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

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

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

RE: McKesson Corporation Drug Distribution Delays

MEMORANDUM

The purpose of this memorandum is to inform sites of potential changes in delivery of drugs distributed by McKesson Corporation (formerly Biologics, Inc.).

McKesson has indicated that they may hold shipments to zip codes in the path of hurricane Florence due to forecasted delivery issues posed by the storm. They will continue to reach out to patients and sites in the most impacted areas in the Carolinas, Virginia and Washington, D.C. to help plan for delays, non-delivery, and closures. They will monitor the storm and sites will be notified of updates as they arise.

For urgent needs and questions regarding specific deliveries, please contact the team at clinicalresearchservices@mckesson.com or 1-800-693-4906.

This memorandum pertains to the following studies:

S1014 Genitourinary
S1216 Genitourinary
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal
S1602 Genitourinary
S1613 Gastrointestinal
S1701 Lung

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

cc: Elliott Lee – McKesson Corporation

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Distribution Date: March 1, 2017
E-mail Date February 16, 2017

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Change in e-mail address for Biologics, Inc.

MEMORANDUM

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

MEMORANDUM

The purpose of this memorandum is to alert sites to a change in email address for Biologics, Inc., the drug distributor for the following studies:

S1014
S1216
S1304
S1313
S1403
S1406
S1602

Beginning **February 20th, 2017**, the email address clinicaltrials@biologicsinc.com will no longer be valid and clinicalresearchservices@biologicsinc.com will no longer be accepting drug order submissions.

Please ensure all clinical trial drug order submissions that are emailed are being addressed to CRSorders@biologicsinc.com; all other communication outside of drug order submissions may continue to be addressed to clinicalresearchservices@biologicsinc.com.

Please note CRSorders@biologicsinc.com will only allow for inbound submission. If you require a response to an inquiry regarding an order please ensure it is addressed to clinicalresearchservices@biologicsinc.com.

Drug orders submitted via fax to 919-256-0794 will still be processed as usual.

cc: PROTOCOL & INFORMATION OFFICE

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November 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure: Permanent
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

The purpose of this memorandum is to clarify an error noted in protocol Section 11.8 Toxicity Monitoring. The first paragraph of Section 11.8 (excerpted below for ease of reference) currently indicates, "With 72 patients per treatment arm." This statement is incorrect and will be modified in the next revision to the protocol to read "With **63** patients per treatment arm," as is congruent with the protocol design.

> "All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. With ***72*** patients per study arm, the probability of any particular toxicity can be

estimated within ±14% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more within one of the treatment arms is very likely to be observed in at least one patient (probability ≥ 96%)."

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Joe Connell – Amgen

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June 1, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements
( ) Full board review required
( ) Expedited review allowed
(√) No review required

Status Change
( ) IRB Review only
( ) Activation
( ) Closure: Permanent
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

MEMORANDUM

As stated in the Activation Memorandum distributed November 1, 2013, ECHO results were to be submitted for central review after funding and logistical details had been finalized. At this time, details have been finalized and ECHOs must be submitted. Please follow the instructions in Sections 15.3 and 18.2 of the protocol, and submit ECHO images for all patients at your earliest convenience.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Joe Connell - Amgen

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May 15, 2016

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

STATUS NOTICE

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements
( ) Full board review required
(√) Expedited review allowed
( ) No review required

Status Change
( ) IRB Review only
( ) Activation
(√) Closure: Permanent
( ) Reactivation

Protocol changes
( ) Eligibility changes
( ) Treatment / Dose Modification / Study Calendar changes
( ) Informed Consent changes
  ( ) Patient notification not required
  ( ) Patient notification required
( ) Scientific / Statistical Consideration changes
( ) Specimen Submission changes
( ) Data Submission / Forms changes
( ) Editorial / Administrative changes
( ) Other:

PERMANENT CLOSURE

The above-referenced study was temporarily closed to accrual on November 6, 2015. It was anticipated that the study would be re-opened to accrual (subsequent to an accrual target increase due to a higher than anticipated ineligibility rate). It has since been determined that the accrual target increase is not necessary for endpoint assessment. This study is now **permanently closed to accrual, effective immediately.**

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
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Joe Connell - Amgen

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Distribution Date: January 15, 2016
CTEP Submission Date: December 10, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #6

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #6

This revision updates the protocol and Model Consent Form in accordance with the Amgen Safety Information, that was distributed December 1, 2015 regarding:

i) Gastrointestinal Perforation
ii) Pericardial Effusion, and
iii) Pericarditis.

This study remains temporarily closed to accrual. The study team will be requesting an increase in the accrual target due to a higher than anticipated ineligibility rate.

This revision also incorporates additional information about the central review of ECHO images. Sites are requested to continue to hold all ECHO images and reports for retrospective submission to SWOG (as previously indicated at time of protocol activation). Submission of ECHO images and reports for retrospective review is anticipated to be requested with Revision #7 to be distributed on or around February 15, 2016.

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

2. Page 1, Title Page: Stephen Heitner, MD has been added as the ECHO translational medicine study chair.

3. Page 3-4 Table of Contents: Content has been inserted into Sections 1.3, 2.0, 3.1 on Pages 7, 9, 11-12, respectively, and this has caused subsequent page numbers to shift. Section 15.3 ECHO Image (mandatory) and the title for Section 18.2 has been updated to reflect the addition of ECHO images.

4. Page 7, Section 1.3: Objectives (d), (e), and (f), pertaining to translational medicine objectives (correlation of ECHOs with cardiac test results to evaluate cardiovascular toxicity) have been added.

5. Pages 10-11, Section 2.0: Seven paragraphs of background information for the ECHO translational medicine objectives have been inserted. This has also caused a shift in text on subsequent pages.

6. Pages 13-14 and 18, Section 3.1: This section has been updated to be congruent with the information distributed in the 25 September 2015 Investigator letter:
   - Section 3.1c.1: The following changes have been made to the Adverse Events with Possible Relationship to Carfilzomib table:
     - The following risks were added:
       - Rare but Serious (≤3%):
         - ✓ Cardiac Disorders: Pericardial Effusion, Pericarditis
         - ✓ Gastrointestinal Disorders: Gastrointestinal Perforation
   - Section 3.1g.1: The following sentence has been inserted at the end of the first paragraph of this section, "Biologics will be closed for the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, Thanksgiving Friday, Christmas Eve, and Christmas Day."

7. Page 23, Section 5.1a: The following phrase was added at the beginning of the second sentence of this section to clarify that some eligibility tests have a shorter window than within 28 days prior to registration, "Except where otherwise indicated below that assessment is required within 14 days,."

8. Page 23, Section 5.1b: The following sentence was added to the end of this section to better clarify timing of testing as currently indicated in Sections 9.0 and 10.2d of the protocol, "Patients must have SPEP and UPEP within 14 days prior to registration."

9. Page 25, Section 5.1x: The phrase "or any other cancer in-situ" was inserted to allow exception for any prior CIS, and the criterion now reads as follows, "No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or any other cancer in situ, 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 three years."

10. Page 35, Section 9.0:

    - Footnote (9): A sentence has been added at the end of this footnote to reference Sections 15.3 and 18.2 for additional information on ECHO submission.
    - The following clarification has been added at the end of footnote (19), "Assessments completed at time of progression on Arm 1, do not need to be repeated on Arm 3 (crossover) C1, D1, provided that ANC, platelets, SGOT, SGPT, serum creatinine, SPEP, and lambda light chain assessments are accomplished within 14 days prior to registration to Arm 3. All other assessments may have been accomplished anytime within 28 days prior to registration to Arm 3 (i.e. at time of progression on Arm 1). Note: Per eligibility criterion 5.2b, at least 14 days and no more than 28 days must have elapsed between the last day of treatment on Arm 1 and registration to Arm 3."

11. Page 42, Section 11.6: A paragraph pertaining to the statistical analysis and endpoints of the ECHO translational medicine objectives has been inserted prior to the last paragraph of this section.

12. Pages 50-51, Section 14.4: This section has been modified to reflect inclusion of submission of ECHO images to AG Mednet (per Section 18.2). This is reflected in Sections 14.4a, 14.4c, 14.4d, and 14.4h. The following text has also been added to the end of Section 14.4c to clarify timing of submission for crossover patients, "(For crossover patients, ECHOs must be submitted every 3 cycles from the date of previous measurement.). This has caused a shift in the text on all subsequent pages.

13. Page 53, Section 15.3: This section has been inserted. This has caused a shift in text on subsequent pages.

14. Pages 61-62, Section 17.0: References #22-33 have been inserted in support of ECHO translational medicine objectives. This has caused a shift in text on all subsequent pages.

15. Pages 63 and 66, Section 18.0: The title of Section 18.2 has been updated to reflect ECHO submission guidelines.

Patients **currently receiving treatment must have** been informed (by phone or in person) of the additional risks that are now being added to the Model Consent Form within **30 days of distribution of the Memorandum that was e-distributed on 11/20/2015**. Patients who will sign a consent form prior to local implementation of the consent form changes must be informed of these additions prior to consent. Patients on follow-up on this study must be informed of these additions at the next scheduled visit. The manner by which this notification takes place is at the discretion of the local institution.

The Model Consent Form has been modified as follows:

16. Page 10, “RARE, AND SERIOUS”: This section has been updated as follows. The addition of text to this section has caused the table to be expanded and a shift in text on subsequent pages.

    - The following risks have been added to this section:
        - Inflammation (swelling and redness) of the sac around the heart
        - Fluid in the sac around the heart
        - Hole in the stomach or bowel

17. Page 14, "Who will see my medical information?": The description of AG Mednet services has been modified to reflect the inclusion of ECHO images.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers – Onyx
Joe Connell - Amgen

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swog.org

Distribution Date: December 1, 2015
E-mailed Date: November 20, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

MEMORANDUM

The purpose of this memorandum is to notify sites of an Investigator Letter received from Onyx/Amgen regarding new and/or modified risk information associated with carfilzomib and associated site/investigator action required to notify patients participating in **S1304**.

SWOG is developing a revision incorporating the changes requested in the attached Investigator Letter which is anticipated to be distributed to participating sites within the next 30 days.

Patients currently receiving treatment must be informed (by phone or in person) of the additional risks listed in the Investigator Letter **within 30 days of distribution of this memorandum**. In the event of study reactivation, patients who will sign a consent form prior to local implementation of forthcoming consent form changes must be informed of these additions prior to consent. Patients on follow-up on this study must be informed of these additions at the next scheduled visit. The manner by which this notification takes place is at the discretion of the local institution.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers – Onyx
Joe Connell - Amgen

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-1000

Friday, 25 September 2015

RE: Kyprolis (Carfilzomib) – Important New Safety Information

Dear Investigator:

This letter is being sent to all investigators participating in active studies related to Kyprolis (Carfilzomib).

Summary

Onyx, an Amgen subsidiary, would like to inform you of important new safety information associated with the use of carfilzomib. As part of Onyx's continuous evaluation of product safety information, the following adverse drug reactions have been identified for carfilzomib based on comprehensive safety assessments:

- Gastrointestinal Perforation
- Pericardial Effusion
- Pericarditis

Safety information in the Informed Consent Form and the Company Core Safety Information (Appendix A of the Investigator's Brochure) will be updated to reflect these findings. The updated Informed Consent Form must be used to advise all current and future subjects of these risks.

Carfilzomib is a proteasome inhibitor being evaluated for the treatment of subjects with multiple myeloma (MM) or other hematologic/solid tumors. As of 10 July 2015, 2,921 subjects have been treated with carfilzomib in Amgen-sponsored clinical trials, approximately 2,546 patients have been enrolled into carfilzomib arm in investigator-sponsored clinical trials, and an estimated 20,555 subjects have been exposed to Kyprolis in the post-marketing setting. The exposure number (2,921) from Amgen-sponsored clinical trials in this DIL is less than the number (2,949) in the previous DIL because of double counting of data from study PX-171-010.

Cases of gastrointestinal perforation, pericardial effusion and pericarditis have been uncommonly (< 1%) reported each in subjects treated with carfilzomib in clinical trials. These events have also been reported in the post-marketing setting.

Actions Implemented by Amgen

- The Informed Consent Form (ICF) will be updated to inform subjects that events of gastrointestinal perforation, pericardial effusion and pericarditis have been observed in subjects receiving carfilzomib. Subjects will be advised to report signs and symptoms of the above mentioned events immediately to study personnel.
- Update the Investigator's Brochure (IB)

- Update the Company Core Safety Information (CCSI)

Actions for the Investigator

- Amgen requests that investigators communicate, by phone or in-person, the safety findings described above to study subjects receiving investigational product within 30 days of receipt of this notification.
- For subjects who are not currently receiving study drug, but are still participating in a study, investigators are requested to communicate the safety findings at the next regularly scheduled contact with the subject.
- Please ensure these communications to subjects are documented in the source medical records for the subject.
- The revised informed consent form will be sent to you shortly. Please submit to your Ethics Committee/ Institutional Review Board per usual procedures and reconsent your subjects once approved.
- Please file a copy of this letter in your trial file.

If you have any questions regarding this letter, please contact Sanjay Aggarwal MB BChir (Cantab) at 805.447.0162 (office) or sanjaya@amgen.com.

Sincerely,

Roger Sidhu, MD
Executive Medical Director Global Development
Amgen Inc.

Larry N. Johnson, MD
Senior Medical Director, Drug Safety Site Head
Onyx Pharmaceuticals, an Amgen Subsidiary

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swog.org

November 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Offices

RE: Holiday Closure

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

Biologics, Inc. Clinical Trials Services will be closed Thursday, November 26, 2015 and Friday November 27, 2015 (in observance of Thanksgiving), Thursday December 24, 2015 and Friday December 25, 2015 (in observance of Christmas), and Friday January 1, 2016 (in celebration of the New Year).

