOGY

Mechanism of Action: Following initial administration in males, goserelin causes an initial increase in serum luteinizing hormone (LH) and follicle stimulating hormone (FSH) levels with subsequent increases in serum levels of testosterone. Chronic administration of goserelin leads to sustained suppression of pituitary gonadotropins, and serum levels of testosterone consequently fall into the range normally seen in surgically castrated men approximately 2-4 weeks after initiation of therapy.

In females, a similar down-regulation of the pituitary gland by chronic exposure to goserelin leads to suppression of gonadotropin secretion, a decrease in serum estradiol levels consistent with the postmenopausal state, and would be expected to lead to a reduction in ovarian size and function, reduction in the size of the uterus and mammary gland, as well as a regression of sex hormone-responsive tumors, if present. Serum estradiol is suppressed to levels similar to those observed in postmenopausal women within 3 weeks following initial administration; however, after suppression was attained, isolated elevations of estradiol were seen in 10% of the patients enrolled in clinical trials. Serum LH and FSH are suppressed to follicular phase levels within four weeks after initial administration of drug and are usually maintained at that range with continued use of goserelin.

b. PHARMACOKINETICS

1. Absorption: Goserelin 3.6 mg is released slowly in first 8 days, and then rapid and continuous release for the remainder of the 28 day dosing period. Time to peak concentration for goserelin 3.6 mg is 12-15 days in males and 8-22 days in females. Goserelin 10.8 mg exhibits an initial rapid release resulting in a peak concentration at 2 hours after dosing. From Day 4 until the end of the 12-week dosing interval, the sustained release of goserelin produces a reasonably stable systemic exposure.

2. Distribution: Apparent volumes of distribution determined after subcutaneous administration of 250 mcg aqueous solution of goserelin were 44.1 and 20.3 liters for males and females, respectively. Goserelin is approximately 27% protein bound.

3. Metabolism: Metabolism of goserelin by hydrolysis of the C-terminal amino acids is the major clearance mechanism. The half-life elimination ($t_{1/2}$) is approximately 4 hours in males and 2 hours in females

4. Elimination: Clearance of goserelin is very rapid and occurs primarily via urinary excretion (>90%; 20% as unchanged drug).

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Goserelin		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Anemia	
CARDIAC DISORDERS		
	Congestive heart failure	Cerebrovascular accident
	Hypertension	Myocardial infarction
	Palpitation	
	Vasodilatation	
	Tachycardia	

EYE DISORDERS		
	Amblyopia	
	Dry eyes	
GASTROINTESTINAL DISORDERS		
	Anorexia	
	Appetite increased	
	Nausea	
	Abdominal pain	
	Constipation	
	Diarrhea	
	Dyspepsia	
	Flatulence	
	Ulcer	
	Vomiting	
	Xerostomia	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Sweating	Injection site reactions	
Tumor flare	Voice alterations	
IMMUNE SYSTEM DISORDERS		
	Fever	
INFECTIONS AND INFESTATIONS		
	Infection	
	Flu syndrome	
METABOLISM AND NUTRITION DISORDERS		
	Weight gain / loss	
	Hyperglycemia	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
Bone mineral density decreased	Weakness	
	Arthralgia	
	Back pain	
	Hypertonia	
	Bone / joint pain	
	Leg cramps	
	Myalgia	
	Paresthesia	
NERVOUS SYSTEM DISORDERS		
Headache	Dizziness	
	Pain	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Depression	
	Insomnia	
	Emotional lability	
RENAL AND URINARY DISORDERS		
	Urinary frequency	
	Urinary obstruction	
	Urinary tract infection	

REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Hot flashes	Vaginal hemorrhage	
Libido decreased	Vulvovaginitis	
Sexual dysfunction	Pelvic symptoms	
Vaginitis	Dyspareunia	
Breast atrophy	Breast enlargement	
	Erections decreased	
	Libido increased	
	Breast pain/swelling	
	Dysmenorrhea	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Pharyngitis	
	Upper respiratory infection	
	Chronic obstructive pulmonary disease	
	Cough	
	Bronchitis	
	Sinusitis	
	Epistaxis	
	Rhinitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
Acne	Hair disorders	
Seborrhea	Hirsutism	
	Pruritus	
	Rash	
	Skin discoloration / bruising	
VASCULAR DISORDERS		
Peripheral edema	Hemorrhage	Thromboembolism

Adverse effects occurring in <1%, postmarketing, and/or case reports: ALT increased, anaphylaxis, AST increased, diabetes, glucose tolerance decreased, hypercalcemia, hypercholesterolemia, hyperlipidemia, hypersensitivity reactions, hypotension, ovarian cyst, pituitary apoplexy, psychotic disorders, urticaria.

2. Pregnancy and Lactation: Pregnancy category X in patients with endometriosis and endometrial thinning. Pregnancy category D in patients with advanced breast cancer. It is not known if goserelin is excreted in human milk, however goserelin is excreted in the milk of lactating rats.

3. Drug Interactions: Luteinizing hormone-releasing hormone analogs may diminish the therapeutic effect of antidiabetic agents. No formal drug-drug interaction studies have been performed. Please refer to the current FDA-approved package insert for additional information.

4. The FDA issued a safety communication in October 2010 based on their ongoing safety review of LHRH agonists. The safety communication discusses the potential for an increased risk of diabetes and cardiovascular disease (myocardial infarction, sudden cardiac death,

stroke) associated with these agents. The risk is thought to be low in men receiving LHRH agonists for prostate cancer. In this trial, LHRH agonists are being administered for a short period of time. FDA recommendations include management of cardiovascular risk factors according to current standards of practice.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Goserelin is administered subcutaneously into the anterior abdominal wall below the navel line using aseptic technique.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Goserelin acetate implant is available in a 3.6 mg or 10.8 mg disposable syringe device. The unit is sterile and comes in a sealed, light- and moisture-proof, aluminum foil laminate pouch containing a desiccant capsule.

2. Goserelin is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

3.4 Leuprolide (Eligard®, Lupron Depot®) (NSC-377526)

a. PHARMACOLOGY

Mechanism of Action: Leuprolide inhibits gonadotropin secretion by acting as an luteinizing hormone-releasing hormone (LHRH) agonist. Continuous administration results in suppression of ovarian and testicular steroidogenesis due to decreased levels of LH and FSH with subsequent decrease in testosterone (male) and estrogen (female) levels. In males, testosterone levels are reduced to below castrate levels. Leuprolide may also act directly on the testes as well as act by a different mechanism not directly related to reduction in serum testosterone.

b. PHARMACOKINETICS

1. Absorption: After the initial increase of leuprolide following each injection, mean serum concentrations remain relatively constant.

2. Distribution: The mean steady-state volume of distribution of leuprolide following intravenous bolus administration to healthy male volunteers was 27 L. In vitro binding to human plasma proteins ranged from 43% to 49%.

3. Metabolism: Upon administration with different leuprolide acetate formulations, the major metabolite of leuprolide acetate is a pentapeptide (M-I) metabolite.

4. Elimination: Less than 5% of the leuprolide dose was recovered as parent and M-I metabolite in the urine following the 3.5 mg depot injection.

c. ADVERSE EFFECTS

1. Refer to the package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions.

Adverse Events with Possible Relationship to Leuprolide		
Likely (>20%)	**Less Likely (≤20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
	Edema	
CARDIAC DISORDERS		
	Hyper- / hypotension	Arrhythmia
	Tachycardia	Atrial fibrillation
	Bradycardia	Congestive heart failure
	Angina	Syncope
	Palpitation	
GASTROINTESTINAL DISORDERS		
Nausea	Altered bowel function	Gastrointestinal hemorrhage
Vomiting	Ulcer	
	Intestinal obstruction	
	Constipation	
	Diarrhea	
	Gastroenteritis/colitis	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Local injection site burning/stinging	Skin reaction	
IMMUNE SYSTEM DISORDERS		
	Flu-like syndrome	Allergic reaction
INFECTIONS AND INFESTATIONS		
	Urinary tract infection	
	Infection	
INVESTIGATIONS		
	BUN increased	
	Creatinine increased	
	Bicarbonate decreased	
	Hyperphosphatemia	
	Hyperuricemia	
	Hypoalbuminemia	
	Hypoproteinemia	

METABOLISM AND NUTRITION DISORDERS		
	Dehydration	
	Hyperlipidemia	
	Weight gain/loss	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Weakness	
	Bone pain	
	Joint disorder	
	Myalgia	
	Paresthesia	
NERVOUS SYSTEM DISORDERS		
Headache	Nervousness	Seizure
Pain	Anxiety	
Insomnia	Confusion	
	Fatigue	
	Dizziness/vertigo	
PSYCHIATRIC DISORDERS		
Depression		
RENAL AND URINARY DISORDERS		
	Urinary disorders	
	Bladder spasm	
	Urinary retention	
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
Hot flashes / sweats	Vaginitis	
Testicular atrophy	Gynecomastia	
	Breast tenderness	
	Menstrual disorder	
	Lactation	
	Testicular Pain	
	Impotence	
	Libido decreased	
	Nocturia	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Emphysema	
	Epistaxis	
	Pleural effusion	
	Pulmonary edema	
	Dyspnea	
	Cough	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Acne	
	Alopecia	
	Bruising	
	Cellulitis	
	Pruritus	
	Rash	
	Hirsutism	
VASCULAR DISORDERS		
	Varicose vein	
	Deep thrombophlebitis	

<1%, postmarketing, and/or case reports: Abdominal pain, anaphylactic/anaphylactoid reactions, asthmatic reactions, bone density decreased, coronary artery disease, diabetes; fibromyalgia-like symptoms; flushing, hemoptysis, hepatic dysfunction, hypokalemia, hypoproteinemia, injection site induration/abscess, liver injury, myocardial infarction, pelvic fibrosis, penile swelling, peripheral neuropathy, photosensitivity; pituitary apoplexy; prostate pain, pulmonary embolism, pulmonary infiltrate, seizure, spinal fracture/paralysis, stroke suicidal ideation/attempt (rare), tenosynovitis-like symptoms, thrombocytopenia, transient ischemic attack, uric acid increased, urticaria, WBC decreased/increased.

2. Pregnancy and Lactation: Leuprolide is pregnancy category X and excretion into breast milk is unknown / contraindicated.

3. Drug Interactions: Luteinizing hormone-releasing hormone analogs may diminish the therapeutic effect of antidiabetic agents. No pharmacokinetic-based drug-drug interaction studies have been performed. Because leuprolide is a peptide that is primarily degraded by peptidase and not by Cytochrome P-450 enzymes and the drug is only about 46% protein bound, drug interactions would not be expected to occur.

4. The FDA issued a safety communication in October 2010 based on their ongoing safety review of LHRH agonists. The safety communication discusses the potential for an increased risk of diabetes and cardiovascular disease (myocardial infarction, sudden cardiac death, stroke) associated with these agents. The risk is thought to be low in men receiving LHRH agonists for prostate cancer. In this trial, LHRH agonists are being administered for a short period of time. FDA recommendations include management of cardiovascular risk factors according to current standards of practice.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Leuprolide is administered intramuscular (Lupron Depot®) or subcutaneous (Eligard®) injection based on commercial depot formulation. Injection sites should be varied periodically.

e. STORAGE & STABILITY

Refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Leuprolide acetate is available in 3.75 mg, 7.5 mg, 11.25 mg, 22.5 mg, 30mg, or 45 mg depot formulation kit with accompanying diluent. The prefilled dual-chamber syringe contains lyophilized microspheres of leuprolide acetate incorporated in a biodegradable lactic acid polymer.

2. Leuprolide is commercially available and will not be supplied. Refer to the current FDA-approved package insert for additional information.

4.0 STAGING CRITERIA

Distant metastasis (M) - AJCC Seventh Edition, 2010

M1: Distant metastasis

Note: regional lymph node metastasis by itself is insufficient for the classification of M1 disease.

Severity of Disease: minimal or extensive (as assessed at the diagnosis of M1 cancer of the prostate).

Minimal: Patients with involvement of axial skeleton ONLY, without tumor present in ribs, long bones, skull, or soft tissue other than lymph nodes.

Extensive: Patients with diffuse bone disease (ribs, long bone, skull) and/or parenchymal organ involvement.

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 **S0925** 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 2 weeks later would be considered Day 14. This allows for efficient patient scheduling without exceeding the guidelines. If Day 14, 28, 30, 42, or 90 falls on a weekend or holiday, the limit may be extended to the next working day.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.1 Disease Related Criteria

____ a. All patients must have a histologically or cytologically proven diagnosis of adenocarcinoma of the prostate. Note: If there is no formal biopsy report documenting the diagnosis of prostate cancer, the patient can be allowed on trial if the PSA level is at least 20, and there are at least three definitive metastatic lesions seen on scan. All patients must have had metastatic (M1) disease as evidenced by soft tissue and/or bony metastases prior to androgen deprivation therapy initiation. Patients must have at least one of the following at the time they started androgen deprivation therapy:

1. Visceral disease (liver, lung, other viscera),

2. Bone metastases to sites in either the axial (spine, pelvis, ribs, skull) and/or the appendicular (clavicle, humerus, femur) skeleton,

3. Lymph node disease not considered to be encompassed within a single radiation therapy port (e.g. above the aortic bifurcation, etc.).

____ b. Patients who have measurable disease must have radiographic assessment (at least an abdominal/pelvic CT) within 28 days prior to registration. Non-measurable disease must also be assessed (e.g., bone scan) in all patients within 56 days prior to registration. All disease must be assessed and documented on the Baseline Tumor Assessment Form.

____ c. Patients must have a PSA ≥ 5 ng/mL obtained within 90 days prior to initiation of androgen deprivation therapy.

____ d. Patients with known brain metastases are not eligible. Brain imaging studies are not required for eligibility if the patient has no neurologic signs or symptoms, but if brain imaging studies are performed, they must be negative for disease.

—— e. Patient must have had no more than 30 days of prior medical castration for metastatic prostate cancer (prior androgen deprivation therapy is allowed if it was received with curative intent in the neoadjuvant, concurrent, and/or adjuvant fashion and at least 2 years have elapsed since completion of androgen deprivation therapy). The start date of medical castration is considered the day the patient first received an injection of a LHRH agonist, not an oral antiandrogen. If the method of castration is luteinizing hormone releasing hormone (LHRH) agonists (i.e., leuprolide or goserelin), the patient must be willing to continue the use of LHRH agonists and add bicalutamide for combined androgen deprivation therapy (ADT) during protocol treatment. The 30 day window begins from the date of receiving the LHRH agonist, not the oral antiandrogen. If the patient was on a different antiandrogen (e.g. flutamide), the patient must be willing to switch over to bicalutamide. Patients must not have received bilateral orchiectomy. Patients must not have received or be planning to receive LHRH antagonists (i.e., Degarelix). However, if the patient was initiated on a LHRH antagonist within the 30 day window and is willing to switch to a LHRH agonist with bicalutamide, he may enroll on the late induction group.

As a result, there are two patient populations eligible for the study: those who have not started any androgen deprivation therapy (early induction group) and those who have already started androgen deprivation therapy within the last 30 days (late induction group). Patients must be registered within 30 days of first injection of the LHRH agonist or antagonist.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.2 Prior Therapy Criteria

____ f. Patients who have not already started androgen deprivation therapy must be offered the opportunity to participate in the translational medicine studies outlined in Section 15.0. Once a patient has started any form of antiandrogen (i.e., either bicalutamide or LHRH agonist), he is not eligible for any translational medicine studies outlined in Section 15.0.

____ g. Patients must not have received any prior cytotoxic chemotherapy for metastatic prostate cancer. Prior cytotoxic chemotherapy with curative intent in the neoadjuvant or adjuvant setting is allowed. Patients must not have received any prior treatment with agents that directly inhibit IGF or IGFRs (see Appendix 18.3).

____ h. Patients must not have received prior strontium-89, rhenium-186, rhenium-188, or samarium-153 radionuclide therapy within 28 days prior to registration.

____ i. Patients may have received prior radiation therapy or biologic therapy (e.g. vaccines, immunotherapy, anti-sense, small molecules, monoclonal antibodies) not excluded by Sections 5.1e, 5.2g, and 5.2h. However, at least 28 days must have elapsed since completion of therapy and patient must have recovered from all side effects.

____ j. Patients may have received prior surgery. For all major surgeries, at least 28 days must have elapsed since completion and patient must have recovered from all side effects.

5.3 Clinical/Laboratory Criteria

____ k. Patient must have adequate hematologic function as evidenced by leukocytes ≥ 3,000 mcL, absolute neutrophil count (ANC) ≥ 1,500 mcL, hemoglobin ≥ 9 g/dL, and platelets ≥ 100,000/mcL. These results must be obtained within 28 days prior to registration.

____ l. Patient must have adequate hepatic function as evidenced by bilirubin ≤ 1.5 times the institutional upper limit of normal (ULN) (unless documented Gilbert's disease), SGOT (AST) and SGPT (ALT) ≤ 3 times the institutional ULN, or ≤ 5 times the institutional ULN if liver metastases are present. These results must be obtained within 28 days prior to registration.

____ m. Patients must have adequate renal function as evidenced by creatinine ≤ 2.0 x the institutional ULN or calculated creatinine clearance ≥ 40 mL/min obtained within 28 days prior to registration.

Calculated creatinine clearance = $\frac{(140 - \text{age}) \times \text{wt (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{creatinine (mg/dl)}}$

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

____ n. Patients must have adequate coagulation function as defined by an international normalized ratio (INR) ≤ 1.5 and partial thromboplastin time (PTT) no more than 5 seconds above the institutional ULN. These results must be obtained within 28 days prior to registration. Patients receiving prophylactic low dose coumadin or low molecular weight heparin are eligible as long as they meet these coagulation criteria. Patients requiring full-dose (therapeutic) anticoagulation are eligible provided that they have been on a stable dose of anticoagulation and the coagulation parameters are stable within the therapeutic range (e.g., INR 2-3 for patients on therapeutic warfarin).

____ o. Patients must have a hemoglobin A1c (HgA1c) ≤ 7% AND fasting glucose of < 160 mg/dL or below the institutional ULN within 14 days prior to registration. Patients with diabetes mellitus who meet this criterion must be on a stable dietary or therapeutic regimen for this condition.

____ p. Patients must not have a history of symptomatic congestive heart failure or a known ejection fraction (LVEF) that is ≥ 10% below the LLN. If LV dysfunction is suspected, but not confirmed by review of past medical history, a MUGA or echocardiogram must be obtained within 90 days prior to registration.

____ q. Patient must not have a history of allergic reaction attributed to compounds of similar chemical or biologic composition to IMC-A12. Patients must not have received prior chimerized or murine monoclonal antibody therapy.

____ r. Patients must have a Zubrod performance status of 0 - 2 (see Section 10.3). Zubrod performance status 3 will be allowed if from bone pain only.

____ s. Patients with HIV positivity requiring antiretroviral therapy are not eligible for this study.

____ t. Patients must have no plans to receive concurrent chemotherapy, hormonal therapy (other than the LHRH agonist and oral anti-androgen), radiotherapy, immunotherapy or any other type of therapy for treatment of cancer while on this protocol treatment. Concurrent bone targeting agents that do not have effect on PSA (i.e. denosumab or zoledronic acid) are allowed.

____ u. Patients must have no plans to receive concurrent five-alpha reductase inhibitors (e.g. finasteride and dutasteride), ketoconazole, diethylstilbestrol/DES, or other estrogen-based therapy while on this protocol treatment.

____ v. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin 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.

____ w. Men of reproductive potential must have agreed to use an effective contraceptive method while receiving treatment on this study and for at least three months after protocol treatment ends.

SWOG Patient No. _____

Patient's Initials (L, F, M) _____

5.4 Regulatory Criteria

____ x. 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.

____ y. As part of the OPEN registration process (see Section 13.3 for OPEN access instructions), the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

6.0 STRATIFICATION FACTORS

Patients will be randomized using a dynamic balancing algorithm (Pocock and Simon, 1975) with stratification based on:

Zubrod Performance Status (0-1 vs. 2-3),
Baseline PSA pre-LHRH (< 20 ng/mL vs. ≥ 20 ng/mL).

7.0 TREATMENT PLAN

For treatment or dose modification related questions, please contact Dr. Evan Yu at 206/288-1152 or Dr. Celestia Higano at 206/288-1152. 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 tests (and/or assessments) 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.