Biologics, Inc. Clinical Trials Services will be open on New Year's Eve (Thursday December 31, 2015).

Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern. Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1202 Cancer Control
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

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Distribution Date: November 1, 2015
E-mailed Date: October 23, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

STATUS NOTICE

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

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

TEMPORARY CLOSURE

The above-referenced study is fast-approaching its accrual target and will temporarily close to accrual **effective November 6, 2015** at 11:59 pm Pacific Time, pending CTEP review of revision to increase the accrual target due to a higher than anticipated ineligibility rate. Please contact Cara Laubach at claubach@swog.org for questions pertaining to the temporary closure.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers – Onyx
Joe Connell – Amgen

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swog.org

October 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that a new online **S1304** Pulmonary Function Test Form has been created and an updated Master Forms Set, reflecting this change, has been posted on the SWOG protocol abstract page (www.swog.org).

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
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August 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

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 purpose of this memorandum is to inform sites that Biologics, Inc. has developed a new form for sites to designate non-prescribers to order investigational agent. Please note this is an optional form and submission of the form will apply to all studies the treating investigator has registered patients on that utilize Biologics Inc. as a distributor. This form is available on the protocol abstract page on the SWOG website (www.swog.org). The drug order forms for the studies listed below have been updated to include this option.

The Primary Shipping Address and Designee Form pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

Please also note that Biologics, Inc. Clinical Trials Services will be closed Monday, September 7, 2015 in observance of Labor Day.

Regular business hours will resume on Tuesday, September 8, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S0635 Lung
S1014 Genitourinary
S1202 Cancer Control
S1216 Genitourinary
S1300 Lung
S1304 Myeloma
S1313 Gastrointestinal
S1403 Lung
S1406 Gastrointestinal

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Amy Johnson
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Monica Yee
Stephanie Edwards
Vicki Green
Destin Carlisle – Alliance
Elliott Lee, Biologics, Inc.
Becky Fillingham – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN

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Distribution Date: August 15, 2015
CTEP Submission Date: July 27, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #5

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #5

The purpose of this revision is to update the protocol and Model Consent Form in accordance with the Amgen Safety Information, dated Tuesday 09 June 2015 (attached), which pertains to the following additional risk information from a recently-completed Phase III clinical trial and other safety information:

i) Hypertension including hypertensive crisis
ii) Pulmonary hypertension, and
iii) Pulmonary Toxicities: Interstitial Lung Disease (including pneumonitis), Acute Respiratory Failure, and Acute Respiratory Distress Syndrome (ARDS).

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

2. Pages 3-4 Table of Contents: Content has been inserted into Section 3.1 on Page 13 and this has caused subsequent page numbers to shift.

3. Pages 11-13, Section 3.1: This section has been updated to be congruent with the information distributed in the 09 June 2015 Investigator letter and supporting documents:
   - Section 3.1c.1: The following changes have been made to the Adverse Events with Possible Relationship to Carfilzomib table:
     - The following risks were added:
       - Less Likely(4-≤20%):
         - ✓ Blood and Lymphatic System Disorders: Lymphopenia
         - ✓ Infections and Infestations: Bronchitis
         - ✓ Metabolism and Nutrition Disorders: Decreased appetite and Hypolcalcemia
         - ✓ Skin and Subcutaneous Tissue Disorders: Diaphoresis
       - Rare but Serious (≤3%):
         - ✓ Blood and Lymphatic System Disorders: Thrombotic Thrombocytopenic Purpura/ Hemolytic Uremic Syndrome (TTP/HUS) and Thrombotic Microangiopathy
         - ✓ Cardiac Disorders: Hypertensive crisis
         - ✓ Gastrointestinal Disorders: Toothache
         - ✓ Infections and Infestations: Influenza
         - ✓ Nervous System Disorders: Posterior Reversible Encephalopathy Syndrome
         - ✓ Respiratory, Thoracic and Mediastinal Disorders: Pulmonary toxicities: Interstitial Lung Disease (including pneumonitis), Acute Respiratory Failure and Acute Respiratory Distress Syndrome (ARDS)
         - ✓ Vascular Disorders: Stroke
     - The following risks were removed:
       - Less Likely(4-≤20%):
         - ✓ Psychiatric Disorders: Confusion and Mental status change
         - ✓ Skin and Subcutaneous Tissue Disorders: Dry Skin
       - Rare but Serious (≤3%):
         - ✓ Renal and Urinary Disorders: BUN increased
     - The following risk was moved from Rare but Serious (≤3%) to Less Likely(4-≤20%):
       - Cardiac Disorders: Congestive Heart Failure
     - The following risk was moved from Likely (>20%) to Less Likely(4-≤20%):
       - Musculoskeletal and Connective Tissue Disorders: Chest pain

4. Page 29, Section 8.3a: The carfilzomib dose reduction for toxicity has been adjusted to allow treatment to be resumed in event that patients experience a ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity that is considered related to carfilzomib provided that the toxicity has resolved to Grade 2 or better (instead of resolution to Grade 1 or better, as previously indicated).

5. Page 31, Section 9.0: The "9" in column C7 for Serum β2 Microglobulin was a typographical error, and has been removed.

6. Page 33, Section 9.0: The following clarifications have been made to footnotes (9) and (13)

    - Footnote (9): A sentence has been added to the end of this footnote to clarify that, "Crossover patients do not need to repeat Cycle 1, Day 1 tests as long as patient is starting Arm 3 treatment within 28 days of prior testing (at time of progression) and the previous test results did not show a significant change from baseline.
    - Footnote (13): The last sentence of this footnote has been modified to clarify that response assessments are no longer required for study purposes once a patient has been removed from the trial due to toxicity.

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 treatment must** be informed (by phone or in person) of the additional risks listed below within **30 days of distribution of this revision**. Patients who will sign a consent form prior to local implementation of the consent form changes must be informed of these additions prior to consent. Patients on follow-up on this study must be informed of these additions at the next scheduled visit. The manner by which this notification takes place is at the discretion of the local institution.

The Model Consent Form has been modified as follows to update the "Possible Side Effects of Carfilzomib" risk tables to be consistent with Amgen Carfilzomib ICF Risk Template updates distributed with the 09 June 2015:

7. Page 8, "COMMON, SOME MAY BE SERIOUS:
    - The following risks have been removed, as they are now reflected in the Occasional, Some May Be Serious section:
        - Lower number of white blood cells that help fight infection
        - Chest pain

8. Page 9, "OCCASIONAL, SOME MAY BE SERIOUS":
    - The following risks have been added to this section:
        - Inability of the heart to adequately pump blood to supply oxygen to the body
        - Chest pain
        - Bronchitis
        - Lower number of white blood cells that help fight infection

    - The following risks have been updated and now read as follows:
        - Rash, itching dry skin, redness of the skin, excessive perspiration
        - Pain, including: joint pain, or pain in arms and/or legs, abdominal pain, back pain, muscle pain
        - Muscle spasms, pain and weakness
        - Numbness, tingling, burning sensations
        - Increased or decreased blood levels of sugar, potassium or calcium
        - Decreased blood levels of phosphate, magnesium, sodium, or a blood protein called albumin

    - The following risks have been combined with similar risks in this section (for patient ease of reading):
        - High blood sugar
        - Belly pain (upset stomach)

- Back pain

- The following risks have been removed from this section to be congruent with the updated drug information:
  - Confusion or changes in mental state

9. Pages 10-11, "RARE, AND SERIOUS": This section has been updated as follows. The addition of text to this section has caused the table to be expanded to Page 11 and a shift in text on all subsequent pages.

   - The following risks have been added to this section:
     - Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea, vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis
     - Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML)
     - Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells
     - Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
     - Stroke (or lack of blood flow to an area of the brain)
     - Flu-like symptoms
     - Toothache

   - The following risks have been updated and now read as follows:
     - Reduced blood flow to the heart or loss of some of the heart's function
     - Build up of fluid in the lungs, scarring of lung tissue, inflammation of the lungs, or sudden failure of the respiratory system that prevents oxygen from getting into the lungs and blood that may be life-threatening

   - The following risks have been removed to be congruent with the updated drug section:
     - Cancer that develops as a result of treatment for a previous cancer
     - Increase in levels of blood urea nitrogen (which is formed when protein breaks down)

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers – Onyx

Amgen Inc.
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Phone: 805-447-1000

Tuesday, 09 June 2015

RE: Carfilzomib (Kyprolis) – Important New Safety Information

Dear Investigator:

This letter is being sent to all investigators participating in active studies related to Kyprolis (Carfilzomib).

Summary

Onyx, an Amgen subsidiary, would like to inform you of important new safety information associated with the use of carfilzomib. As part of Onyx's continuous evaluation of product safety information, the following adverse drug reactions have been identified for carfilzomib from the recently completed Phase 3 clinical trial and/or other accumulating safety information;

- Hypertension including hypertensive crises
- Pulmonary Hypertension
- Pulmonary Toxicities: Interstitial Lung Disease (including pneumonitis), Acute Respiratory Failure and Acute Respiratory Distress Syndrome (ARDS).

Safety information in the Informed Consent Form and the Company Core Safety Information (Appendix A of the Investigator's Brochure) will be updated to reflect these findings. The updated Informed Consent Form must be used to advise all current and future subjects of these risks.

Carfilzomib is a proteasome inhibitor being evaluated for the treatment of subjects with multiple myeloma (MM) or other hematologic/solid tumors. As of 12 January 2015, 2949 individual subjects who have been treated with carfilzomib in Amgen-sponsored clinical trials and an estimated 16,500 subjects have been exposed to commercial drug.

<u>Hypertension including hypertensive crises</u>

Hypertensive crises have been infrequently reported in subjects (< 1%) treated with carfilzomib in Amgen-sponsored clinical trials. These events have also been reported in the post-marketing setting. Hypertensive crises can present as hypertensive urgency or as a hypertensive emergency. Hypertensive urgency is defined as sustained or persistent systolic blood pressure 180 mmHg or higher or diastolic blood pressure 110 mmHg or higher, with no associated organ damage. A hypertensive emergency occurs when blood pressure reaches levels that result in end organ damage.

Pulmonary Hypertension

Cases of pulmonary hypertension have been commonly reported in subjects (approximately 1%) treated with carfilzomib in Amgen-sponsored clinical trials. These events have also been reported in the post-marketing setting. Pulmonary hypertension is generally defined as a mean pulmonary arterial pressure ≥25 mmHg at rest. Echocardiography is usually the first test to suggest pulmonary hypertension. Pulmonary hypertension can be a progressive, fatal disease if untreated, although the rate of progression is highly variable.

Pulmonary Toxicities: Interstitial Lung Disease (including Pneumonitis), Acute Respiratory Failure and Acute Respiratory Distress Syndrome (ARDS).

Cases of interstitial lung disease (including pneumonitis), acute respiratory failure, and ARDS have been uncommonly reported in subjects (< 1%) treated with carfilzomib in Amgen-sponsored clinical trials. These events have also been reported in the post-marketing setting.

Based on substantial improvement in progression free survival observed in two Phase 3 trials in the relapsed multiple myeloma setting (Study PX-171-009 [carfilzomib in combination with lenalidomide and dexamethasone] and Study 2011-003 [carfilzomib in combination with dexamethasone]), the overall benefit: risk profile of carfilzomib remains favorable in subjects with relapsed/refractory multiple myeloma and other indications under study.

Actions Implemented by Amgen

- The Informed Consent Form (ICF) (in the Core Risks and Discomforts section) will be updated to inform subjects that events of hypertensive crises, pulmonary hypertension, and pulmonary toxicities have been observed in subjects receiving carfilzomib. Subjects will be advised to report signs and symptoms immediately to study personnel.
- Update the Investigator's Brochure (IB)
- Update the Company Core Safety Information (CCSI)

Actions for the Investigator

- Amgen requests that investigators communicate, by phone or in-person, the safety findings described above to study subjects receiving investigational product within 30 days of receipt of this notification.
- For subjects who are not currently receiving study drug, but are still participating in the study, investigators are requested to communicate the safety findings at the next regularly scheduled contact with the subject.
- Please ensure these communications to subjects are documented in the source medical records for the subject.

  The revised informed consent form will be sent to you shortly. Please submit to your Ethics Committee/ Institutional Review Board per usual procedures.
- **For Hypertension including hypertensive crises**
- All patients should be routinely evaluated for hypertension and treated as needed. If the hypertension cannot be controlled, the carfilzomib dose should be reduced, per protocol. In case of hypertensive crisis, stop carfilzomib until resolved or returned to baseline and consider whether to restart carfilzomib based on a benefit/risk assessment.
- **For Pulmonary Toxicity**

- Evaluate and stop carfilzomib until resolved and consider whether to restart carfilzomib based on a benefit/risk assessment.

- **For Pulmonary Hypertension**
  - Stop carfilzomib until pulmonary hypertension has resolved or returned to baseline, and consider whether to restart carfilzomib based on a benefit/risk assessment.
- Please file a copy of this letter in your trial file.

If you have any questions regarding this letter, please contact Sanjay Aggarwal MB BChir (Cantab) at 650.266.1459 (office) or saggarwal@onyx.com.

Sincerely,

Barbara Klencke MD

Barbara Klencke, MD
Senior Vice President Global Development,
Onyx Pharmaceuticals, an Amgen Subsidiary

Larry N. Johnson, MD
Senior Medical Director, Drug Safety Site Head
Onyx Pharmaceuticals, an Amgen Subsidiary

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swog.org

August 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that the online **S1304** Cardiac Assessment Form has been updated to incorporate fields for reporting both Troponin I and T testing and an updated Master Forms Set, reflecting this change, has been posted on the SWOG protocol abstract page (www.swog.org).