Suggested pre-study tests for good medical practice include the following:

a. Testosterone for patients who have not received castration therapy (early induction group)

b. Lipid profile to include cholesterol, LDL, HDL and triglycerides.

7.2 Pre-Medication

Routine premedication is not required for the first dose of IMC-A12. If infusional reactions occur, acetaminophen, diphenhydramine, steroids or other medications may be given for symptom control and premedication as needed.

Prolonged use of systemic corticosteroids to prevent allergic reactions is discouraged because of their potential to cause and exacerbate hyperglycemia. Intermittent use of corticosteroids is permitted. Anaphylactic precautions should be observed during IMC-A12 administration.

7.3 Treatment Schedule

Patients will be randomized to either Arm 1: androgen deprivation therapy (bicalutamide with a LHRH agonist) + IMC-A12 or Arm 2: androgen deprivation therapy (bicalutamide with a LHRH agonist). Patients will receive protocol treatment for seven cycles (28 weeks).

All patients with pain from bone metastasis who have yet to start any androgen deprivation therapy, i.e. those patients who are early induction patients, are required to receive 7 days of bicalutamide prior to receiving the LHRH agonist. This is to prevent a clinical flare reaction. Should the patient be asymptomatic without pain, bicalutamide may be started on the same day as the LHRH agonist. Patients on other anti-androgens must switch to bicalutamide without lead-in.

a. Treatment schedule for Arm 1: Bicalutamide + LHRH agonist + IMC-A12

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Bicalutamide (Casodex™)	50 mg	PO	QD	
(See bolded note above)				
LHRH Agonist (see Section 7.4)				
IMC-A12	10 mg/kg	IV over 60 minutes	1, 15	q 28 days

NOTE: Regular glucose monitoring will be obtained prior to treatment on the day of each administered dose of IMC-A12.

NOTE: One hour of monitoring is required after the first infusion of IMC-A12 is administered.

Cycle 1, Day 1 is designated as the day the patient receives IMC-A12, regardless of whether the patient is an early induction or late induction patient. Early induction patients should also receive their first injection of the LHRH agonist on Cycle 1, Day 1 with IMC-A12.

b. Treatment schedule for Arm 2: Bicalutamide + LHRH agonist

AGENT	DOSE	ROUTE	DAYS	INTERVAL
Bicalutamide (Casodex™)	50 mg	PO	QD	
(See bolded note above)				
LHRH Agonist (see Section 7.4)				

Cycle 1, Day 1 is designated as the day the patient receives the first LHRH agonist injection on the early induction arm. The late induction arm patients will have received their first LHRH agonist or antagonist injection already. As a result, the date of randomization will be used as Cycle 1, Day 1.

PSA values will be assessed prior to treatment, and then with each cycle (every 4 weeks). The PSA obtained prior to initiating any androgen deprivation therapy, including bicalutamide, should be used as the baseline PSA. More frequent PSA monitoring is acceptable, but all measures should be reported on the **S0925** Prostate Specific Antigen Reporting Form.

At the completion of seven cycles (28 weeks) of protocol treatment, patients will be evaluated for efficacy by absolute PSA level. The patient will effectively be finished with treatment on protocol at that point. Further treatment with either continuous androgen deprivation or intermittent androgen deprivation will be up to the individual patient and treating physician at that point. However, no further IMC-A12 will be provided.

7.4 Androgen Deprivation Therapy

All patients will receive androgen deprivation therapy with a LHRH agonist (goserelin acetate or leuprolide acetate) per the treating physician and this will be given continuously until the seven cycles (28 weeks) of protocol therapy is complete or evidence of early disease progression (see Section 10.2). One, three, four and six month or one year depots will be acceptable. Bilateral surgical orchiectomy is also acceptable. Oral anti-androgen will be bicalutamide.

7.5 Concomitant Medications

The use of supportive care medications is allowed according to institutional standards. However prolonged use of systemic corticosteroids for prevention of allergic reactions is discouraged because of their potential to cause and exacerbate hyperglycemia. Intermittent use of corticosteroids is permitted. LHRH agonist (e.g. goserelin and leuprolide) must be continued throughout protocol treatment and are considered a standard of care treatment for this patient population.

Several medications are specifically disallowed. Five-alpha reductase inhibitor (e.g. finasteride and dutasteride) are not permitted. Other excluded therapies include ketoconazole, diethylstilbestrol/DES, and other estrogen preparations.

7.6 CTEP Requirements

Because this study contains an investigational drug for which CTEP holds the IND, it falls under CTEP requirement for full reporting. This involves required submission of cycle-specific toxicity and dose information (see Section 14.4b, the **S0925** Treatment Form and the **S0925** Adverse Event Form). A cycle is defined as 28 days.

7.7 Drug Compliance

Drug compliance will be recorded by patients in the Intake Calendar (see Appendix 18.4). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking patient compliance. Sites may utilize institutional pill diaries or other source documentation in place of the Intake Calendar at the discretion of the treating physician.

7.8 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.2).

b. Development of castration-resistant prostate cancer as determined by two serial rises in PSA while on protocol treatment with castrate testosterone levels (total testosterone < 50 ng/dL).

c. Unacceptable toxicity.

d. Protocol treatment is held for any reason > 4 weeks.

e. Completion of 7 cycles (28 weeks) of protocol treatment.

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

7.9 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the study forms.

7.10 Follow Up Period

All patients will be followed for a maximum of five years.

8.0 DOSAGE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4.0 for toxicity and Serious Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (http://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

a. Missed doses are to be omitted rather than made up.

b. If multiple toxicities are seen for any given single agent, administer dose based on greatest reduction required for any single toxicity observed.

c. Reductions apply to treatment given in the preceding cycle and are based on toxicities observed since the prior dose.

d. Once dose is reduced, patients will continue at new dose. No dose re-escalations are allowed.

e. If protocol treatment is held for any reason > 4 weeks, patient should be removed from protocol treatment.

8.3 Dose modifications for ADT and LHRH Agonist

a. There are no dosage adjustments for hematologic toxicity. The need for the use of G-CSF is not anticipated.

b. Dosage adjustments for Non-hematologic Toxicity:

Diarrhea Toxicity:

The major toxic effect of bicalutamide is moderate diarrhea which is very rarely severe (exclusion of other causes of diarrhea should be considered in severe cases). The dose modifications for this will be as follows.

1. Grade 2 diarrhea, treat symptomatically with anti-diarrhea drugs.

2. Grade 2 diarrhea unresponsive to symptomatic treatment or Grade 3/4 diarrhea - discontinue bicalutamide until complete recovery.

In case of any diarrhea ≥ Grade 1, please check:

- WBC in stools
- stool cultures
- difficile titers

Further tests are up to discretion of treating physician. Restart treatment as per protocol when diarrhea resolves to ≤ Grade 1.

c. **ABNORMAL LIVER FUNCTION TESTS (SGOT/AST, SGPT/ALT, BILIRUBIN)**

Grade 2 or greater toxicity - Stop bicalutamide; wait until LFTs are normal (Grade 0). Hepatitis screening (A, B, C) should be done in all cases of abnormal LFTs which could be consistent with infectious hepatitis. To assess return to normal, abnormal liver function tests should be done weekly. Tests may also be done with more frequency, as per the discretion of the treating physician.

Restart treatment when LFTs return to normal. If toxicity (Grade 2 or worse) occurs again, discontinue all protocol treatment. Patients requiring delay greater than 4 weeks should be removed from protocol treatment per Section 7.8d.

d. Patients may complain of flatulence, bloating and mild "gas pains" which should not result in changes in treatment. Symptomatic treatment should be employed with antacids, simethicone, etc.

8.4 Dose modifications for IMC-A12

a. Dose Levels

Starting Dose	10 mg/kg
Dose Level -1	8 mg/kg
Dose level -2*	6 mg/kg

***** Patients who require more than two dose reductions of IMC-A12 will be removed permanently from protocol treatment and treated at the physician's discretion.

b. Treatment Modification for IMC-A12-Related Adverse Events

Event	CTCAE Version 4.0 Grade	Action to be taken
Allergic reactions or anaphylaxis or Acute infusional reactions/cytokine release syndrome	G1 Allergic or infusional reactions	• Slow infusion rate by 50% and monitor patient for worsening of condition
	G2 Allergic or infusional reactions	• Stop infusion; symptom control (diphenhydramine hydrochloride 50 mg IV, acetaminophen 650 mg for fever, and oxygen if needed) • Resume infusion at 50% of the prior rate once the reaction has decreased to ≤ Grade 1. Monitor patient for worsening condition • For subsequent dose, premedicate with diphenhydramine hydrochloride 50 mg IV • If Grade 1-2 infusion reactions reoccur with subsequent dose, add dexamethasone 10 mg IV or equivalent to premedications above **(Only dose interruption/discontinuation, but not dose reduction, is required for allergic/infusional reactions)**
	G3 Allergic or infusional reactions or anaphylaxis	• Stop infusion immediately and remove the infusion tube • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV (or equivalent), bronchodilators for bronchospasms, and other medications as medically indicated. Hospital admission should be considered • **Discontinue** IMC-A12 treatment
	G4 Allergic or infusional reactions or anaphylaxis	• Stop infusion and remove the infusion tube • Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV (or equivalent), and other anaphylaxis medications as indicated. Epinephrine or bronchodilators should be administered as indicated. Hospital admission for observation may be indicated. • **Discontinue** IMC-A12 treatment

Event	CTCAE Version 4.0 Grade	Action to be taken
Hyperglycemia	G1-2	• Continue IMC-A12 • Initiate or increase oral diabetic agents as clinically indicated
	G3 NO symptoms AND glucose < 300 mg/mL	• Initiate/increase insulin and /or oral diabetic agents • May continue IMC-A12
	G3 Symptomatic OR glucose ≥ 300 mg/mL	• **Hold** IMC-A12 • Initiate/increase insulin and/or oral diabetic agents • Resume IMC-A12 with one dose reduction IF patient is asymptomatic, AND glucose is consistently < 220 mg/mL on stable dose of insulin and /or oral diabetic agents
	G4	• **Hold** IMC-A12 • Resume IMC-A12 with one dose reduction IF patient is asymptomatic, AND glucose is consistently < 220 mg/mL on stable dose of insulin and /or oral diabetic agents
Blood and Lymphatic System Disorders (Neutropenia, or thrombocytopenia)	G1-2	• Continue IMC-A12
	G3-4	• **Hold** IMC-A12 until grade decreases to < Grade 2 • Resume with one dose reduction (if cytopenia is judged to be related to IMC-A12)
Other unspecified IMC-A12-related AEs (except controlled nausea/vomiting)	G2	• IMC-A12 may continue or be held at physician's discretion depending on the nature of the AE • If held, may resume at initial or one dose reduction depending on nature of the AE at the treating physician's discretion.
	G3	• **Hold** IMC-A12 until symptoms resolve to ≤ Grade 1 • Resume with one dose reduction
	G4	• If event is related to IMC-A12, is clinically significant, and cannot be managed with supportive care, discontinue IMC-A12 • Upon consultation with the Study Chair, resumption of IMC-A12 may be considered if a patient is benefiting from therapy (and the Grade 4 toxicity is transient), has recovered to ≤ Grade 1 and unlikely to recur with retreatment

c. Hyperglycemia

CTCAE 4.0 criteria for "Glucose Intolerance" should be referred to in the Metabolism and Nutrition Disorders section. Dose modifications of IMC-A12 for diabetes/hyperglycemia should be based on fasting serum glucose levels. If random serum glucose levels are significantly and unexpectedly elevated (e.g., not immediately after meals), then a fasting glucose should be done to determine the dosage modification.