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
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swog.org

July 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Updated Drug Order Form and Holiday Closure

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 purpose of this memorandum is to inform sites that Biologics, Inc has updated all SWOG Drug Order Forms to clarify that the prescriber's signature is required.

The updated Drug Order Form pertains to the following studies:

S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)
S0635 (Lung
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma)

Please also note that Biologics, Inc will be closed Friday, July 3, 2015 in observance of Independence Day. Biologics, Inc. will resume regular business hours (M-F, 9-6 ET) on Monday July 6, 2015.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S1202 (Cancer Control – Symptomatic)
S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)
S0535 (Leukemia)
S0635 (Lung)
S0709 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma)

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Amy Johnson
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Larry Kaye
Louise Highleyman
Monica Yee
Stephanie Edwards
Vicki Green
Guadalupe Aquino – Alliance
Samantha Sublett – Alliance
Elliott Lee, Biologics, Inc.
Mary Alice Norrison - Boehringer Ingelheim
Linda Fischer - Bristol-Myers Squibb
Becky Fillingham – ECOG-ACRIN
Laura Gagnon – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN
April Noska – Genentech
NCI Coop Coverage - Genentech
Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Mohan Chelladurai, Ph.D. M.S.A. – Janssen Services, LLC
Royce-Ann Adkins, Janssen Services, LLC
William Heckman - Lilly
Theresa Bucher, R.N., Millennium
Mark Showers – Onyx
Kellis Snodgrass – Pfizer
Afrouz Bazmi – Quintiles, Inc.
Steve Shuey – Halozyme Therapeutics

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swog.org

June 15, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that an updated Funding Memorandum has been posted on the SWOG protocol abstract page (www.swog.org) and the CTSU protocol abstract page (www.ctsu.org).

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers – Onyx

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swog.org

Distribution Date: June 1, 2015
E-Mailed Date: May 19, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS

FROM: SWOG Operations Office

RE: Holiday Closure for Monday, May 25, 2015 in Observance of Memorial Day

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 purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 25, 2015 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 26, 2015. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

This Holiday Closure pertains to the following studies:

S1202 (Cancer Control – Symptomatic)
S1313 (Gastrointestinal)
S1406 (Gastrointestinal)
S1014 (Genitourinary)
S1216 (Genitourinary)
S0535 (Leukemia)
S0635 (Lung)
S0709 (Lung)
S1300 (Lung)
S1403 (Lung)
S1304 (Myeloma - Active)

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

cc: PROTOCOL & INFORMATION OFFICE
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Amy Johnson
Austin Hamm.
Brian Zeller
Christine McLeod
Jean Barce
Jeri Jardine
Larry Kaye
Louise Highleyman
Monica Yee
Stephanie Edwards
Vicki Green
Guadalupe Aquino – Alliance
Samantha Sublett – Alliance
Elliott Lee, Biologics, Inc.
Mary Alice Norrison - Boehringer Ingelheim
Linda Fischer - Bristol-Myers Squibb
Becky Fillingham – ECOG-ACRIN
Laura Gagnon – ECOG-ACRIN
Mary Bonds – ECOG-ACRIN
April Noska – Genentech
NCI Coop Coverage - Genentech
Leta Truett, Ph.D., M.N. – Janssen Services, LLC
Mohan Chelladurai, Ph.D. M.S.A. – Janssen Services, LLC
Royce-Ann Adkins, Janssen Services, LLC
William Heckman - Lilly
Theresa Bucher, R.N., Millennium
Mark Showers – Onyx
Kellis Snodgrass – Pfizer
Afrouz Bazmi – Quintiles, Inc.
Steve Shuey – Halozyme Therapeutics

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swog.org

Distribution Date: May 1, 2015
CTEP Submission Date: April 6, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #4

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

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 purpose of this revision is to clarify the intent of the protocol as it pertains to interpretation of the patient having received the "full assigned dose" and course of treatment in event of progression while still on Cycle 1 for both Arm 1 and Arm 2 of the protocol.

- If a patient progresses prior to completion of Cycle 1 on either Arm 1 or 2, the patient should continue on protocol therapy through Cycle 2.
- If a patient randomized to Arm 1 progresses on or after Cycle 2, then the patient will be eligible for crossover to Arm 3.
- If a patient randomized to Arm 2 progresses on or after Cycle 2, then the patient will be removed from protocol treatment.

The revision also includes several clarifications regarding treatment/assessment protocols for patients that crossover to Arm 3.

The above clarifications are reflected throughout the protocol, as follows:

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

2. Page 4, Table of Contents: Page numbers for Section 13.3 and subsequent sections have been updated.

3. Pages 11-13, Section 3.1c.1: This section has been updated to be congruent with the Carfilzomib Investigator Brochure, Version 15 (26 February 2015), and reflects the following changes to the Adverse Events with Possible Relationship to Carfilzomib table:

    - The following risks were added:
        - Likely (>20%): Chest pain
        - Less Likely (4 to ≤20%): Dehydration, Hyperkalemia, Hypoalbuminemia, Back pain (moved from Likely), Myalgia, Muscular weakness, Insomnia, Increased creatinine (moved from likely), Renal impairment, Epistaxis, Erythema
        - Rare but Serious (≤3%): Cataract, Multiorgan failure, C-reactive protein increase, BUN increased, Dysphonia, Pulmonary embolism

    - The following risks were removed:
        - Likely (>20%): Lymphopenia, Back pain (moved to Less Likely), Blood creatinine increased (moved to less likely)
        - Less Likely (4 to ≤20%): Double vision
        - Rare but Serious (<3%): Pancreatitis

    - The following risks were moved:
        - Likely (>20%): Peripheral edema (Previously "Edema periphereal" - moved from Vascular Disorders to General Disorders and Administration Site Conditions)
        - Rare but Serious(<3%): Pulmonary edema and Pulmonary hypertension (both moved from Cardiac Disorders to Respiratory, Thoracic and Mediastinal Disorders)

4. Page 21, Section 5.1 g: This section has been revised to clarify that a standard of care PET, obtained within the same timeline, may also be accepted. The section which previously read, “Patients must have baseline PET scan within 28 days prior to registration. Note that images are submitted centrally for review as outlined in Section 15.1.” now reads as follows, “Patients must have baseline PET scan within 28 days prior to registration. In the event that a patient had a standard of care PET scan prior to providing informed consent, the scan need not be repeated provided that it occurred within the 28 day window. Note that images are submitted centrally for review as outlined in Section 15.1.”

5. Page 23, Sections 5.2a and 5.2d: These criteria have been revised to clarify that the patients will begin receiving the “full assigned dose” for Arm 1 in Cycle 2. Section 5.2a, which previously read, “Patient must have been eligible for and initially randomized to Arm 1 (low dose carfilzomib) and progressed prior to completing 12 cycles of protocol therapy.” now reads as follows, “Patient must have been eligible for and initially randomized to Arm 1 (low dose carfilzomib), begun Cycle 2 of treatment, and progressed prior to completing 12 cycles of protocol therapy.” Section 5.2d, which previously read, “Patients must have been able to complete their last treatment cycle prior to progression at the full assigned dose (i.e. no dose reduction for toxicity).” now reads as follows, “Patients must have begun Cycle 2 (carfilzomib - 27mg/m^2) and must not have

received any dose reduction for toxicity in the last cycle of treatment immediately preceding progression."

6. Page 24, Section 7.1d: This section has been added, and now reads, "Patients on Arm 2 will receive dexamethasone/high dose carfilzomib for up to 12 cycles or until progression that occurs after the start of Cycle 2, whichever comes first. If a patient progresses after the start of Cycle 2, the patient will discontinue protocol treatment."

7. Page 24, Section 7.2: A sentence has been added to the end of this section to clarify that, "In the event of patient crossover to Arm 3, Cycle 1 intravenous hydration can be administered at physician discretion."

8. Pages 30-32, Section 9.0: Footnote (19) has been added to this section to clarify that, "For patients that crossover to Arm 3, return to Cycle 1, Day 1, and follow the same study calendar."

9. Page 35, Section 10.2d: The following clarification has been inserted at the beginning of this section: "Both serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) must be conducted at timepoints indicated in Section 9.0."

10. Page 36, Section 10.5: In the first paragraph of this section, the following language was inserted: "after having received the full-assigned Arm-specific dose of carfilzomib (27 mg/m^2 or 56 mg/m^2)".

11. Pages 40-43 and Page 45, Sections 13.0 and 14.0: The following changes have been made to include standard language required by the CTSU:

    - Sections 13.2 and 14.3a have been replaced in their entirety.
    - Section 13.3: The second paragraph has been added and item (e) "Cooperative Group Credit" has been removed from the list of questions the individual registering the patient must be prepared to answer. Subsequent items have been renumbered.
    - Section 13.4a: The text, "a web-based application that is" has been removed from the second sentence of this section.
    - Section 13.4b: The last bullet point, which previously read, "The study site is listed as "approved" in the CTSU RSS." has been removed from this section to be consistent with the revised standard CTSU template language.

12. Page 46, Section 14.4c: The title of this section has been revised to clarify that this data is also required for Arm 3 crossover patients.

13. Page 47, Section 15.1: The following clarifying note has been inserted as the second sentence of the first paragraph of this section, "Note: The baseline PET scan may have been obtained as part of standard of care (prior to patient informed consent) provided that it was obtained within 28 days prior to registration."

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 6 weeks of distribution of this notice.

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 treatment or on follow-up on this study, and patients who sign a consent form prior to local implementation of the consent form changes, **must** be informed of the following 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 by the next visit and this notification process must be documented in the patient chart.

The Model Consent Form has been modified as follows to update the "Possible Side Effects of Carfilzomib" risk tables to be consistent with the revised Investigator's Brochure:

14. Page 8, "COMMON, SOME MAY BE SERIOUS": "Back Pain" has been removed from this section.

15. Page 9, "OCCASIONAL, SOME MAY BE SERIOUS":

    - The following risks have been added to this section:
        - Back pain
        - Dehydration
        - Nose bleed
        - Increased blood level of potassium
        - Decreased levels of a blood protein called albumin
        - Increased blood level of creatinine (a substance normally eliminated by the kidneys in the urine)

    - The following risks have been updated and now read as follows:
        - Rash, itching dry skin, redness of the skin
        - Muscle spasms, pain, and weakness
        - Blurred vision

16. Page 10, "RARE, AND SERIOUS":

    - The following risks have been added to this section:
        - Cataract
        - Failure of multiple organs
        - Loss or impairment of your voice
        - Increase in a protein called c-reactive protein, which is a substance produced by the liver that increases inflammation throughout the body
        - Increase in levels of blood urea nitrogen (which is formed when protein breaks down)

    - The following risk has been removed from this section:
        - Inflammation of the pancreas

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: PROTOCOL AND INFORMATION OFFICE
Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
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April 1, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to clarify the intent of the protocol as it pertains to interpretation of the patient having received the "full assigned dose" and the associated course of treatment in event of progression while still on Cycle 1 for both Arm 1 and Arm 2 of the protocol.

The intent of the protocol is that for both Arm 1 and Arm 2 the "full assigned dose" is achieved in Cycle 2, wherein, the "full assigned dose" for Arm 1 is 27 mg/m^2 and the "full assigned dose" for Arm 2 is 56 mg/m2.

Herein, this memorandum provides the following additional clarifications to the protocol:

- If a patient progresses prior to completion of Cycle 1 on either Arm 1 or 2, the patient should continue on protocol therapy through Cycle 2.
- If a patient randomized to Arm 1 progresses on or after Cycle 2, then the patient will be eligible for crossover to Arm 3.
- If a patient randomized to Arm 2 progresses on or after Cycle 2, then the patient will be removed from the protocol.

These clarifications will be addressed in a forthcoming revision to Sections 5.2, 5.2d, 7.1d, 7.2, and 10.5 of the protocl.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Destin Carlisle – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
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swog.org

Distribution Date: April 1, 2015
CTEP Submission Date: March 12, 2015

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Cara Laubach, MIIM, Protocol Coordinator (E-mail: claubach@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #3

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #3

Revision #3 incorporates requirement for troponin testing and pulmonary function testing (in the event of Grade 3 or 4 dyspnea). With this revision, the troponin, PFT (in event of Grade 3 or 4 dyspnea), ECGs, and CK, CK-MB, and BNP and/or pro-BNP (for crossover patients) will be paid for by Onyx. This revision also incorporates minor administrative clarifications and updates to the Model Consent Form.

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

2. Page, 24, Section 7.1a: The requirement for cardiac-specific troponin T and/or troponin I testing prior to Cycle 1, Day 1 has been added to the first sentence of this section. The following sentences have been added to the end of this section for clarity:

"In the event that Cycle 1, Day 1 laboratory tests are resulted and the patient no longer meets one or more of the eligibility criteria, treatment must be held. Laboratory tests and any associated supportive care must be repeated. If the repeat lab results fall within the eligibility criteria, treatment may be resumed. In the event that treatment must be held for ≥ 28 days, the patient must be removed from the protocol."

3. Page 24, Section 7.1c: This section has been added to the protocol to clarify that results of Day 1 laboratory tests are not required prior to starting treatment in each cycle, and reads as follows:

   "Results of Day 1 laboratory tests are not required prior to starting treatment for each cycle subsequent to Cycle 1 (see Section 7.1a for instructions regarding D1, C1 results). If lab results are abnormal or indicative of adverse events, the treating physician should refer to Section 8.0 for dose modifications, and Response Assessments should be conducted at time of dose modification and as indicated in Section 9.0. If dose modification is not indicated, the physician should otherwise continue treatment at physician discretion."