For persistently elevated glucose levels in symptomatic patients, dietary modification or treatment with an oral hypoglycemic agent such as the sulfonylurea glipizide should be considered. **With the sulfonylurea glipizide, hypoglycemia is a common side effect and can be severe. Risk factors include increasing age, alcohol abuse, poor nutrition and renal insufficiency. Patients on glipizide need to be cautioned about hypoglycemia and monitored closely.**

A second choice for an oral hypoglycemic agent could be metformin. An uncommon but serious side effect of metformin is lactic acidosis, which is fatal in 50% of cases. Metformin accumulation can lead to lactic acidosis. Metformin is 100% excreted in the urine. Lactic acidosis occurs in patients with renal insufficiency, hepatic insufficiency, sepsis, dehydration, and excess alcohol intake. Patients on this study will commonly have some degree of hepatic insufficiency. Metformin should be held prior to any intravascular x-ray contrast dye study with the potential for contrast induced renal failure. Metformin should be temporarily discontinued prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been reevaluated and found to be normal. The symptoms of lactic acidosis are subtle and non-specific including malaise, myalgias, increased somnolence, and nonspecific abdominal distress, all of which may be present in this patient population. Therefore metformin must be used with caution.

Refer to the package insert for additional information about these and other agents. In more severe cases, treatment with insulin may be considered. Consider consultation with an endocrinologist experienced in the management of diabetes mellitus.

8.5 Dose Modifications Contact

For treatment or dose modification related questions, please contact Dr. Evan Yu at 206/288-1152 or Dr. Celestia Higano at 206/288-1152.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.1 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

		Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7			Off Treatment Prior to Prog Follow-Up
REQUIRED STUDIES	PRE	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	Wk	
	STUDY	1	3	5	7	9	11	13	15	17	19	21	23	25	27	29	π
PHYSICAL																	
History and Physical Exam	X			X		X		X		X		X		X			X
Weight and Performance Status	X			X		X		X		X		X		X			
Disease Assessment ≠	X															X§	X
Toxicity Notation £				X		X		X		X		X		X			
Baseline Abnormalities Assessment	X																
LABORATORY																	
PSA	X			X		X		X		X		X		X		X§	X
CBC/Differential/ Platelets/ Hemoglobin	X			X		X		X		X		X		X			
Bilirubin	X			X		X		X		X		X		X			
SGOT/SGPT	X			X		X		X		X		X		X			
Serum Creatinine or Calculated Creatinine Clearance	X			X		X		X		X		X		X			
INR and PTT	X																
HgA1C	X																

Calendar continued on next page.

Fasting Serum Glucose Ɵ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
MUGA or Echocardiogram Я	X																
Testosterone ф*	X																
Lipid Profile *	X																
SPECIMEN SAMPLES (CORRELATIVE STUDIES)																	
Blood Specimens ¥	X							X√									
X-RAYS AND SCANS																	
CT or MRI of Abdomen & Pelvis ≠	X															X	X
Bone Scan	X															X	X
Brain CT †	X																
TREATMENT (see Section 7.4)																	
ARM 1:																	
Bicalutamide Ω		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Goserelin Acetate or Leuprolide Acetate		X		X		X		X		X		X		X			
IMC-A12		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ARM 2:																	
Bicalutamide Ω		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Goserelin Acetate or Leuprolide Acetate		X		X		X		X		X		X		X			

Calendar continued on next page.

NOTE: Refer to Master Forms instructions in Section 14.2. Forms submission guidelines may be found in Section 14.0.

≠ Disease assessment will be done after 7 cycles by the same methods used at baseline.

§ In order to assess the primary endpoint of this study, disease must be assessed and PSA obtained at Week 29 for all patients who have not progressed.

£ Patients should be monitored for toxicity prior to each cycle or at more frequent intervals appropriate for that patient as judged by the treating physician.

Я If LV dysfunction is suspected, but not confirmed by review of past medical history, a MUGA or echocardigram should be obtained prior to registration per Section 5.3p.

ф For patients who have not received castration therapy (early induction group).

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

Ω Bicalutamide is to be taken daily. Early induction patients with cancer-associated pain are required to receive 7 days of bicalutamide prior to Day 1, which will be designated as the day to receive the LHRH agonist +/- IMC-A12.

π Once off protocol treatment, patients should have disease assessed by PSA, bone scan and a CT or MRI of chest/abdomen/pelvis every 6 months for the first two years and then annually for up to 5 years after registration or until death. After disease progression, follow-up for survival status will continue to be assessed every 6 months for the first two years and then annually for up to 5 years after registration or until death.

¥ Collection of CTCs, blood for IGF biomarkers, and blood for microRNAs is collected before ADT for patients who have consented (see Section 15.0).

√ If patient develops clinical progression or clear castration-resistant disease prior to Cycle 4, Day 1, correlative blood specimens should be obtained earlier as the patient goes off protocol treatment before initiation of next line therapy.

† See Section 5.1d.

¶ One, three, four and six month or one year depots will be acceptable. (This calendar however is based off a monthly depot.) Bilateral orchiectomy in lieu of LHRH agonist is also acceptable.

Θ Fasting serum glucose must be obtained during treatment for all patients on Arm 1.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Measurability of lesions

a. **Measurable disease**

Measurable disease is defined differently for lymph nodes compared with other disease and will be addressed in a separate section below.

1. Lesions that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 2.0 cm by chest x-ray, by ≥ 1.0 cm with CT or MRI scans, or ≥ 1.0 cm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters (or millimeters).

   The defined measurability of lesions on CT scan is based on the assumption that CT slice thickness is 0.5 cm or less. If CT scans have slice thickness greater than 0.5 cm, the minimum size for a measurable lesion should be twice the slice thickness.

2. Malignant lymph nodes are to be considered pathologically enlarged and measurable if it measures ≥ 1.5 cm in **SHORT AXIS** (greatest diameter perpendicular to the long axis of the lymph node) when assessed by scan (CT scan slice recommended being no greater than 0.5 cm).

b. **Non-measurable disease**: All other lesions (or sites of disease), including small lesions (longest diameter < 1.0 cm or pathologic lymph nodes with ≥ 1.0 cm to <1.5 cm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered non-measurable as are previously radiated lesions that have not progressed.

c. **Notes on measurability**

1. For CT and MRIs, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should by performed with breath-hold scanning techniques, if possible.
2. PET-CT: At present, the low dose or attenuation correction CT portion of a PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT, then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT.
3. Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.
4. Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition simple cysts.
5. If a target lesion becomes very small some radiologists indicate that it is too small to measure. If the lesion is actually still present, a default measurement of 0.5 cm should be applied. If the radiologist believes the lesion has gone, a default measurement of 0.0cm should be recorded.

10.2 Objective status at each disease evaluation

Objective Status is to be recorded at each evaluation. All measurable lesions up to a maximum of 2 lesions per organ 5 lesions in total, representative of all involved organs, should be identified as ***target*** lesions at baseline. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as ***non-target*** lesions. Measurements must be provided for target measurable lesions, while presence or absence must be noted for non-target measurable and non-measurable disease.

For studies that use disease progression as an endpoint, whole body scanning at specific intervals is necessary to determine that progression is NOT present outside of the "target" areas. Therefore, in these studies it is not acceptable to image only the "target" areas of the body in follow-up scans. For study-specific imaging requirements, see the Study Calendar in Section 9.0.

a. **Complete Response (CR):** Complete disappearance of all target and non-target lesions (with the exception of lymph nodes mentioned below). No new lesions. No disease related symptoms. Any lymph nodes (whether target or non-target) must have reduction in short axis to < 1.0 cm. All disease must be assessed using the same technique as baseline.

b. **Partial Response (PR):** Applies only to patients with at least one measurable lesion. Greater than or equal to 30% decrease under baseline of the sum of appropriate diameters of all target measurable lesions. No unequivocal progression of non-measurable disease. No new lesions. All target measurable lesions must be assessed using the same techniques as baseline.

c. **Stable:** Does not qualify for CR, PR, Progression or Symptomatic Deterioration. All target measurable lesions must be assessed using the same techniques as baseline.

d. **Progression**: One or more of the following must occur: 20% increase in the sum of appropriate diameters of target measurable lesions over smallest sum observed (over baseline if no decrease during therapy) using the same techniques as baseline, as well as an absolute increase of at least 0.5 cm. Unequivocal progression of non-measurable disease in the opinion of the treating physician (an explanation must be provided). Appearance of any new lesion/site. Death due to disease without prior documentation of progression and without symptomatic deterioration (see Section 10.2e).

Notes regarding new lesions: FDG-PET imaging can complement regular scans in identifying new lesions according to the following algorithm.

1. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of progression based on a new lesion.
2. No FDG-PET at baseline and a positive FDG-PET at follow-up corresponding to a potential new site of disease must have a confirmation by anatomical assessment (e.g. CT, MRI, x-ray) as new site of disease to be considered progressive disease. In such a case, the date of progressive disease will be the date of the initial abnormal FDG-PET.

e. **Symptomatic deterioration**: Global deterioration of health status requiring discontinuation of treatment without objective evidence of progression. Efforts should be made to obtain objective evidence of progression after discontinuation.

f. **Assessment inadequate, objective status unknown**. Progression or symptomatic deterioration has not been documented, and one or more target measurable lesions have not been assessed or inconsistent assessment methods were used.

g. Objective status notes:

1. Non-measurable and non-target measurable disease do not affect Objective Status in determination of CR (must be absent--a patient who otherwise has a CR, but who has non-measurable or non-target measurable disease present or not assessed, will be classified as having a PR). However, non-measurable and non-target lesions are included in determination of progression (if new sites of disease develop or if unequivocal progression occurs in the opinion of the treating physician).
2. An objective status of PR or stable cannot follow one of CR. Stable can follow PR only in the rare case that tumor increases too little to qualify as progression, but enough that a previously documented 30% decrease no longer holds.
3. In cases for which initial flare reaction is possible (hypercalcemia, increased bone pain, erythema of skin lesions), objective status is not progression unless either symptoms persist beyond 4 weeks or there is additional evidence of progression.
4. Lesions that appear to increase in size due to presence of necrotic tissue will not be considered to have progressed.
5. For bone disease documented on bone scan only, increased uptake does not constitute unequivocal progression. However, increase in the soft tissue component of a lesion as measured by CT or MRI would constitute progression.
6. Appearance of new pleural effusions does not constitute unequivocal progression unless cytologically proven of neoplastic origin, since some effusions are a toxicity related to therapy or other medical conditions. Increase in the size of an existing effusion does not constitute unequivocal progression, since the fluid status of the patient could alter the size of the effusion.
7. If CR determination depends on a lesion for which the status is unclear by the required tests, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate.

10.3 Performance Status

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

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.

4 Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

10.4 Time to Treatment Failure

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined above), early discontinuation of treatment, or death due to any cause. Patients last known not to have failed treatment are censored at the date of last contact.

10.5 Progression-Free Survival

From date of registration to date of first observation of progression or symptomatic deterioration (as defined in Section 10.2e), or death to any cause. Patients without progression are censored at last date of contact.

10.6 Time to Death

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

10.7 Undetectable PSA

Undetectable PSA is the primary endpoint and is defined as a PSA level of ≤ 0.2 ng/mL after seven cycles, without evidence of progression or symptomatic deterioration, as defined in Section 10.2d-e. A PSA partial response (PSA PR) after seven cycles is defined as a PSA that is between 0.2 and 4 ng/mL.

10.8 PSA Progression

PSA progression is defined by two consecutive increases in PSA over the nadir PSA, at least two weeks apart. If no on-study reduction has occurred, nadir would be the baseline PSA level.

11.0 STATISTICAL CONSIDERATIONS

11.1 Accrual goal

The accrual goal for this study is 180 eligible patients. Based on SWOG accrual to **SWOG-9346** (100 patients/year), this study should take approximately two years to complete accrual, and then one additional year of follow-up to assess the primary endpoint, undetectable PSA (PSA < 0.2 ng/mL) at seven months, on all patients.

11.2 Analysis of Primary Endpoint

The primary objective is to compare the undetectable PSA rates at 7 months between patients randomized to a LHRH agonist and bicalutamide and patients randomized to a LHRH agonist, bicalutamide and IMC-A12. We assume a 45% undetectable PSA rate in the control arm based on data from **SWOG-9346**. Using a one-sided type I error rate of 0.10, we will have 0.90 statistical power to detect an absolute difference of 20% in the undetectable PSA rate between treatment arms (i.e., 45% undetectable PSA rate in the control arm vs. 65% in the experimental arm). The primary analysis will be on an intent-to-treat basis.

When half of the patients have been evaluated for undetectable PSA status at 7 months, an interim analysis of the primary endpoint will be performed with the intent of testing the alternative hypothesis (i.e., terminate the study early if a relative risk of 1.44 [0.65/0.45] is deemed to be highly unlikely [p<0.005]).

11.3 Analysis of Secondary Endpoints

The secondary endpoints of the study are to assess the safety and tolerability of the combination of IMC-A12 with LHRH agonists and bicalutimide, the proportion of men who do not achieve a partial PSA response (PSA < 4 ng/mL), the accuracy of the prognostic model of undetectable PSA (developed from **SWOG-9346**), and biologic correlative studies.

A stratified chi-square test will be used to compare toxicity and partial PSA response rates between the two arms. Additionally, with 90 patients accrued to each arm, toxicity can be estimated to within ± 11% and any toxicity occurring with at least a 5% probability is likely to be seen at least once (99% chance).

The logistic regression algorithm for predicting undetectable PSA that was developed for **SWOG-9346** using its baseline risk factors (age at registration, performance status, baseline PSA, and bone pain) will be applied to each arm of this trial to evaluate the level of agreement between the observed and predicted undetectable PSA rates. Additionally, if the observed undetectable PSA rate in the hormones only arm is consistent with a rate of 45% then we will be assured that this patient sample is similar to that seen on **SWOG-9346**, and we will test Ho: the undetectable PSA rate equals 45% vs. Ha: the undetectable PSA rate is 60% in the experimental arm as if this were a one-arm Phase II pilot. Although this is a secondary aim, it will provide some information about whether a randomized Phase II trial was necessary versus relying on contemporary controls.

Biologic correlative studies will assess baseline, pre-treatment CTC and micro-RNA levels, as well as 12 week levels after combined therapy. Due to the limited sample size in a Phase II setting, correlative studies will be considered exploratory in nature and will be used to formulate hypotheses that can be tested using correlative data from a Phase III setting.

11.4 Analysis of Translational Medicine (TM) Endpoints

TM Objective 1 will involve testing whether treatment with IMC-A12 affects serum measures related to the IGF axis. The distribution of the change in serum measures such as IGF1 and IGFB3 will be tested between the two treatment arms from baseline to 12 weeks post-treatment. With 50 patients per treatment arm, and assuming appropriate data transformations as needed to obtain a roughly normal distribution, an effect size of 0.4 standard deviations between the change in the standard arm versus the arm with IMC-A12 can be detected applying a two sample t-test.

In TM Objective 2 we will correlate the baseline circulating tumor cells (CTCs) and change in CTCs from baseline to 12 weeks with undetectable PSA (< 0.2 ng/ml) and normalized (< 4 ng/ml) PSA response. For ease of power calculations, we dichotomize baseline CTC as high versus low based on a split at the median. Under the null hypothesis, we would expect 45% of patients will have an undetectable PSA at 7 months. With 100 patients with baseline CTC measures and using a two-sided alpha=0.05, there will be 80% statistical power to detect a difference of an undetectable PSA response rate of 60% for those with low CTC count compared to a 30% PSA undetectable rate for those with a high CTC count. Similar power applies to CTC change from baseline to week 12. These analyses will be conducted in the pooled treatment groups. However, there will be inadequate statistical power to evaluate whether there is an interaction of treatment arm with the CTC/PSA response relationship.

For TM Objective 3, Pearson and Spearman correlations will be initially evaluated between microRNA measures and CTC counts at both baseline and at 12 weeks. Analysis of covariance will be used to assess the relationship between microRNA and CTC, after adjusting for stratification factors. We will then assess whether microRNA such as mi-141 is an independent predictor of PSA response (looking at undetectable and normalized response separately) after adjusting for CTC count and stratification factors.

Due to the limited sample size in this Phase II setting, correlative studies will be considered exploratory in nature and no adjustments will be made for the multiple marker comparisons being explored. The results will be used to formulate hypotheses that can be tested using correlative data from a Phase III setting.

11.5 Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee will oversee the conduct of the study. The Committee consists of four members from outside of SWOG, 3 SWOG members, 3 non-voting representatives from the National Cancer Institute (NCI), and the Group Statistician (non-voting). The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings as necessary. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review done in conjunction with this study.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered prior to initiation of treatment (no more than 10 working days prior to planned start of treatment).

13.2 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. Credit Investigator

f. Patient Initials

g. Patient's Date of Birth

h. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

i. Country of Residence

j. ZIP Code

k. Gender (select one):
- Female Gender
- Male Gender

l. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

m. 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

n. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.3 Registration Procedures

a. All site staff 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).

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 on SWOG protocols, you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

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 on the CTSU members' side of the 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.

13.4 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirements

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

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 SWOG 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 include the SWOG patient number, study ID and patient initials.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit copies of the following:

S0925 Prestudy Form

Baseline Tumor Assessment Form

S0925 Baseline Abnormalities Form

Pathology Report

Radiology Report

b. WITHIN 7 DAYS OF COMPLETION OF EACH CYCLE WHILE ON PROTOCOL TREATMENT:

S0925 Treatment Form

S0925 Adverse Event Form

S0925 Prostate Specific Antigen Reporting Form

c. AT WEEK 29 FOR ALL PATIENTS WHO HAVE NOT PROGRESSED:

S0925 Prostate Specific Antigen Reporting Form

Follow-Up Tumor Assessment Form

Radiology Report

d. IF PATIENT HAS CONSENTED, WITHIN 7 DAYS OF REGISTRATION AND AFTER 12 WEEKS OF PROTOCOL TREATMENT:

Specimens outlined in Section 15.0

e. WITHIN 14 DAYS OF DISCONTINUATION OF ALL PROTOCOL TREATMENT:

Off Treatment Notice

Final **S0925** Treatment Form

Final **S0925** Adverse Event Form

S0925 Prostate Specific Antigen Reporting Form

f. AFTER OFF ALL PROTOCOL TREATMENT, EVERY SIX MONTHS FOR TWO YEARS AND ANNUALLY UNTIL FIVE YEARS AFTER REGISTRATION OR UNTIL DEATH:

Follow Up Form

S0925 Prostate Specific Antigen Reporting Form (if disease has not progressed)

g. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

If the patient was no longer on treatment, please submit the Follow-Up Form documenting the date and site of progression/relapse.