4. Page 29, Section 8.4e: The requirement for pulmonary function testing in the event of Grade 3 or 4 dyspnea has been added. Therefore, the first sentence of this section now reads as follows, "Pulmonary function testing is required and chest x-ray is strongly recommended in the event of Grade 3 or 4 dyspnea."

5. Pages 30-31, Section 9.0: The requirement for troponin T and/or Troponin I testing has been inserted into the "LABORATORY STUDIES" section on Page 30. Troponin T and/or Troponin I testing is required to be done on Day 1 of Cycle 1, and after completion of Cycles 3, 6, 9, and 12. The "C-reactive protein" has been moved from the "RESPONSE ASSESSMENT" section on Page 31 to the "LABORATORY STUDIES" section on Page 30. There has been no change in the timing of this testing. The "X" for EKG and ECHO under the "X-RAYS AND SCANS" Section on Page 31 has been replaced with "$\overline{p}$ Tx" for Cycle 3/Week 9, Cycle 6/Week 21, Cycle 9/Week 33, and Cycle 12/Week 45 to clarify that the EKGs and ECHOs should be completed after treatment.

6. Page 34, Section 10.1.b: "or Progression" has been added to the "NOTE" at the end of this section to clarify that a second disease assessment is required at time of progression.

7. Page 50, Section 16.1f.2: The following sentence has been inserted as the last bullet of this section, "Should pregnancy be reported in association with Section 16.1h, any lactation exposure should also be reported."

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice.
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 treatment or on follow-up on this study, and patients who sign a consent form prior to local implementation of the consent form changes, **must** be informed of the following 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 by the next visit and this notification process must be documented in the patient chart.

8. Page 9, Model Consent Form: The following risks have been added to the "OCCASIONAL, SOME MAY BE SERIOUS" risk section for carfilzomib. These risks were added to Section 3.1c of the protocol with Revision #2, and were inadvertently omitted from the consent at that time.
    - Increased blood level of uric acid, a waste material from food digestion
    - Increased blood level of liver enzymes

9. Page 12, Model Consent Form, "What are the costs of taking part in this study?":
    - The second paragraph of this section has been revised to indicate that EKGs will be paid for by the study sponsor and now reads as follows, "The blood tests to check the heart throughout the study, *the EKGs*, the ECHOs throughout the study, and the extra PET scan (if needed) will be paid for by the study sponsor."

10. Pages 12-13, Model Consent Form, "Who will see my medical information?": The following cooperative group participants and the CTSU have been included in the list of organizations that have access to information. The last sentence of this section now reads as follows:

    "Some of these organizations are:

    - The study sponsor and any drug company supporting the study.
    - The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
    - The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
    - *The Cancer Trials Support Unit (CTSU), a service sponsored by the NCI to provide greater access to clinical trials,*
    - *SWOG*
    - *The Alliance for Clinical Trials in Oncology*
    - *The ECOG-ACRIN cancer research group*
    - *NRG Oncology*
    - *The NCIC-CTG/NCIC Clinical Trials Group*
    - AG Mednet, the service that will transmit your PET images."

    This addition has caused subsequent sections to be displaced to the next page.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
Mary Bonds – ECOG-ACRIN
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Distribution Date: January 15, 2015
CTEP Submission Date: December 22, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #2

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #2

The above-referenced study has been revised as follows:

1. Page 1, Title Page: The version date has been updated. The e-mail address for each SWOG Study Chair has been updated to S1304SC@swog.org. The blank e-mail address for the ECOG-ACRIN Study Chair has been removed.

2. Pages 3-4, Table of Contents: The page numbers in the Table of Contents have been updated.

3. Pages 10-17, Section 3.1: This section has been updated to reflect updates that have been made to the carfilzomib investigator's brochure. Specifically, the following changes should be noted:

- Minor informational updates have been made in the "Absorption," "Distribution," "Metabolism," and "Elimination" sections.
- The headings in the adverse event table have been corrected to "Less Likely *4* - ≤ 20%" and "Rare but Serious (≤ 3%)."
- The following item has been added to the Likely section of the adverse events table: Chest pain.
- The following items have been added to the Less Likely section of the adverse events table: Hypotension; ALT increased; Urinary tract infection; Hyperuricemia; Renal failure (moved from Rare but Serious); Nasopharyngitis, Pneumonia; Rash; Pruritis; Dry skin
- The following items have been added to the Rare but Serious section of the adverse events table: Febrile neutropenia; Acute myeloid leukemia; Myelodysplastic syndrome
- "Pulmonary hypertension" was removed from the Respiratory, Thoracic and Mediastinal Disorders, as it is already listed in Cardiac Disorders.
- Information regarding posterior reversible encephalopathy syndrome has been added to the end of Section 3.1c.1.
- The animal data information has been removed.
- The section has been rearranged into the updated standard investigational drug template, rearranging drug storage, preparation, stability, ordering, and handling information. The overall content of these sections has not changed.

This caused information to be displaced to a newly inserted Page 17. Subsequent pages have been renumbered accordingly.

4. Page 19, Section 4.1: The note at the end of the section has been updated to clarify that patients with light chain myeloma are eligible.

5. Page 20, Section 5.1a: The reference to Section 4.1 has been removed. The word "currently" has been added to the first sentence.

6. Page 20, Section 5.1c: The timeframe from completion of prior chemotherapy has been updated from 28 days to 21 days. The last bullet has been updated to include allogeneic transplants, as patients with previous allogeneic transplant may also be eligible.

7. Page 21, Section 5.1q: Footnotes have been added to the creatinine clearance calculation to help define kilogram weight and creatinine value.

8. Page 22, Section 5.1u: This criterion has been updated to allow non-curative XRT as long as it is completed at least 7 days prior to registration.

9. Page 24, Section 7.1a: These instructions have been updated to allow BNP "and*/or*" proBNP, as either test will be sufficient.

10. Pages 30-32, Section 9.0: The following changes have been made to the study calendar:

    - "CK, CK-MB, BNP, pro-BNP" has been changed to "CK, CK-MB, and BNP or pro-BNP" to be consistent with the change in Section 7.1a.
    - The Xs in the CK, CK-MB, and BNP or pro-BNP row have been removed and replaced with notes to clarify the timing of the required tests.
    - A row for "C-reactive protein [11]" has been added to the Response Assessment section. The time points for these tests are consistent with the other response assessment tests.

- Footnote 9 has been updated to clarify that the tests are required "(unless *EKG or* ECHO has been performed within previous 28 days.
- Footnote 2 has been updated to note that results of Day 1 labs are not required prior to starting treatment each cycle, and that if lab results show an adverse event exists, the treating physician should refer to Section 8.0 and otherwise continue treatment at their discretion.
- Footnote 11 has been updated to require these tests be performed monthly after Cycle 12 until progression.
- Footnote 13 has been updated to indicate that response assessments are not required after progression.

11. Page 34, Section 10.1b: Progression has been added to the list of responses requiring confirmation assessment.

12. Page 35, Section 10.2d: This section has been removed. Subsequent sections have been renumbered accordingly.

13. Page 40-43, Section 13.0: The registration guidelines have been updated to the intergroup standard version (to include relevant information for non-SWOG sites). This has caused displacement of information through a newly inserted Page 43. Subsequent pages have been renumbered accordingly.

14. Page 46, Section 15.2c: The last sentence has been updated as follows: "If this is a biopsy ~~core~~ process the sample…"

15. Page 50, Section 16.1g: The definition of second malignancy has been added.

The following section refers to change to the Model Consent Form.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form within 90 days of distribution of this notice.

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 carfilzomib and patients who sign a consent form prior to local implementation of the consent form changes **must** be informed of the bolded changes below. The manner by which this notification takes place is at the discretion of the local institution. At a minimum, the patient must be notified by the next visit and this notification process must be documented in the patient chart.

Patients need not be informed of the non-bolded changes below unless required by the local IRB.

1. The Version Date has been updated.

2. Pages 8-10: The following items have been added to the carfilzomib risk table:

   <u>COMMON, SOME MAY BE SERIOUS</u>
   Chest pain

   <u>OCCASIONAL, SOME MAY BE SERIOUS</u>
   High **or low** blood pressure
   Rash, itching, dry skin
   Lung**/respiratory tract** infection
   Urinary tract infection
   Kidney failure

RARE, AND SERIOUS
Fever with low white blood cell count
Cancer that develops as a result of treatment for a previous cancer
Posterior reversible encephalopathy syndrome (PRES): abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss, and is associated with MRI findings.

These changes have caused information to be displaced to a newly inserted Page 10. Subsequent pages have been renumbered accordingly.

3. Page 12: The costs section has been updated to indicate that blood tests to check the heart throughout the study will be paid for by the study sponsor.

This memorandum serves to notify the NCI, Alliance, ECOG-ACRIN, and the SWOG Statistical Center.

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
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swog.org

December 15, 2014

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

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Wednesday, December 24, 2014, Thursday, December 25, 2014, and Thursday, January 1, 2015, in observance of the seasonal holidays.

Regular business hours will continue on December 26 and January 2 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Guadalupe Aquino – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
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swog.org

November 1, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: S1304SC@swog.org

IRB Review Requirements

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Thursday, November 27 and Friday, November 28, 2014 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 1, 2014. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906 or via email at clinicaltrials@biologicsinc.com.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
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Laura Kingsbury, M.R.T.
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August 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Sandi Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease." Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren

MEMORANDUM

Study Chair: Sikander Ailawadhi, M.D.
Phone: 904/953-7290
Email: ailawadhi.sikander@mayo.edu

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

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, September 1, 2014, in observance of Labor Day.

Regular business hours will resume on Tuesday, September 2, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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

cc: PROTOCOL & INFORMATION OFFICE
Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
Mary Bonds – ECOG-ACRIN
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August 1, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Sandi Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease." Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren

MEMORANDUM

Study Chair: Sikander Ailawadhi, M.D.
Phone: 904/953-7290
Email: ailawadhi.sikander@mayo.edu

IRB Review Requirements
( ) Full board review required. Reason:
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- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed

(√) No review required

MEMORANDUM

The FDA has confirmed an ongoing drug shortage for the injectable form of the drug dexamethasone, which is commercially available for use on the above-referenced study. An anticipated end-date for the shortage is not known at this time.

For sites experiencing dexamethasone shortage, please note the following protocol treatment allowance:

Currently, on both Arms 1 and 2, dexamethasone is administered via IV 30 minutes prior to carfilzomib infusion. **If IV dexamethasone is not available due to the current shortage, oral (PO) dexamethasone may be substituted at the same dose (20 mg) given 30 minutes prior to the carfilzomib infusion.**

Protocol revisions are not anticipated at this time, however, if the ongoing shortage becomes problematic, a revision to include this allowance may be considered in the future.

Please attach this memorandum to the front of your copy of the protocol.

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

cc: PROTOCOL & INFORMATION OFFICE
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June 15, 2014

TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate, for sites that have not yet received full board review)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Friday, July 4, 2014 in observance of Independence Day.

Regular business hours will resume on Monday, July 7, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

Please contact the Biologics Clinical Research Services team (800/693-4906; clinicaltrials@biologicsinc.com) with any questions or concerns.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
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May 15, 2014

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK (NCTN) MEMBERS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate, for sites that have not yet received full board review)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Monday, May 26, 2014 in observance of Memorial Day.

Regular business hours will resume on Tuesday, May 27, 2014. Regular business hours are Monday through Friday, 9:00 a.m. - 6:00 p.m. Eastern.

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

cc: Antje Hoering, Ph.D.
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Tracy Maher, C.C.R.P.
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Distribution Date: May 15, 2014
CTEP Submission Date: April 23, 2014

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TO: ALL NATIONAL CLINICAL TRIALS NETWORK MEMBERS; CTSU

FROM: Sandi Jo Fredette, Protocol Coordinator (E-mail: sfredette@swog.org)

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

REVISION #1

Study Chair: Sikander A. Ailawadhi
Phone number: 904/953-7290
E-mail: ailawadhi.sikander@mayo.edu

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #1

The above-referenced study has been revised as follows:

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

2. Page 1, Title Page: The NCT number has been added below the title. Dr. Ailawadhi's contact information has been updated. "ECOG" has been updated to "ECOG-ACRIN". The participants list has been removed.

3. Page 2, Participants Table: A participants table in the new NCI standard format has been added. Subsequent pages have been renumbered accordingly.

4. Pages 3-4, Table of Contents: The Table of Contents has been updated.

5. Page 13, Section 3.1d: Administration information has been updated to instruct that higher doses (> 27 mg/m^2) should be diluted into 100 mL instead of 50 mL.

6. Page 23 and 28, Section 7.0 and 8.5: Dr. Aliawadhi's phone number has been updated.

7. Throughout the protocol, the Adverse Event Reporting System has been changed from AdEERS (Adverse Event Expedited Reporting System) to CTEP-AERS (Cancer Therapy Evaluation Program Adverse Event Reporting System). This change has taken place in Sections 8.6 (Page 28), 16.1b, 16.1c and 16.1e (Page 46), Table 16.1 (Page 47), and 16.1f-g (Pages 48-49). Associated weblinks on these pages have also been updated.