If the patient was still on protocol treatment, please submit the Follow-Up Tumor Assessment Form and the off-treatment submissions according to Section 14.4e**.**

h. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Please submit the Notice of Death. If the patient was no longer on treatment, please submit the Follow-Up Form documenting death information. If the patient was still on protocol treatment, please submit the off-treatment submissions according to Section 14.4e.

15.0 SPECIAL INSTRUCTIONS

Patient blood biomarker specimens are to be collected only in patients who begin androgen deprivation treatment after randomization, regardless of treatment arm. Those that began androgen deprivation therapy prior to registration (i.e., late induction registrations) should not be offered participation on the translational medicine studies. All prestudy blood specimens must be obtained prior to initiation of bicalutamide. Repeat specimens should be obtained on Cycle 4, Day 1 or at the time the patient develops clinical progression or clear castration-resistant disease should that occur prior to Cycle 4, Day 1.

15.1 General Specimen Submission Instructions

a. Specimen Tracking System

All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking system. SWOG members may log on to the Specimen Tracking system via the CRA Workbench (https://gill.crab.org/txwb/logon.aspx) using their SWOG roster ID numbers and passwords. First-time non-SWOG users must refer to start-up instructions located at https://gill.crab.org/SpecTrack/.

In the online Specimen Tracking system, laboratory ID numbers are used to identify the laboratories to which specimens are shipped. The laboratory ID numbers for this study may be found listed next to the laboratory names in Section 15.10.

ALL SPECIMENS MUST BE LOGGED VIA THIS SYSTEM; THERE ARE NO EXCEPTIONS.

To report technical problems with Specimen Tracking, such as database errors or connectivity issues, please send an email to technicalquestion@crab.org. For procedural help with logging and shipping specimens, there is an introduction to the system on the Specimen Tracking main page (https://gill.crab.org/SpecTrack/Documents/Instructions.pdf); or contact the Data Operations Center at 206/652-2267 to be routed to the Data Coordinator for further assistance.

A copy of the Shipment Packing List produced by the Specimen Tracking system should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag.

b. All submitted specimens must be labeled with the protocol number (**S0925**), SWOG patient number, patient's initials and date and time of specimen collection.

c. The Federal guidelines for shipment are as follows:

1. The specimen must be wrapped in an absorbable material.

2. The specimen must be placed in an AIRTIGHT container (like a resealable bag).

3. Pack the resealable bag and specimen in a Styrofoam shipping container.

4. Pack the Styrofoam shipping container in a cardboard box.

5. The cardboard box must be marked as "BIOHAZARD".

15.2 Obtaining Consent

After obtaining consent for a patient not pretreated with androgen deprivation (as described above) each site must call the University of Washington to provide their contact and same day FEDEX mailing information for shipment of study-specific kits.

University of Washington contact: (206) 288-2155

15.3 Instructions for Blood Biomarker Specimens

A kit for blood biomarker specimens will be mailed via FEDEX to your site. Each kit will contain one green top heparin tube, one lavender EDTA tube, one Tempus™ Blood RNA tube, two CellSave® blood collection tubes for circulating tumor cells (CTCs), frozen aliquots, frozen Tempus tube shipping supplies, a CTC tube shipping box, and instructions. FEDEX labels will be included to return samples to two separate labs. The Cycle 4, Day 1 kit will be mailed directly to your site approximately 2 weeks prior to planned visit date.

15.4 Obtaining Specimens

Specimens should be obtained in this order from the same venipuncture:

a. 1 - 4 mL green top heparin tube to obtain plasma to measure insulin, IGF-I, free IGF-I, growth hormone, and IGFBP-3.

b. 1 – 6 mL purple top EDTA tube to obtain plasma to measure microRNAs

c. 1 - 3 mL Tempus™ Blood RNA Tube for whole blood collection to measure RNA

d. 2 - CellSave® blood collection tubes to measure circulating tumor cells (CTCs) and measure IGF-IR on any CTCs. Ensure both tubes are completely full for adequate processing of samples.

NOTE: SPECIMENS MUST BE DRAWN AND MAILED ON THE SAME DAY TO ENSURE ARRIVAL AT THE LABS FOR PROCESSING WITHIN 24 HOURS OF COLLECTION. SPECIMENS MUST BE DRAWN AND SHIPPED TO ARRIVE MONDAY THROUGH FRIDAY.

15.5 General specimen submission instructions

a. All submitted specimens must be labeled with the protocol number (**S0925**), SWOG patient number, patient's initials, and date and time of specimen collection.

b. The CellSave® blood tubes should be kept at room temperature and shipped in the special container and package at room temperature on the day of collection.

c. The green top heparin (see 15.6 below) and purple top EDTA (see 15.7 below) tubes must first be centrifuged with plasma aliquotted into 500 uL microtainers and shipped on dry ice. These microtainers should also be labeled with "H" for heparin or "E" for EDTA. These are to be shipped together in a container on dry ice with the Tempus™ Blood RNA Tube (see 15.8 below) and not in the room temperature container as the CellSave® (see 15.9 below) blood tubes to measure CTCs.

d. The 3 mL Tempus™ Blood RNA Tube must be also shipped on dry ice in the same container as the aliquoted plasma with heparin and EDTA above.

15.6 Directions for obtaining, handling, and submission of plasma specimens on heparin for IGF biomarkers

a. Draw aseptically 1x4 mL of venous blood into BD Vacutainer green top heparin Blood Collection Tubes and invert 5 times (do not shake).

b. Store blood at 4ºC until processed. Blood should be processed within 2 hours of collection.

c. Centrifuge tubes for 15 minutes at 1,300xg at 4ºC.

d. Using a 3 mL non-sterile transfer pipette, aliquot 500 uL plasma into 500 Ul microtainers.

e. Tubes should be labeled with SWOG **S0925**, SWOG patient number, patient's initials, date and time of specimen acquisition, and “H’ for heparin.

f. Place samples in dry ice for shipping.

15.7 Directions for obtaining, handling, and submission of plasma specimens on EDTA for microRNA analysis

a. Draw aseptically 1x6 mL of venous blood into BD Vacutainer purple top EDTA Blood Collection Tubes and invert 5 times (do not shake).

b. Store blood at 4ºC until processed. Blood should be processed within 2 hours of collection.

c. Centrifuge tubes for 15 minutes at 1300xg at 4ºC.

d. Using a 3 mL non-sterile transfer pipette, transfer the plasma into a disposable plastic tube. To avoid disturbing the pellet, leave 0.5 cm height of plasma above the cell pellet in the blood collection tube.

e. Using a 3 mL non-sterile transfer pipette, mix the recovered plasma by pipetting up and down gently 10 times. Avoid generating any bubbles or foaming.

f. Using a 3 mL non-sterile transfer pipette, aliquot 500 uL plasma into 500 uL microtainers.

g. Mircotainer tubes should be labeled with SWOG **S0925**, SWOG patient number, patient's initials, date and time of specimen acquisition, and “E” for EDTA.

h. Place samples in dry ice for shipping.

15.8 Directions for obtaining, handling, and submission of whole blood samples in Tempus tube for RNAs analysis

a. Follow Tempus™ Blood RNA Tube manual to collect blood from 3mL Tempus™ Blood RNA Tubes, ABI 4342792.

b. Immediately after blood collection, shake vigorously for a full 10 seconds.

c. Incubate for 5 minutes at room temperature.

d. Freeze tube UPRIGHT at -80^{o}C or UPRIGHT on dry ice. If freezing on dry ice, wrap tube in bubble wrap or a stack of paper towels before putting on dry ice, as the tube may crack if put in direct contact with dry ice.

e. After freezing, the tubes may be stored horizontally.

f. Shipment must occur on dry ice. Tubes must be wrapped in bubble wrap before placing on dry ice, as they may crack if put in direct contact with dry ice.

15.9 Directions for obtaining, handling, and submission of blood for analysis of circulating tumor cells (CTC)

a. Materials required for blood collections are two (2) 10 mL purple/yellow top CellSave® blood collection tubes, Vacutainer® brand adapter, and needles. The blood may be drawn by a physician, registered nurse, or a licensed phlebotomist at the clinical site. All Cellsave**®** tubes must be completely filled. **NOTE: The CellSave® tubes should be collected last of all the blood tubes obtained using the same needle stick. This decreases the chance of contamination of the CTC sample with skin epithelial cells, which may occur when the needle enters the skin.**

b. For each patient, perform a venous puncture using a Vacutainer® brand adapter and needle and **fill each of the blood collection tubes (minimum blood volume of 9 mL for each tube)**. Alternatively, blood samples may be obtained from a port or other central venous catheter using appropriate access needles and techniques. Invert each tube a minimum of eight (8) times to ensure proper mixing of the additives contained in each tube. Write the SWOG patient number and the date of collection on the tubes.

c. The filled CellSave® tubes must be maintained at ambient (15–30°C) temperature, avoiding extremes of heat and cold, at all times.

d. Wrap the CellSave® tubes in the shipping blanket. This gives added thermal protection during shipment. Place the samples inside the plastic bag, then into the jar. Cap the jar and place it in the styrofoam shipping box. Place the completed lab requisition form in the box. Place ROOM TEMPERATURE gel packs in the box to stabilize the temperature at 15-30ºC. Place the styrofoam lid. Seal the insulated box.

e. Remove the sticky backing from the airbill and place it on the insulated shipper.

f. Seal the insulated shipper box and contact your local Fed-Ex representative for pick-up (800-463-3339). Be sure to notify Dr. Dan Sabath's lab via e-mail addressed to Karen Koehler at the following address: kkoehler@u.washington.edu with the SWOG patient ID number and the tracking number on the Fed-Ex airbill(s).

15.10 Shipping Directions

Ship all specimens by overnight delivery in the two separate shipping containers (one on dry ice and the other at room temperature) to Seattle, WA on the same date as the blood draw using Federal Express Priority Overnight Service. Specimens must be shipped to arrive Monday through Friday. Please double check the packaging label addresses:

Dry ice package with microtainers containing heparin plasma, EDTA plasma, and the separate Tempus™ Blood RNA Tube should be addressed to Lab #196 – Dr. Muneesh Tewari.

Room temperature package with the 2 CellSave® tubes should be addressed to Lab #197 – Dr. Daniel Sabath.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Publication and Industry Contact

The agent (hereinafter referred to as "Agent"), IMC-A12 used in this protocol is provided to the NCI under a Clinical Trials Agreement (CTA) between ImClone Systems, Inc. (hereinafter referred to as "Collaborator") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to the Collaborator and should be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and

should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with another investigational Agent, each the subject of different CTAs or CRADAs, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI must provide all Collaborators with written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations which would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for cooperative group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to the Collaborator for Phase III studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to the Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to the Collaborator's intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to the Collaborator for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentation must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX: 301/402-1584
E-mail: anshers@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to the Collaborator. No publication, manuscript or other form of public disclosure shall contain any of the Collaborator's confidential/proprietary information.

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.

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.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines describe expedited adverse event reporting for this protocol. See also Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use the CTEP Adverse Event Reporting System (CTEP-AERS). The NCI's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event, as specified in Table 16.1 or 16.2, as applicable.

In the rare event when internet connectivity is disrupted a 24-hour notification must be made to the NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection. Please note that all paper CTEP-AERS forms have been removed from the CTEP website and will NO LONGER be accepted.

Any supporting documentation requested by CTEP should be submitted in accordance with instructions provided by the CTEP-AERS system.

d. Other recipients of adverse event reports

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

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

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent used in Arm 1 of this study is IMC-A12. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]IMC-A12.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a CTEP-IND:**

1) **Group-specific instructions.**

Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Office in order to complete the evaluation of the event. If requested, the supporting data should be sent within **5 calendar days** by fax to 210/614-0006. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical source documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of the Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below do **not** require expedited reporting via CTEP-AERS:
- Grade 4 myelosuppression

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agents used in this study are bicalutamide (Casodex), luprolide acetate (Lupron) and goserelin acetate (Zoladex). 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 16.2. Expedited reporting requirements for adverse events experienced by patients on study arm 2 who have received only the commercial drug(s) listed in 16.1g above within 30 days of the last administration of the commercial agent(s).

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

CTEP-AERS: Indicates an expedited report is to be submitted via NCI CTEP-AERS within 10 calendar days of learning of the event[b].

a This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

b Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

1. A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

   CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

   - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
   - Myelodysplastic syndrome (MDS)
   - Treatment-related secondary malignancy

   Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

   Second Malignancy: A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

For more information see:
http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_ctep-aers.

2. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

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

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions** SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available in the NCI Guidelines for Investigators: Adverse Event Reporting Requirements (see Appendix 7) http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 Translational Medicine

18.3 Agents That Directly Inhibit IGT or IGFRS

18.4 Intake Calendar

18.1 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.

An 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 16.1 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.

18.2 Translational Medicine

a. Assess potential biomarkers for IMC-A12 pharmacodynamic activity obtained from serum samples and peripheral blood mononuclear cells (PBMNC) (including, but not limited to, IGF-1, free IGF-1, IGF-II, IGFBP2, IGFBP3, Growth Hormone, insulin and C-peptide) and optional tumor specimens. Cell surface IGF-IR will be assessed on PBMNCs by flow cytometry before treatment and 3 months later to help determine IMC-A12 target efficacy. Disappearance of IGF-IR from the cell surface in response to IMC-A12 induced IGF-IR lysosomal degradation is a measurement that is informative of the effectiveness of IMC-A12. In addition, simultaneous suppression of AKT phosphorylation will provide excellent confirmation that IMC-A12 has taken effect. This analysis will be performed on the **FIRST 50 patients on each arm (100 patients total)** who start ADT on study. Patients who have started ADT prior to randomization on our study are not eligible for this analysis.

Dr. Stephen Plymate is a basic scientist at the University of Washington who leads a major project on the Pacific Northwest Prostate Cancer SPORE evaluating the role of the IGF pathway in prostate cancer. He will evaluate these potential pharmacodynamic correlatives of IMC-A12 as a component of his SPORE project.

b. In a subset of patients (the **FIRST 50 patients on each arm** who start ADT on our study, if ADT is started within a month of accrual the patient is not eligible for this analysis), determine baseline pre-treatment circulating tumor cell (CTC) quantities. For those patients with detectable CTC levels (≥ 1) changes in response to therapy will be assessed with another measurement 3 months later. In patients in whom adequate numbers of CTC's are obtained, IGF-IR expression will be determined on the CTC's. Correlations will be made with absolute PSA level after 7 months of combined therapy. Specifically, we will directly compare decline in CTC levels with decline in PSA i.e. proportion of patients with undetectable CTC levels and proportion with CTC levels < 5 with proportion of patients with PSA < 0.2.

c. In the same subset of patients where CTC levels are obtained, determine baseline serum levels of microRNAs to include but not limited to mi-141. Since microRNA measurements may be extremely sensitive, another measurement will be obtained from **ALL 100** patients to assess for change in response to therapy 3 months after initiation of treatment, even if no CTC levels were detected initially at the baseline measurement. Correlations will be made with absolute PSA level after 7 months of combined therapy. Additionally, we will directly compare mi-141 levels and potentially other miRNAs with both PSA and quantifiable CTC numbers.

Circulating, cell-free microRNAs (miRNAs) have recently been shown to be an important new class of blood-based prostate cancer biomarkers that are highly stable in plasma and serum and readily measured by quantitative RT-PCR. *(29)* However, the relationship between serum levels of tumor-derived miRNA and therapeutic response, PSA level or circulating tumor cells is not known. We will measure levels of miR-141, a prostate cancer-derived miRNA shown to be present at high serum levels in most metastatic prostate cancer patients, at the

time of each PSA measurement and at each circulating tumor cell measurement. We hypothesize that because miRNAs can be released from cells in exosomes (i.e., in the absence of circulating cells), they may likewise provide independent information from circulating tumor cell numbers. *(29-31)* This study is well-suited to test these hypotheses. As additional miRNA markers of metastatic prostate cancer are identified (in current, ongoing studies), we may add additional serum miRNA markers to our analyses.

Dr. Muneesh Tewari is a basic scientist at the Fred Hutchinson Cancer Research Center who has a Pacific Northwest Prostate Cancer SPORE pilot project to evaluate microRNAs in prostate cancer. He has already made seminal contributions to the field with his work with miR-141 in prostate cancer, and he will lead this work.

18.3 Agents That Directly Inhibit IGF or IGFRS

Table 1 IGF1R TKIs and antibodies

Agent	Company/ Institute	Phase	Comments
IGF1R TKIs			
A-928605	Abbott	Preclinical	Pyrazolopyrimidine TKI
BMS-536924	Bristol-Myers Squibb	Preclinical	Atp-competitive, equipotent inhibition of IGF1R and IR
BMS-55417			
INSM-18 (NDGA)	Insmed	Phase I-II	Duel inhibitor of the IGF-1 and HER2 receptor kinases Phase I data suggest modest PSA responses in patients with nonmetastatic prostate cancer
PPP	Karolinska Cancer Institute and Biovitrum	Preclinical	Inhibits phosphorylation of Y1136 in the kinase activation loop. Does not inhibit IR Preferentially inhibits P13K-Akt pathway, blocks growth of a range of tumors in vitro and in vivo. Induces IGF1R down-regulation via involvement of β-arrestin 1/MDM2
NVP-ADW742	Novartis Pharma	Preclinical	ATP-competitive inhibitor, shows ~15-fold selectivity for IFG1R relative to IR intact cells. In SCLC, inhibits P13K-AKT and induces synergy in combination with chemotherapy.
NPV-AEW541	Novartis Pharma	Preclinical	ATP-competitive inhibitor, shows ~27-fold selectivity for IFG1R relative to IR intact cells Inhibits Akt/mTOR pathway, enhances growth inhibition of MM cells in combination with dexamethasone and bortezomib
OSI-906	OSI Pharmaceuticals	Phase I	Shows ~10-fold selectivity for IFG1R relative to IR. Synergistic antiproliferative effects in combination with erlotinib in CRC cells via blockade of AKT and ERK phosphorylation
XL-228	Exelixis	Phase I	Inhibitor of IGF1R, BCR-ABL and Src

(contd.)

Agent	Company/Institute	Phase	Comments
IGF1R antibodies			
AVE1642	Sanofi-Aventis	Phase I-II	Humanized version of murine EM164 IgG_1 antibody. Phase I single agent in MM, with docetaxel in solid tumors, well tolerated, no DLT. Planned combination with bortezomib in MM
SCH-717454 (19D12)	Schering-Plough	Phase I-II	Fully human monoclonal antibody Activity against IGF1R/IR hybrid receptors via interaction with the IGF1R component
CP-751, 871	Pfizer	Phase I-III	Fully human IgG_2 Phase I: mild hyperglycemia, no DLT, MTD not achieved. At 20 mg/kg, 10 of 15 patients had SD. Phase II in adrenocortical carcinoma, sarcoma: SD in 60% patients. Phase II in NSCLC: RR 51% to CP-751,871 with TC vs. 36% on TC alone. Objective responses to TC with antibody in 72% of squamous tumors, including "striking" responses in bulky disease, and some PR/SD on CP-751,871 after PD on TC alone.
IMC-A12	ImClone Systems, Inc.	Phase I-II	Recombinant human monoclonal IgG_1 antibody, binds IGF1R and IGF1R/IR hybrid receptors but not IR alone. Stable disease in 46% of patients with solid tumors in Phase I
BIIB022	Biogen Idec	Phase I-II	Fully human nonglycosylated version of IgG4.P antibody lacking Fc-effector function.
MK-0646	Merck	Phase I-III	Humanized monoclonal IgG_1: Phase I toxicity hyperglycemia and thrombocytopenia. Current studies: phase II in neuroendocrine tumors and NSCLC; Phase II/III in metastatic CRC with cetuximab and irinotecan.
R1507	Roche	Phase I-II	Human monoclonal IgG_1: antibody Phase I showed PR in four of eight patients with sarcoma
AMG 479	Amgen	Phase I-II	Fully human monoclonal IgG_1 antibody. Phase I activity: CR in Ewing's, PR in neuroendocrine tumor. Phase IB with panitumumab or gemcitabine: one DLT (hyperglycemia).

From Chitnis, M et al., Clin Canc Res 2008;14(20) 6364-6370 (from clinicaltrials.gov and clinicaltrialsfeed.org) websites

18.4 Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #**_____

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

S0925, "A Randomized Phase II Study of Androgen Deprivation Combined with IMC-A12 Versus Androgen Deprivation Alone for Patients with New Hormone-Sensitive Metastatic Prostate Cancer." *(11/30/10)*

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 newly diagnosed prostate cancer that has spread and you are beginning hormone therapy for the first time.