8. Pages 30-31, Section 9.0: The following changes have been made to the study calendar:

   - A row for "Serum Quantitative Immunoglobulins" has been added with time points to match the other response assessments.
   - "Protein Electrophoresis" has been updated to "24 hour Urine for: Protein Electrophoresis".
   - "Immunofixation electrophoresis" has been updated to "Serum and Urine Immunofixation Electrophoresis".
   - "Free Light" has been updated to "Serum Free Light Chains".
   - "For patients who cross over, to be performed every 3 cycles based on date of previous measurement." has been added to the "9" footnote.

9. Page 33, Section 10.1b: The second and fourth bullets of the progression definition have been updated to include "…(or lowest response level)…".

10. Page 40, Section 13.3b: Information has been added to this section to indicate that the affirmation of eligibility on the Registration Worksheet must have been signed by the registering investigator or another investigator designate prior to accessing OPEN.

11. Page 43, Section 15.1: Information has been added to this section to clarify the funding of the second PET scan will be provided by the sponsor for the first 30 patients.

12. Page 44, Section 15.2.a.1 and 15.2.b.1: The statement has been corrected to state within 28 days *prior to* Step 1 registration to ensure consistency with the informed consent.

13. Page 46, Section 16.1b: This information has been updated to the current reporting standards, removing information referring to loss of internet connectivity.

14. Page 46, Section 16.1.c: SWOG was updated to the SWOG Operations Office.

15. Pages 49-50, Section 16.1: A new standard Section 16.1h was added to include Adverse Event Reporting Requirements of Pregnancy, Fetal Death, and Death Neonatal. Subsequent pages have been renumbered accordingly.

16. Page 56, Section 18.2.b: "Site Number (optional)" has been updated to "NCI Site Code" as this information is required to set up user access in AG Mednet.

The following section refers to changes made to the Model Consent Form.

Institutions **must** update their local consent forms to include the changes to the Model Consent Form outlined in the section below within 90 days of distribution of this notice.

SWOG considers that these 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 need not be informed of the following changes unless required by the local IRB.

1. The Version Date of the Model Consent Form has been updated.

2. Page 6: The Skeletal survey during the study was removed from the "What extra tests and procedures will I have if I take part in the study?" section. The survey is standard of care.

3. Page 10: The information in the "Will I benefit from this study?" was corrected from "*[procedures, drugs, interventions, devices]*" to "this study".

4. Page 11: Information was added to the section "What are the costs of taking part in this study?" to indicate the ECHO and second PET scan (if needed) costs will be covered by the study sponsor.

5. Page 13: In the second sentence of item #1 in the "What is Involved?" section, "bone marrow" has been updated to "a tissue sample", as the EMD may not be in the marrow.

6. Page 17: In the "How could the records be used in ways that might be harmful to me?" section, new standard GINA information has replaced the previous explanation of genetic discrimination.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
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Laura Kingsbury, M.R.T.
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March 15, 2014

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swog.org

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

IRB Review Requirements

( ) Full board review required. Reason:
- ( ) Initial activation (should your institution choose to participate, for sites that have not yet received full board review)
- ( ) Increased risk to patient
- ( ) Complete study redesign
- ( ) Addition of tissue banking requirements
- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of an updated **S1304** Drug Order Form (carfilzomib) for the above-referenced study. The study title has been added to the order form in order to ensure proper processing. Sites are requested to begin using the updated form immediately. The updated form can be found on the protocol abstract page on the SWOG website (www.swog.org).

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
Mary Bonds – ECOG-ACRIN
Becky Fillingham – ECOG-ACRIN
Elliott Lee – Biologics
Mark Showers - Onyx

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swog.org

February 1, 2014

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

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- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of a change to the Master Forms Set for the above-referenced study.

The **S1304** Registration Worksheet has been updated to make the questions in the "Indicate how the patient answered the following questions on the consent form" section consistent with the questions in the consent. The form Version 1.1 has been added to the bottom of the form; the form number has not been changed.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
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swog.org

December 15, 2013

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

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- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites that Biologics, Inc. Clinical Trials Services will be closed Tuesday, December 24, 2013, Wednesday, December 25, 2013, and Wednesday, January 1, 2014, in observance of the seasonal holidays.

Regular business hours will continue December 26-27 and December 30-31 from 9:00 a.m. – 6:00 p.m. Eastern.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Research Services team at 800/693-4906 or via e-mail at clinicaltrials@biologicsinc.com.

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

cc: Antje Hoering, Ph.D.
Rachael Sexton, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
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swog.org

November 15, 2013

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

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- ( ) Study closure due to new risk information

( ) Expedited review allowed (for sites that have received full board review)

(√) No review required

MEMORANDUM

The purpose of this memorandum is to inform sites of a change to the Master Forms Set for the above-referenced study.

The Cardiac Assessment Form has been updated to correct the assessment timepoints. Assessments should be performed at baseline (Day 1 of Cycle 1), after Cycles 3, 6, 9 and 12, and at completion of treatment for any reason (unless performed within the previous 28 days). The form date and number have not been changed.

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

cc: Antje Hoering, Ph.D.
Shannon McDonough, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
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November 1, 2013

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

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MEMORANDUM

The purpose of this memorandum is to inform sites of a holiday closure of Biologics, Inc. Biologics, Inc. Clinical Trials Services is closed Thursday, November 28 and Friday, November 29, 2013 in observance of the Thanksgiving holiday.

Regular business hours will resume on Monday, December 2, 2013. Regular business hours are Monday through Friday, 9:00 a.m. – 6:00 p.m. Eastern.

For additional information, please access Biologics' website at www.biologicsinc.com.

If you have questions or need to coordinate shipments in advance, please contact your Clinical Trial Project Manager at 800/693-4906.

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

cc: Antje Hoering, Ph.D.
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Distribution Date: November 1, 2013
E-mailed Date: October 18, 2013

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

STATUS NOTICE

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

IRB Review Requirements

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( ) No review required

ACTIVATION

The above-referenced study is now open for patient accrual **effective October 18, 2013 at 2:00 p.m. Eastern Time**.

Please note that the infusion times for low-dose carfilzomib and high-dose carfilzomib are different. See Sections 7.3 and 7.4 for infusion times.

Additionally please note that central submission of ECHO results via AG Mednet will be added when funding and logistical details have been finalized. Sites should keep all ECHO results obtained prior to this addition to be submitted retrospectively at the time the submission guidelines are added to the protocol.

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

cc: Antje Hoering, Ph.D.
Shannon McDonough, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
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swog.org

October 1, 2013

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

FROM: Sandi Jo Fredette, Protocol Coordinator

RE: **S1304**, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease". Study Chairs: Drs. S. Ailawadhi, M.H. Abidi, S. Lentzsch, R.Z. Orlowski and E.M. Rohren.

MEMORANDUM

Study Chair: Sikander A. Ailawadhi
Phone number: 323/865-3913
E-mail: ailawadh@usc.edu

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( ) No review required

MEMORANDUM

This protocol is being distributed at this time **for Institutional Review Board (IRB) review only**. Institutions will be notified when the study is activated for patient registrations.

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

cc: Antje Hoering, Ph.D.
Shannon McDonough, M.S.
Jeri Jardine
Laura Kingsbury, M.R.T.
Tracy Maher, C.C.R.P.
Guadalupe Aquino – Alliance
Becky Fillingham – ECOG/ACRIN

PRIVILEGED COMMUNICATION
FOR INVESTIGATIONAL USE ONLY

Distributed for IRB Review 10/1/2013
Activated 10/18/13

SWOG

A PHASE II RANDOMIZED STUDY COMPARING TWO DOSES OF CARFILZOMIB (NSC-756640) WITH DEXAMETHASONE FOR MULTIPLE MYELOMA PATIENTS WITH RELAPSED OR REFRACTORY DISEASE

NCT #01903811

STUDY CHAIRS:

Sikander Ailawadhi, M.D. (Medical Oncology)
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Eric M. Rohren, M.D., Ph.D. (PET)
MD Anderson Cancer Center
Department of Nuclear Medicine
1400 Pressler, Unit 1483
Houston, TX 77030
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FAX: 713/563-3694
E-mail: S1304SC@swog.org

AGENTS:

IND-Exempt Agent:
Dexamethasone (Decadron) (NSC-34521)

SWOG-Held IND Agent:
Carfilzomib (Kyprolis) (NSC-756640)
(IND-118110)

BIOSTATISTICIANS:

Antje Hoering, Ph.D. (Biostatistics)
Rachael Sexton, M.S. (Biostatistics)
Cancer Research and Biostatistics
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E-mail: rachaels@crab.org

ALLIANCE STUDY CHAIR:

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University of North Carolina
Email: peter_voorhees@med.unc.edu

ECOG-ACRIN STUDY CHAIR:

Adam D. Cohen, M.D. (Medical Oncology)
Fox Chase Cancer Center

STUDY CHAIRS (contd.):

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PARTICIPANTS

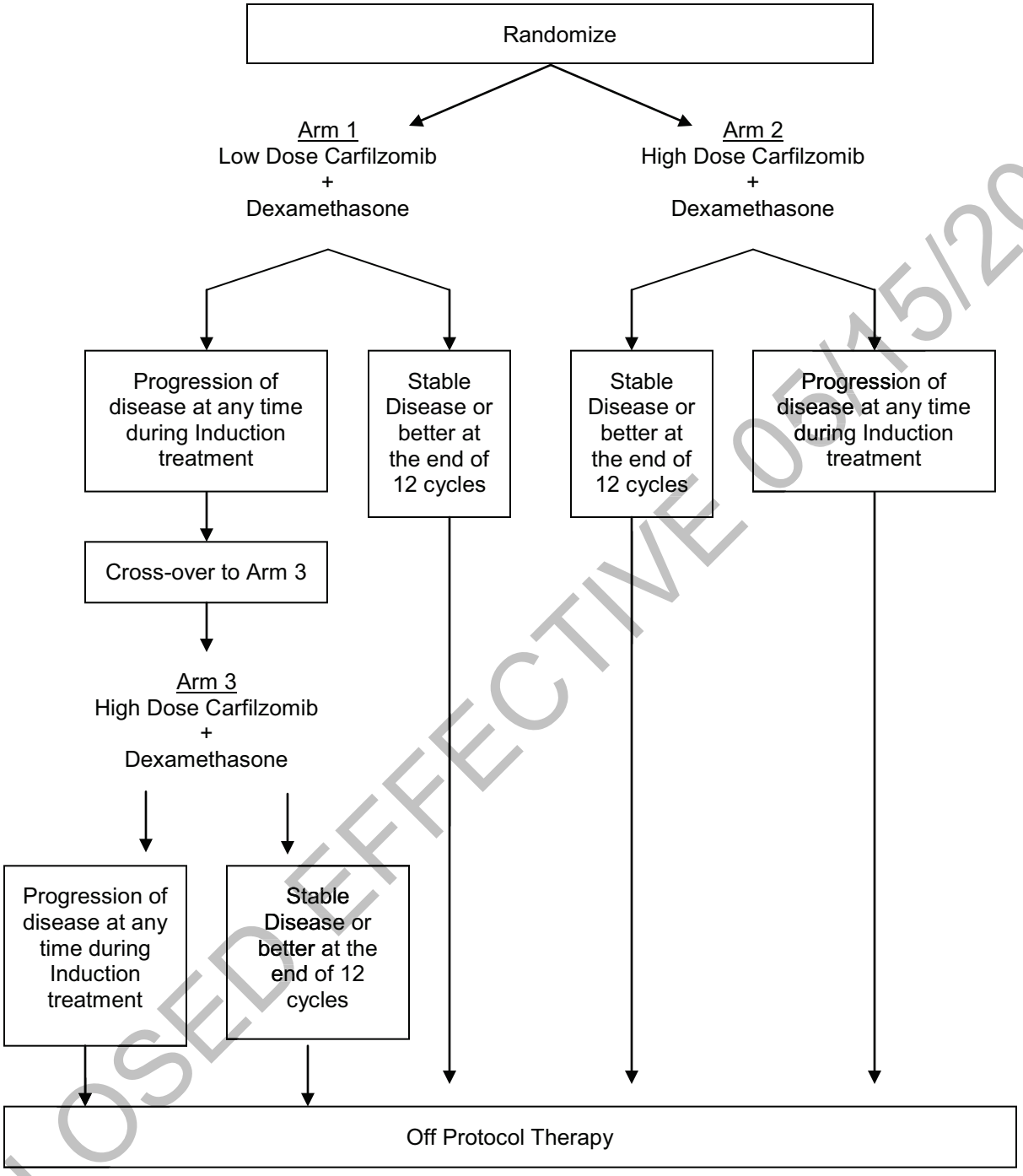
ALLIANCE/Alliance for Clinical Trials in Oncology
ECOG-ACRIN/ECOG-ACRIN Cancer Research Group
NRG/NRG Oncology
SWOG/SWOG
NCIC-CTG/NCIC Clinical Trials Group

TABLE OF CONTENTS

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: This protocol will use Medidata Rave® for electronic data submission. Access Rave® using your active CTEP-IAM userid and password at the following url: https://login.imedidata.com/selectlogin Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 myelomaquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission Contact the CTSU Help Desk by phone or e-mail: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.org		

SCHEMA



1.0 OBJECTIVES

1.1 Primary Objective

To evaluate and compare progression free survival (PFS) of two different doses of carfilzomib with dexamethasone in multiple myeloma (MM) patients with relapsed and/or refractory disease.