Who is doing this study?

SWOG is sponsoring this trial. *(5/11/12)* SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of about four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, there are to adding the new investigational drug, IMC-A12 (also called cixutumumab), to standard hormone therapy which is used to treat prostate cancer. *(5/11/12)* **IMC-A12 is a new drug that affects the insulin-like growth factor pathway. Laboratory studies show that this pathway may interact with standard male hormone pathways. Laboratory studies have shown combinations of IMC-A12 with standard hormonal treatments offer improved anti-prostate cancer effect. This study has the goal of confirming this in patients in terms of PSA results.** *(11/30/10)*

How many people will take part in the study?

About 180 men will take part in this study. *(11/30/10)*

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 – Therapies and medication you have received to treat your tumor and how you responded to them as well as your current health status
- Physical examination – including height and weight and how well you are able to carry out your normal everyday activities
- Blood tests including those to assess your blood counts including your cholesterol and triglycerides, blood sugar level (which will be done after fasting), kidney and liver function, and how your blood is clotting *(11/30/10)*
- Prostate-specific antigen (PSA) level – measures the amount of tumor marker in your blood
- Testosterone level if you have not already started hormone therapy
- If you have had a LVEF (left ejection fraction test) that is considered lower than normal, you will have an additional test (either a MUGA or echocardiogram) to evaluate your heart function *(11/30/10)*
- CT or MRI of your abdomen and pelvis – these scans will be compared to later CTs or MRIs to see how your tumors are responding to study treatment *(5/11/12)*
- Bone scan – a nuclear medicine test that looks for cancer in the bones.

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.

After every 4 weeks:

- Side effect evaluation
- Physical examination (including weight)
- Lab tests
- Fasting blood draw (about 3 teaspoons of blood drawn from a needle in your vein) to check blood counts and chemistries. *(11/30/10)* If the study doctor finds that your blood sugar levels are high, more testing may be needed.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Fasting blood sugar levels will be obtained once every 2 weeks if you are in the group of patients that receives IMC-A12. *(11/30/10)*

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- PSA will be obtained every four weeks
- Imaging studies with bone scan and CT or MRI will be performed near the end of the 28 weeks of treatment (regular cancer care).

You will be "randomized" into one of the study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being placed in either group. *(11/30/10)*

If you are in Group 1 (often called "Arm 1") you will receive standard hormone therapy plus IMC-A12. Leuprolide acetate (Lupron) or goserelin acetate (Zoladex) will be given as a shot in the muscle once either every 4, 12, 16, 24 or 52 weeks at the discretion of your physician. You will take bicalutamide (Casodex) as a tablet once every day. This is standard hormone therapy that you would be given to you even if you were not in this research study. If you have not received hormone therapy before and you have pain from your cancer, you will take bicalutamide (Casodex) for seven days before receiving leuprolide acetate (Lupron) or goserelin acetate (Zoladex). *(11/30/10) (5/11/12)* If you have no pain, you may start bicalutamide (Casodex) on the same day as leuprolide acetate (Lupron) or goserelin acetate (Zoladex). *(sentence added 5/11/12)* You will also receive IMC-A12 once every 2 weeks. This drug is also given through a needle but it will be given directly into your vein over 60 minutes. After the first dose of IMC-A12, you will be asked to remain for one extra hour for observation. Each 28 day period is called a cycle. You will receive seven cycles of treatment.

If you are in Group 2 (often called "Arm 2") you will receive standard treatment with hormone therapies. Leuprolide acetate (Lupron) or goserelin acetate (Zoladex) will be given as a shot in the muscle once either every 4, 12, 16, 24 or 52 weeks at the discretion of your physician. You will take bicalutamide (Casodex) as a tablet once every day. This is standard hormone therapy that you would be given to you even if you were not in this research study. If you have not received hormone therapy before and you have pain from your cancer, you will take bicalutamide (Casodex) for seven days before receiving leuprolide acetate (Lupron) or goserelin acetate (Zoladex). *(11/30/10) (5/11/12)* If you have no pain, you may start bicalutamide (Casodex) on the same day as leuprolide acetate (Lupron) or goserelin acetate (Zoladex). *(sentence added 5/11/12)* Each 28 day period is called a cycle. You will receive seven cycles of treatment.

When you are finished taking the leuprolide acetate (Lupron) or goserelin acetate (Zoladex), bicalutamide (Casodex), and IMC-A12 (if you are on Arm 1), you will be followed every six months for the first two years and then yearly after that for a maximum of five years from the time you began the study. At those times, you will have a PSA, bone scan and a CT scan of your abdomen/pelvis. *(5/11/12)*

How long will I be in the study?

You will be asked to take leuprolide acetate (Lupron) or goserelin acetate (Zoladex), bicalutamide (Casodex), and IMC-A12 (if you are on Arm 1) for seven cycles (28 weeks). After you are finished taking leuprolide acetate (Lupron) or goserelin acetate (Zoladex), bicalutamide (Casodex), and IMC-A12 (if you are on Arm 1) the study doctor will ask you to visit the office for follow-up exams every six months for the first two years and then once a year for a maximum of five years from the time you began the study. *(11/30/10)* You will stop IMC-A12 (if you are on Arm 1) and your health care provider will discuss risks and benefits of the options for further treatment. You may decide to stay on leuprolide acetate (Lupron) or goserelin acetate (Zoladex) with bicalutamide (Casodex) or decide to take a break.

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 drugs can be evaluated by your doctor. *(11/30/10)* 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 you stop taking the drugs. In some cases, side effects can be serious, long lasting, or may never go away. There is also a risk of death.

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 IMC-A12 treatment include those that are *(11/30/10)***:**

<u>Likely</u>

- **Fatigue or tiredness** *(11/30/10)*
- **Increased blood sugar level** *(2/24/12)*

<u>Less Likely</u>

- **Lack of enough red blood cells (anemia)** *(11/30/10)*
- **Hearing loss** *(11/30/10)*
- **Blurred vision** *(2/24/12)*

- **Seeing flashing lights**
- **Seeing spots before the eyes (floaters)** *(11/30/10)*
- **Diarrhea** *(11/30/10)*
- **Nausea or the urge to vomit** *(11/30/10)*
- **Vomiting**
- **Reaction that can occur during or following infusion of the drug. The reaction may include fever, chills, rash, low blood pressure, and difficulty breathing.** *(11/30/10)*
- **Allergic reaction by your body to the drug product that can occur immediately or may be delayed. The reaction may include hives, low blood pressure, wheezing, swelling of the throat, and difficulty breathing.** *(11/30/10)*
- **Decreased number of a type of white blood cell (lymphocyte)***)*
- **Decreased number of a type of blood cell that help to clot blood (platelet)**
- **Weight loss**
- **Loss of appetite**
- *(deleted 2/24/12)*
- **Dehydration (when you body does not have as much water and fluid as it should)** *(added 2/24/12)*
- **Muscle spasms** *(added 2/24/12)*
- **Muscle pain** *(added 2/24/12)*
- **Dizziness (or sensation of lightheadedness, unsteadiness, or giddiness)** *(11/30/10)*
- **Stuffy or runny nose, sneezing** *(11/30/10)*
- **Itching** *(11/30/10)*
- **Acne** *(11/30/10)*
- **Skin rash with the presence of macules (flat discolored area) and papules (raised bump)** *(11/30/10)*
- **Hives**

<u>Rare but serious</u>

- **Serious, life-threatening allergic reaction requiring immediate medical treatment by your doctor. The reaction may include extremely low blood pressure, swelling of the throat, difficulty breathing, and loss of consciousness.** *(11/30/10)*
- **Kidney failure** *(added 2/24/12)*

Risks and side effects related to the leuprolide acetate (Lupron) or goserelin acetate (Zoladex) and bicalutamide (Casodex) include:

<u>Likely</u>

- **Breast tenderness** *(11/30/10)*
- **Excessive development of the breast in the male** *(11/30/10)*
- **Hot flashes**
- **Sweating**
- **Decreased sexual drive**
- **Nausea**

- **Dizziness**

Less Likely

- **Bone pain**
- **Impotence**
- **Weight loss**
- **Diarrhea**
- **Vomiting**

Rare, but Serious *(section added 10/29/12)*

- **Development of diabetes**
- **Heart attack**
- **Stroke**

Reproductive risks: You should not father a baby while on this study and for at least 3 months after the last dose of IMC-A12 because IMC-A12 can affect an unborn baby. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. Some methods might not be approved for use in this study.

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 IMC-A12 will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about IMC-A12 as a treatment for cancer. 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:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people,
- SWOG *(5/11/12)*
- A qualified representative of the manufacturer of IMC-A12 (ImClone Systems, Inc.) *(11/30/10)*

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

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.

If receiving IMC-A12 on Arm 1, the NCI will provide the IMC-A12 at no charge while you take part in this study. The NCI does not cover the cost of getting the IMC-A12 ready and giving it to you, so you or your insurance company may have to pay for this. Even though it probably won't happen, it is possible that the NCI may not be able to continue to provide the IMC-A12 for some reason. If this would happen, the study may have to close. Your study doctor will talk with you about this, if it happens.

Leuprolide acetate (Lupron), goserelin acetate (Zoladex) and bicalutamide (Casodex) are commercially available. You or your insurer will have to pay for the leuprolide or goserelin, and bicalutamide.

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.

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about important new information from this or other studies that may affect your health, welfare, or willingness to stay in this study. *(paragraph added 11/30/10)*

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 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.

1. Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

2. Submission of specimens for study-specific testing

(Note to sites: This section refers to the study-specific testing described in Appendix 19.2 of the protocol.) If you have not already begun taking drugs to block hormone production prior to starting this study and you agree, a sample of your blood will be sent to an outside lab to study the biology of your cancer. *(5/11/12)* The blood sample (about 2 ½ tablespoons) will be collected separately from other tests before you begin the study treatment and after Week 12. *(11/30/10)* The research that will be done with your blood is 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 blood 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.

My specimens may be used for the special testing described as part of this study. *(11/30/10)*

Yes No

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 _____