1.2 Secondary Objectives

a. To evaluate and compare response rates (RR) for each arm.

b. To evaluate response rates (RR) for patients that relapse on low dose carfilzomib and subsequently cross-over to high dose carfilzomib.

c. To evaluate the safety of this combination for this patient population.

d. To evaluate overall survival (OS)

1.3 Other Objectives

a. To explore the molecular variability in MM cells obtained from extramedullary bone marrow relapse sites.

b. To explore the role of PET scanning in assessing disease burden and as a tool to assess treatment response.

c. To explore changes in Left Ventricular Ejection Fraction (LVEF) in patients with relapsed or refractory multiple myeloma treated with low dose carfilzomib or high dose carfilzomib plus dexamethasone.

d. To evaluate whether there is a difference in the incidence of clinically relevant cardiovascular toxicity between treatment arms (normal- versus high-dose carfilzomib).

e. To assess the timing and onset of clinically significant cardiotoxicity.

f. To assess the relationship between patient characteristics, including demographic data, comorbid conditions, clinical data, echocardiography, and serum biomarkers and the development of clinically significant cardiotoxicity.

2.0 BACKGROUND

Overview of Multiple Myeloma

Multiple Myeloma is the most common malignant plasma cell disorder and accounts for approximately 10% of the incidence and 20% of the mortality from all hematologic malignancies in the US. *(1)* MM is characterized by the neoplastic proliferation of a single clone of plasma cells producing a monoclonal immunoglobulin. This malignant clone proliferates in the bone marrow and often results in extensive skeletal destruction with osteolytic lesions, osteopenia, and/or pathologic fractures. The clinical course of MM may be very heterogeneous. Some patients have an indolent phase that requires no treatment, while others present in an aggressive symptomatic phase of MM that is typically associated with bone marrow infiltration, the characteristic lytic bone lesions, renal dysfunction, immune deficient state and a compromised survival. Despite development of several new therapeutic agents and substantially effective novel combination regimens, myeloma remains, in most cases, an incurable disease. The majority of patients eventually relapse and develop disease that is resistant to therapy.

Proteasome Inhibitors for Multiple Myeloma Treatment

The introduction of novel therapeutic agents has helped change MM from a devastating malignancy with an average survival of 3 years to a chronic disease, where increasing numbers of patients can now expect to live 10 years or more. *(2)* One major class of agents that has significantly improved the outcome of MM patients is proteasome inhibitors. So far, approved proteasome inhibitors for MM treatment are bortezomib and carfilzomib, but bortezomib can be

associated with adverse events e.g., peripheral neuropathy, and with repeated use, resistance can develop to bortezomib-based treatment. *(3,4)* Carfilzomib is a newer agent in the proteasome inhibitor family that has shown very encouraging efficacy in the treatment of MM. *(5)* Carfilzomib has demonstrated high response rates in patients with relapsed and/or refractory MM, when used as a single agent in a dose of 27 mg/m^2. *(6-8)* Furthermore, current studies with carfilzomib as well as previous experience with bortezomib have shown that a combination of proteasome inhibitors with dexamethasone improves their efficacy further. *(9)* One of the current clinical trials using carfilzomib is specifically looking at a patient population that is refractory to bortezomib and an impressive response rate has been reported so far in this trial. *(10)* Based on this data, carfilzomib has been approved by the FDA for use in MM patients with disease refractory to bortezomib treatment. Thus, carfilzomib is a very promising and efficacious novel proteasome inhibitor with a favorable adverse event profile, which demonstrates efficacy in patients who have been previously exposed to and may be refractory to the currently available proteasome inhibitor, bortezomib.

Rationale for the Study Design

The current FDA-approved dose of carfilzomib is 20/27 mg/m^2. *(6,7,10,11)* Recent data have shown that the maximum tolerated dose (MTD) of carfilzomib is higher (20/56 mg/m^2) than this dose of 27 mg/m^2 and may be administered to patients without significant additional toxicity, while improving the agent's efficacy. *(12)* Thus, it is warranted to compare the two different doses of carfilzomib in combination with dexamethasone in a randomized fashion to establish conclusively if a higher dose can indeed improve the agent's efficacy while maintaining a safe toxicity profile. This can potentially change the way physicians may use this agent in the future for the management of MM.

Translational Medicine Objectives

GEP: Extramedullary Disease in Multiple Myeloma and the Molecular Profile of Malignant Clones
The usual natural history of MM involves periods of remission and episodes of relapse, evidenced by increased bone marrow plasmacytosis and end organ damage (renal failure, bone disease, anemia). In some cases, disease relapse is in the form of multiple solid extramedullary tumors, called plasmacytomas (EMP). *(13)* This is contrary to the general understanding of MM pathophysiology that the malignant clone depends heavily on the bone marrow microenvironment for its survival. *(14)* It is hypothesized that the malignant cells in EMP cases may undergo clonal terminal differentiation, so that they are capable of extravasation and homing to the extramedullary sites, and survival independent of the bone marrow cytokine milieu. *(15)* MM patients who have disease relapse with multiple EMPs follow a very aggressive course with extremely poor prognoses, and are resistant to most of the currently available treatment regimens. *(1,16)* So far this clinical entity has been recognized but efforts have not been directed to develop treatment regimens specifically for such MM patients. Furthermore, since the pathophysiology and clinical outcome of extramedullary and medullary relapses in MM are very distinct, exploration of differences in biological characteristics of these two entities is warranted. Recently, molecular profiling of MM cells has been characterized by gene expression profiling (GEP), especially by SWOG member institutions, and this

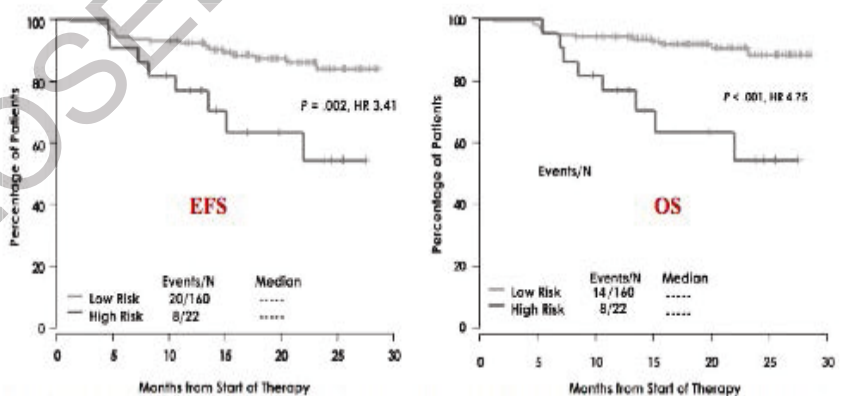


Figure 1: Risk group distribution and survival analyses, with Kaplan-meier estimates of EFS and OS between molecular risk groups in the test cohort.

may be utilized to better understand the differences between medullary and extramedullary relapses of MM. *(17)* The use of GEP has emerged as a sophisticated tool to help delineate a high-risk molecular signature in MM. *(18)* GEP analysis on tumor cells from 532 newly diagnosed MM patients revealed that seventy genes, 30% mapping to chromosome 1 ($P < 0.001$), were linked to early disease-related death. In a comparison of paired baseline and relapse samples, the high-risk score also was an independent predictor of outcome endpoints in univariate analysis ($P < 0.001$) as well as multivariate analysis ($P < 0.001$) that included the ISS and high-risk karyotyping. (Figure 1) The high-risk score frequency rose to 76% at relapse and predicted short post-relapse survival ($P < 0.05$). GEP can thus delineate a high-risk subgroup of MM patients who have a compromised survival, both in the newly diagnosed patients as well as those with relapsed/refractory disease. Such an analysis has not yet been undertaken comparing GEP from the medullary and extramedullary relapse sites.

Mechanism of Resistance to Carfilzomib
So far the details regarding mechanisms of developing resistance to carfilzomib are not known. Since this has shown to be an efficacious agent for the treatment of MM patients with relapsed and/or refractory disease and patients have been reported to have disease that relapses after an initial response to carfilzomib or are inherently refractory to it, it becomes important to attempt to explain what mechanisms may be in play for developing resistance to carfilzomib, and comparing with historical data regarding resistance to other members of this drug group, namely, bortezomib. *(19)*

FDG-PET
There are no current standard diagnostic techniques for extramedullary disease in MM patients. For such patients the use of [18F]-fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET) scanning may be helpful as has been reported in previous studies. *(20)* FDG-PET can play an important complementary role, along with computed tomography (CT), magnetic resonance imaging (MRI), and bone scans, in the diagnosis and staging of individuals with this disease, and further studies will refine its best uses. MRI and CT, while able to identify lesions, have difficulty distinguishing between active disease and scar tissue, bone fractures or benign disease. Thus, PET scanning may help identify sites of occult disease that may be missed by other conventional modalities used currently and may help in assessing disease burden accurately. This proposed clinical trial will attempt to define the frequency of extramedullary disease in patients with relapsed/refractory MM by performing a baseline PET scan, and in patients who are noted to have EMPs prior to starting treatment, response will be assessed by a follow up PET scan. The follow up PET scan will be repeated in such patients when they achieve an adequate biochemical response (> very good partial remission [VGPR]) as measured by serum and/or urine testing, or for patients who fail to achieve a VGPR or better, the follow up PET scan will be done at the end of the intensive phase of the regimen. This will help in better defining the role of PET scanning in assessing disease burden, and its utility as a tool to measure response to treatment in this otherwise difficult to treat subgroup of MM patients.

ECHO
Left ventricular ejection fraction (LVEF), which is widely used to monitor cardiac systolic function after chemotherapy, fails to detect subtle alterations in LV function. Once the LVEF has decreased, it may be too late to reverse the course of the cardiomyopathy. More sensitive and specific markers of chemotherapy-induced cardiac dysfunction or myocardial injury may allow for earlier detection, better prediction of the clinical course, and allow the treating oncologist to better adapt chemotherapeutic and dosing regimens. In certain high-risk cases, cardioprotective agents could be initiated in an effort to blunt cardiotoxic effects. *(22)*

Currently there is evidence supporting the fact that recently developed echocardiographic indices and biomarkers may be useful in the detection of early cardiac injury; In particular abnormalities in myocardial strain and strain rate have been described after anthracyclines-based chemotherapies. *(23-26)*

Proteasome inhibitors are commonly used novel therapeutic agents for multiple myeloma and other B cell malignancies. The ubiquitin proteasome pathway is essential for many cellular regulatory mechanisms, including antigen processing, signal transduction, and cellular homeostasis. Proteasome inhibition results in proteotoxic stress. This may impair the ability of the cell to proliferate and can result in programmed cell death via activation of apoptotic pathways.

In the case of bortezomib, cardiovascular safety pharmacology studies conducted in primates show that the administration of dosages ≥ 3.0 mg/m^2 resulted initially in physiologically significant heart rate elevations, progressive hypotension, bradycardia, and death 12–14 h post-dose. Additional cardiovascular effects have been noted at even lower doses (1.2 – 2.4 mg/m^2). Furthermore, radioactively labeled bortezomib has been detected in the myocardium and histopathological findings in repeat-dose primate studies have showed cardiac necrosis at commonly used therapeutic doses (≥ 0.9 mg/m^2). Whether these findings are associated with direct drug-myocardial toxicity is unknown, but it has been proposed this may occur through direct proteasome inhibition (the ubiquitin–proteasome system). *(27-29)*

In the pivotal clinical trial, of the 669 multiple myeloma patients who were treated with bortezomib, the incidence of cardiac disorders during treatment was 15% and clinical heart failure events occurred in 5% of bortezomib-treated patients. *(30)*

Carfilzomib is a newer irreversible proteasome inhibitor. It has shown good response rates in newly diagnosed and relapsed patients with multiple myeloma in a number of Phase I and II trials. Currently carfilzomib has less clinical data regarding cardiotoxicity than bortezomib, however, there are now over 500 patients with multiple myeloma that have been treated with carfilzomib in Phase II studies, including the AO-003 (20 mg/m$^{2)}$, A1-003 (20/27 mg/m$^{2)}$, 004 (20 and 20/27 mg/m$^{2)}$ and the 005 (15/20 and 27 mg/m^2). The cardiac and pulmonary safety profile of carfilzomib in these 4 studies revealed:

	N= 526	%
Grade ≥ 3 arrythmia	12	2%
Grade ≥ 3 cardiac failure	30	6%
Grade ≥ 3 Cardiomyopathy	3	<1%
Grade ≥ 3 ischemic heart disease	7	1%
Dose reduction due to cardiac AE	6	1%
Discontinuation due to Cardiac AE	23	4%
Cardiac Deaths	5	1%
All grades dyspnea	222	42%
All grades cough	137	26%
(31)		

Carfilzomib at higher doses of 20/ 56mg/m^2 (trials 007 and the IST- CAR 512) in 65 patients resulted in ≥ Grade 3 heart failure in 6% and pulmonary edema in 5%. (32)

Inclusion of Women and Minorities

This study was designed to include women and 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	5	9	14
Not Hispanic or Latino	56	70	126
Total Ethnic	61	79	140
Racial Category			
American Indian or Alaskan Native	0	1	1
Asian	1	2	3
Black or African American	9	11	20
Native Hawaiian or other Pacific Islander	0	1	1
White	51	64	115
Racial Category: Total of all Subjects	61	79	140

3.0 DRUG INFORMATION

Investigator's Brochures

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

For this study, dexamethasone is commercially available; therefore, an Investigator's Brochure is not applicable to this drug. Information about commercial drugs is publicly available in the Physician's Desk Reference (PDR), prescribing information and other resources.

For this study, carfilzomib is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the IRB should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

3.1 Carfilzomib (Kyprolis) (NSC-756640) (IND-118110)

a. PHARMACOLOGY

Mechanism of Action: Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome. The agent has less activity against non-proteasomal serine proteases in non-malignant tissues.

b. PHARMACOKINETICS

1. Absorption: Carfilzomib absorption follows a biphasic distribution following IV administration.Studies comparing administration via IV bolus or infusion noted a higher Cmax with bolus administration. AUC and t/12 were similar in the bolus vs. infusion group. The Cmax and AUC following a single intravenous dose of 27 mg/m^2 was 4232 ng/mL and

2. 379 ng•hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 mg/m^2, there was a dose-dependent increase in exposure.

3. Distribution: The mean steady-state volume of distribution of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested *in vitro*, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar. Distribution of carfilzomib is extensive to all body tissues except brain.

4. Metabolism: Carfilzomib is rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated *in vitro* by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. None of these metabolites show activity. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism.

5. Elimination: Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a pharmacokinetic half-life of ≤ 1 hour on Day 1 of Cycle 1. In humans, the pharmacodynamic half-life was ≥ 24 hours. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. The majority of carfilzomib elimination appears to occur within tissues leading to slow elimination from the body.

c. ADVERSE EFFECTS

1. The following adverse events have been observed in early phase trials with possible relationship to carfilzomib and summarized from the investigator's brochure.

Adverse Events with Possible Relationship to Carfilzomib		
Likely (>20%)	**Less Likely (4 - ≤20%)**	**Rare but Serious (≤3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia	Leukopenia	Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)
Neutropenia	Lymphopenia	Thrombotic Microangiopathy
Thrombocytopenia		
CARDIAC DISORDERS		
	Hypertension	Acute coronary syndrome
	Hypotension	Cardiac arrest
	Congestive heart failure	Cardiac disorder
		Decreased ejection fraction
		Hypertensive crisis
		Pericardial Effusion
		Pericarditis
EYE DISORDERS		
	Blurred vision	Cataract

GASTROINTESTINAL DISORDERS		
Constipation	Anorexia	Toothache
Diarrhea	Abdominal pain	Gastrointestinal perforation
Nausea	Indigestion	
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
Fatigue	AST increased	Bilirubin increased
Pyrexia	ALT increased	Hepatic failure
Peripheral edema	Asthenia	Tumor lysis syndrome
	Chills	Infusion reaction
	Pain	Allergic reaction
		Multiorgan failure
INFECTIONS AND INFESTATIONS		
	Bronchitis	C-reactive protein increase
Upper respiratory tract infection	Pneumonia	Sepsis
	Urinary tract infection	Febrile neutropenia
		Influenza
METABOLISM AND NUTRITION DISORDERS		
	Decreased appetite	
	Dehydration	
	Hypercalcemia	
	Hyperglycemia	
	Hyperkalemia	
	Hypoalbuminemia	
	Hypokalemia	
	Hypomagnesemia	
	Hyponatremia	
	Hypophosphatemia	
	Hyperuricemia	
	Hypocalcemia	
MUSCULOSKELETAL AND CONNECTIVE TISSURE DISORDERS		
	Chest Pain	
	Arthralgia	
	Back pain	
	Muscle spasms	
	Pain in extremity	
	Myalgia	
	Muscular weakness	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED		
		Acute myeloid leukemia
		Myelodysplastic syndrome
NERVOUS SYSTEM DISORDERS		
Headache	Dizziness	Posterior Reversible Encephalopathy Syndrome
	Hypoesthesia	
	Insomnia	
	Paresthesia	
	Peripheral neuropathy	

PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RENAL AND URINARY DISORDERS		
	Increased creatinine	
	Renal impairment	
	Renal failure	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Epistaxis	Dysphonia
	Nasopharyngitis	Pulmonary edema
		Pulmonary embolism
Cough		Pulmonary hypertension
Dyspnea		Pulmonary toxicities: Interstitial Lung Disease (including pneumonitis), Acute Respiratory failure and Acute Respiratory Distress Syndrome (ARDS)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Erythema	
	Rash	
	Pruritis	
	Diaphoresis	
VASCULAR DISORDERS		
		Thromboembolic disorder
		Stroke

Infusion Reactions: Infusion reactions were characterized by a spectrum of systemic symptoms including fever, chills, arthralgia, myalgia, facial flushing, facial edema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration of carfilzomib. Prophylactic treatment, including dexamethasone 4 mg orally or intravenously daily during Cycle 1 with hydration largely eliminated these infusion reactions.

Posterior Reversible Encephalopathy Syndrome (PRES): PRES is a rare, potentially fatal neurological disorder that can present with headaches, altered mental status, seizures, visual loss, and hypertension. PRES may be reversible if diagnosed early. Magnetic resonance imaging (MRI) is used to investigate and confirm the diagnosis.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether carfilzomib is excreted in human milk.

3. Drug Interactions: Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs. Carfilzomib is a P-glycoprotein (P-gp) substrate but is unlikely to be affected by P-gp inhibitors or inducers.

d. DOSING & ADMINISTRATION

1. Dosing – See Section 7.0 Treatment Plan

2. Administration: 4mg of dexamethasone is suggested prior to administration to prevent infusion reactions. In addition, 250-500ml of hydration should be given to patients prior to Cycle 1. The continued use of hydration may be used per the provider's judgment. The intravenous administration line should be flushed with normal saline or 5% Dextrose

3. Injection, USP immediately before and after carfilzomib administration. Carfilzomib should not be administered as a bolus. Low-dose carfilzomib should be administered over 2-10 minutes; high-dose carfilzomib should be administered over 30 minutes (see Sections 7.3b and 7.3c). Do not mix carfilzomib with or administer as an infusion with other medicinal products.

e. HOW SUPPLIED

1. Carfilzomib is commercially available; however it is investigational for this study and will be provided free of charge by Onyx Pharmaceuticals for distribution to sites by Biologics, Inc.

2. Carfilzomib is supplied as an individually cartoned single-use vial containing a dose of 60 mg of carfilzomib as a white to off-white lyophilized cake or powder.

f. STORAGE, PREPARATION & STABILITY

1. Storage: Unopened vials should be stored refrigerated (2°C to 8°C; 36°F to 46°F). Retain in original package to protect from light.

Stability: Carfilzomib vials contain no antimicrobial preservatives and are intended only for single use. Unopened vials of carfilzomib are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. The stabilities of reconstituted carfilzomib under various temperature and container conditions are shown in the table below.

Storage Conditions of Reconstituted Carfilzomib	**Stability[a] per Container**		
	Vial	**Syringe**	**IV Bag (D5W)[b]**
Refrigerated (2°C to 8°C; 36°F to 46°F)	24 hours	24 hours	24 hours
Room Temperature (15°C to 30°C; 59°F to 86°F)	4 hours	4 hours	4 hours

[a] Total time from reconstitution to administration should not exceed 24 hours.
[b] 5% Dextrose Injection, USP.

2. Reconstitution/Preparation: Remove vial from refrigerator just prior to use. Aseptically reconstitute each vial by slowly injecting 29 mL Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides. After reconstitution, carfilzomib is ready for intravenous administration. The reconstituted product should be a clear, colorless to slightly yellow, solution. If any discoloration or particulate matter is observed, do not use the reconstituted product. When

3. administering in an intravenous bag, withdraw the calculated dose from the vial and dilute into 50 mL 5% Dextrose Injection, USP intravenous bag, 50 mL for low dose (≤ 27 mg/m^2) or 100 mL for higher dose (> 27mg/m^2) . Immediately discard the vial containing the unused portion.

g. DRUG ORDERING & ACCOUNTABILITY

1. Carfilzomib may be ordered by faxing the Carfilzomib Drug Order Form to Biologics' Clinical Research Services Division at 919/256-0794. The form can be found on the protocol abstract page of the SWOG website (www.swog.org) or on the protocol abstract page of the CTSU website (www.ctsu.org). Patient initials, SWOG patient ID, dose and signature of the investigator or authorized designate will all be required at the time of drug order.

   Biologics will ship drug on the same day for orders received before 2:00 p.m. Eastern Monday through Thursday. Orders received after 2:00 p.m. Eastern Monday through Thursday or any time Friday through Sunday will be processed and shipped the next business morning. Biologics will be closed for the following holidays: New Year's Day, Memorial Day, Independence Day, Labor Day, Thanksgiving Day, Thanksgiving Friday, Christmas Eve, and Christmas Day.

   Drug will be distributed in the original manufacturer's packaging, within patient-specific labeled bags.

   Initial Orders: Please check "initial order" on the drug order form. An estimated two month supply will be shipped for initial orders.

   Subsequent Orders: Biologics will send a reminder fax/e-mail to the site contact to reorder additional drug supply for the subsequent cycles. Please check "subsequent order" on the drug order form and confirm the cycles for which the drug supply will be used. Subsequent orders require that sites indicate the number of vials currently on site for the patient and this quantity will be considered in each shipment of two cycles of study drug to avoid waste.

   Please note that drug vials are NOT patient specific and may be transferred between patients within an institution.

   Drug Temperature Monitoring

   Upon drug receipt, sites must review the temperature monitor located in the shipping container as outlined in the users manual provided with the shipment.

   If the monitor indicates that drug has reached a temperature outside of the acceptable parameters, place the received drug in quarantine, complete the form in Appendix 18.4 and submit the form and temperature monitor data via e-mail to clinicaltrials@biologicsinc.com or via FAX to 650/266-0135. The temperature profile will be evaluated on the following timelines:

   - Within 24–48 hours for urgent situations (provided all relevant information has been provided).
   - 5 business days for non-urgent situations. Should a formal investigation be required, timelines may increase.

Biologics will notify the site whether the product can be removed from quarantine for clinical use or must be destroyed.

If additional drug shipment is required, contact Biologics at clinicaltrials@biologicsinc.com.

Quarantined Vials

If quarantined product is deemed acceptable for use, Biologics will notify sites. If product is deemed unacceptable for use Biologics will notify sites that vials must be destroyed on site per local procedure, and destruction must be properly recorded the appropriate accountability logs. If the drug destruction is unavailable at the site, contact Biologics at clinicaltrials@biologicsinc.com.

Damaged Vials

In the event that a shipment is received and any vial breakage is observed, notify Biologics by email at clinicaltrials@biologicsinc.com and destroy the entire kit (carton) per local procedures. If drug destruction is unavailable at the site, contact Biologics at clinicaltrials@biologicsinc.com for further instructions.

In the event during storage, that a drug vial(s) is cracked or the seal is disfigured, the damaged vial(s) must be removed from storage, Biologics must be notified, and the vials must be destroyed per local procedures. If drug destruction is unavailable at the site, contact Biologics at clinicaltrials@biologicsinc.com.

2. Drug Handling and Accountability

a. Drug Returns: Unused drug supplies should NOT be returned. Unused drug should be disposed of per local institutional guidelines.

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

Questions about drug orders, transfers, returns, or accountability should be addressed to the Biologics Clinical Trials Department at 800/693-4906.

b. Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF.

3. Drug Disposition Instruction

a. Used vials and expired vials should be destroyed on site per institution SOP and documented accordingly on DARF in a timely manner. Unused vials should be destroyed on site per institution SOP and documented accordingly on the DARF upon study closure and the last enrolled patient has completed treatment.

b. Drug expiration: (If packaging does not have expiration date, check with insert from company when available. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot # and use the drug lots with shorter expiration date first).

3.2 Dexamethasone (Decadron) (NSC-34521)

a. DESCRIPTION

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

b. TOXICOLOGY

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

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

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. Dexamethasone may suppress the body's response to viral and bacterial infections.

Formulation: Dexamethasone is available for injection as follows: EQ 10 mg phosphate/mL, EQ 24 mg phosphate/mL and EQ 4 mg phosphate/mL.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: For this study, the drug is administered by IV.

Supplier: Dexamethasone is commercially available and therefore is to 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.

4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

Multiple Myeloma – normally all three are required, except for circumstances outlined in notes a-c.

Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytoma. [a]

Monoclonal protein present in the serum and/or urine [b]

Myeloma-related organ dysfunction (1 or more from the CRAB list below) [c]

[C] Calcium elevation in the blood (serum calcium > 10.5 mg/L or upper limit of normal)
[R] Renal insufficiency (serum creatinine > 2 mg/dl)
[A] Anemia (hemoglobin < 10 g/dl or 2 g < normal)
[B] Lytic bone lesions or osteoporosis [a]

[a] If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) are the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.
[b] If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
[c] A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

Diagnostic criteria are based on International Myeloma Foundation guidelines (http://myeloma.org/main.jsp?type=article&id=1045).

NOTE: Patients with light chain myeloma are eligible; however, patients with non-secretory disease are not eligible for this study. There are no exceptions to this based on diagnostic criteria in footnote "b" above.

4.2 International Staging System

New International Staging System		
Stage	Criteria	Median Survival (months)
I	Serum β2-microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL	62
II	Not Stage I or III	44
III	Serum β2-microglobulin > 5.5 mg/L	29
There are 2 categories for Stage II: serum β2-microglobulin < 3.5 mg/L but serum albumin < 3.5 g/dL; or serum 3.5 to <5.5 mg/L irrespective of the serum albumin level.		

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 Onstudy Form and submit via Medidata Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 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 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 7, 14 or 28 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 Registration Step 1: Initial Randomization

_____ a. Patients must have a confirmed diagnosis of symptomatic multiple myeloma and must be currently relapsed or refractory. Except where otherwise indicated below that assessment is required within 14 days, all tests for establishing disease status must be completed within 28 days prior to registration and documented on the Baseline Tumor Assessment Form for Multiple Myeloma.

_____ b. Patients must have measurable disease as defined in Section 10.1a within 28 days prior to registration. Patients must have SPEP and UPEP within 14 days prior to registration.

_____ c. Patients must have received at least one prior regimen of chemotherapy for symptomatic multiple myeloma. Patients may not have more than six (6) previous regimens of therapy for the disease. Prior chemotherapy must have been completed at least 21 days prior to registration.

For study purposes, a regimen is defined as follows:

- An anti-myeloma therapy used at the time of initial diagnosis or documented disease progression which is given with the intent to decrease disease burden.
- Any Maintenance therapy used after an Induction should be considered part of that Induction regimen.
- Use of any agent or combination of agents more than once during the patient's disease history for separate documented disease progressions will be counted as separate regimens (e.g., if a patient receives lenalidomide/bortezomib at initial diagnosis and achieves response, but then progresses and receives lenalidomide/bortezomib after progression, these count as 2 separate regimens.)
- In cases of allogeneic or autologous stem cell transplant, the entire Induction + stem cell mobilization + Conditioning + planned Maintenance should be considered one regimen.

_____ d. Patients may not have received any prior carfilzomib treatment.

_____ e. Patients must not be receiving any other concurrent therapy considered to be investigational. Patients must not be planning to receive any radiotherapy (except localized radiation for palliative care). Patients must not be planning to receive any concurrent chemotherapy, immunotherapy, radiotherapy or other treatment with curative intent.

SWOG Patient No. _____

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

_____ f. Patients must have complete history and physical examination within 28 days prior to registration.

_____ g. Patients must have baseline PET scan within 28 days prior to registration. In the event that a patient had a standard of care PET scan prior to providing informed consent, the scan need not be repeated provided that it occurred within the 28 day window. Note that images are submitted centrally for review as outlined in Section 15.1.

_____ h. Patients with non-secretory MM or known primary amyloidosis are not eligible.

_____ i. Patients must be ≥ 18 years of age.

_____ j. Patients must have Zubrod Performance Status 0-2 (see Section 10.6).

_____ k. Patients must not have clinically significant illness including uncontrolled, active infection requiring intravenous antibiotics, New York Heart Association (NYHA) Class III or Class IV heart failure (see Appendix 18.3), unstable angina pectoris, myocardial infarction within the past 6 months, or ≥ Grade 3 cardiac arrhythmias.

_____ l. Patients must have undergone an EKG within 28 days prior to registration.

_____ m. Patients must have an ECHO with ejection fraction ≥ 45% within 28 days prior to registration. .

_____ n. Patients must not have > Grade 2 neuropathy and/or POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

_____ o. Patients must have adequate liver function as evidenced by total bilirubin ≤ 1.5 x upper limit of normal (ULN) and SGOT **and** SGPT ≤ 3 x ULN within 14 days prior to registration.

_____ p. Patients must have adequate bone marrow function as defined by the following within 14 days prior to registration: ANC ≥ 1,000 cell/mm^3 without growth factor support, AND platelets ≥ 50,000 cells/mm^3 for patients who have bone marrow plasmacytosis < 50% or ≥ 30,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥ 50%.

_____ q. Patients must have calculated or measured creatinine clearance ≥ 30 ml/min within 14 days prior to registration.

$$\text{CrCl} = \frac{(140 - \text{patient's age} \times \text{patient's weight in kilograms*}) \times 0.85 \text{ (if female)}}{72 \times \text{patient's serum creatinine**}}$$

* The kilogram weight is the patient weight with an upper limit of 140% of the IBW.

** Actual lab serum creatinine value with a minimum of 0.8 mg/dl.

_____ r. Patients who are known to be HIV+ are eligible providing they meet all of the following additional criteria within 28 days prior to registration:

- CD4 cells ≥ 500/mm^3
- Viral load of < 50 copies HIV mRNA/mm^3 if on cART or < 25,000 copies HIV mRNA if not on cART
- No zidovudine or stavudine as part of cART

Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

SWOG Patient No. _____

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

_____ s. Patients with known Hepatitis B or Hepatitis C infection must have viral load < 800,000 IU/L within 28 days prior to registration.

_____ t. Patients must have baseline skeletal survey to document lytic lesions, osteopenia or compression fracture within 28 days prior to registration.

_____ u. Patients may have received palliative XRT for local disease control with no curative intent. XRT must be completed at least 7 days prior to registration.

_____ v. Patients must be offered participation in specimen submission for translational medicine studies and banking. With patient consent, specimens must be submitted as outlined in Section 15.2.

_____ w. Patients must not be pregnant or nursing due to the teratogenic nature of the study drugs. Women/men of reproductive potential must have agreed to use an effective contraceptive method. A woman is considered to be of "reproductive potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures.

_____ x. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer or any other cancer in situ, 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 three years.

_____ y. Patients or their legally authorized representative 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.

_____ z. As a part of the OPEN registration process (see Section 13.2 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.

SWOG Patient No. _____

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

5.2 Registration Step 2: Crossover

_____ a. Patient must have been eligible for and initially randomized to Arm 1 (low dose carfilzomib), begun Cycle 2 of treatment, and progressed prior to completing 12 cycles of protocol therapy.

_____ b. At least 14 days and no more than 28 days must have elapsed between the last day of treatment on Arm 1 and registration to Arm 3.

_____ c. Patients must have recovered from all non-hematologic toxicities to ≤ Grade 2 and from all hematologic toxicities to ≤ Grade 3 prior to registration.

_____ d. Patients must have begun Cycle 2 (carfilzomib - 27 mg/m^2) and must not have received any dose reduction for toxicity in the last cycle of treatment, immediately preceding progression.

_____ e. Patients must have SPEP and kappa and lambda light chain testing performed within 14 days prior to registration in order to establish baseline measurements.

_____ f. Patients must not have ejection fraction decrease > 10% from baseline (as determined by ECHO), or other ejection fraction decrease accompanied by other clinical signs/symptoms of NYHA Class III or IV heart failure, measured within 28 days prior to registration. If any question exists regarding individual patient eligibility in this situation, contact the Study Chair for determination.

6.0 STRATIFICATION FACTORS

At registration patients will be randomized to receive Dexamethasone + either Low Dose or High Dose Carfilzomib. A dynamic allocation scheme will be used to balance treatment by the following two stratification factors:

1 - 3 prior therapies vs. 4-6 prior therapies.

Refractory to bortezomib vs. not refractory to bortezomib.

7.0 TREATMENT PLAN

For treatment or dose modification questions, please e-mail S1304SC@swog.org and the first available Study Chair will respond. For emergency situations, sites may contact Dr. Sikander Ailawadhi at 904/953-7290, Dr. Muneer Abidi at 313/576-8711 or Dr. Suzanne Lentzsch at 646/317-4840. 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 General Considerations

a. Patients must have creatine kinase (CK), cardiac-specific troponin T (TnT) and/or troponin I (TnI) testing−both TnT and TnI preferred if available, creatine kinase-MB (CK-MB), brain natriuretic peptide (BNP) and/or proBNP performed on Cycle 1, Day 1. See Section 9.0 for additional timepoints. In the event that Cycle 1, Day 1 laboratory tests are resulted and the patient no longer meets one or more of the eligibility criteria, treatment must be held. Laboratory tests and any associated supportive care must be repeated. If the repeat lab results fall within the eligibility criteria, treatment may be resumed. In the event that treatment must be held for ≥ 28 days, the patient must be removed from the protocol.

b. Patients on Arm 1 will receive dexamethasone/low-dose carfilzomib for up to 12 cycles or until progression that occurs after the start of Cycle 2, whichever comes first. If patient progresses after the start of Cycle 2 and prior to completion of 12 cycles, the patient will cross-over and be registered to Arm 3 where they may receive up to an additional 12 cycles of treatment.

c. Results of Day 1 laboratory tests are not required prior to starting treatment for each cycle subsequent Cycle 1 (see Section 7.1a for instructions regarding D1, C1 results). If lab results are abnormal or indicative of adverse events, the treating physician should refer to Section 8.0 for dose modifications, and Response Assessments should be conducted at time of dose modification and as indicated in Section 9.0. If dose modification is not indicated, the physician should otherwise continue treatment at physician discretion.

d. Patients on Arm 2 will receive dexamethasone/high dose carfilzomib for up to 12 cycles, or until progression that occurs after the start of Cycle 2, whichever comes first. If a patient progresses after the start of Cycle 2, the patient will discontinue protocol treatment.

7.2 Pre-Medication

Prior to each dose in Cycle 1, 250-500 mL of intravenous normal saline will be given to reduce the risk of renal toxicity and of tumor lysis syndrome (TLS). An additional 250-500 mL of intravenous fluids as needed may be administered following carfilzomib administration, at the discretion of the treating physician. Intravenous hydration, as needed, may be given in subsequent cycles. Patients should be monitored during this period for fluid overload. Patients should not receive a total of more than 1 liter of intravenous hydration per administration. In the event of patient crossover to Arm 3, Cycle 1 intravenous hydration can be administered at physician discretion.

7.3 Registration Step 1 – Initial Registration (Arms 1 and 2)

a. Carfilzomib Dosing

For both treatment arms of the initial registration (Arms 1 and 2), carfilzomib will be administered at a dose of 20 mg/m^2 for Cycle 1. If tolerated in Cycle 1, the dose will be escalated to 27 mg/m^2 (Arm 1) or 56 mg/m^2 (Arm 2) beginning in Cycle 2 and continued in subsequent cycles. Note: Dose rounding is acceptable at the discretion of the treating physician; this must be documented on the **S1304** Treatment Form.

The carfilzomib dose will be calculated using the patient's actual body surface area at baseline. Patients with a body surface area greater than 2.2 m^2 should receive a dose based upon a body surface area of 2.2 m^2. Dose adjustments do not need to be made for weight changes of less than or equal to 20%.

If a patient experiences any Grade 3 or 4 non-hematologic toxicity or Grade 4 hematologic toxicity in Cycle 1 that is considered to be related to study treatment, the second cycle of treatment will be given with carfilzomib at 20 mg/m^2 prior to escalation to the respective treatment dose for subsequent cycles. If a patient cannot undergo the dose escalation to the treatment dose despite being at 20 mg/m^2 for 2 cycles, they will be removed from protocol therapy.

b. Arm 1 – Dexamethasone + Low Dose Carfilzomib

Agent	Dose	Route	Day	Schedule*
Dexamethasone [b]	20 mg	IV	1, 2, 8, 9, 15, 16	up to 12 cycles
Carfilzomib [a]	20 mg/m^2	IV over 2-10 mins	1, 2, 8, 9, 15, 16	Cycle 1
Carfilzomib	27 mg/m^2	IV over 2-10 mins	1, 2, 8, 9, 15, 16	Cycles 2-12

* Note: 1 cycle = 28 days
[a] See Section 7.3a for Cycle 1 carfilzomib dosing and for dose capping based on BSA.
[b] On all treatment days, dexamethasone will be administered 30 minutes prior to the carfilzomib infusion.

c. Arm 2 – Dexamethasone + High Dose Carfilzomib

Agent	Dose	Route	Day	Schedule*
Dexamethasone [b]	20 mg	IV	1, 2, 8, 9, 15, 16	up to 12 cycles
Carfilzomib [a]	20 mg/m^2	IV over 2-10 mins	1, 2, 8, 9, 15, 16	Cycle 1
Carfilzomib	56 mg/m^2	IV over 30 mins	1, 2, 8, 9, 15, 16	Cycles 2-12

* Note: 1 cycle = 28 days
[a] See Section 7.3a for Cycle 1 carfilzomib dosing and for dose capping based on BSA.
[b] On all treatment days, dexamethasone will be administered 30 minutes prior to the carfilzomib infusion.

7.4 Registration Step – Crossover Registration (Arm 3)

Note that patients who cross over from Arm 1 to Arm 3 must be registered to Step 2 prior to initiation of cross-over treatment on Arm 3.

Agent	Dose	Route	Day	Schedule*
Dexamethasone [b]	20 mg	IV	1, 2, 8, 9, 15, 16	up to 12 cycles
Carfilzomib [a]	56 mg/m^2	IV over 30 mins	1, 2, 8, 9, 15, 16	Cycles 1-12

* Note: 1 cycle = 28 days
[a] For Arm 3, Cycle 1 carfilzomib dosing is not reduced, but given at the full 56 mg/m^2 (see Section 7.3a for dose capping based on BSA).
[b] On all treatment days, dexamethasone will be administered 30 minutes prior to the carfilzomib infusion.

7.5 Supportive Care and Concomitant Medication

a. Antiviral Prophylaxis

All patients should receive antiviral prophylaxis with acyclovir 400 mg orally two times daily (or an equivalent regimen as per institutional guidelines) while they are on study treatment. It is recommended that patients continue antiviral prophylaxis for at least 8 weeks after discontinuing treatment.

b. Pneumocystis Pneumonia (PCP) Prophylaxis

The probability of PCP should be considered based on previous treatments received and prophylaxis should be administered per local institutional guidelines at the discretion of of the treating physician,

c. Concomitant Medication

Any systemic, anti-myeloma therapy or steroids other than those prescribed by the protocol are prohibited while on protocol therapy. Guidelines for selection and use of other concomitant medications should be derived from the carfilzomib and dexamethasone prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study.

d. G-CSF

G-CSF use is allowed in accordance with ASCO guidelines.

e. Bisphosphonates

Bisphosphonate use is allowed per local institutional guidelines at the discretion of the treating investigator.

f. Radiation Therapy

Radiation therapy is allowed per local institutional guidelines at the discretion of the treating investigator ONLY for localized disease symptom control.

g. Additional Monitoring

All patients will undergo EKG, ECHO and cardiac blood marker testing every 12 weeks while on study.

All patients that have evidence of extramedullary progression (EMP) will have a follow-up PET scan at the end of treatment or at the time of achieving VGPR or better, whichever occurs earlier (see Section 15.1).

7.6 Criteria for Removal from Protocol Treatment

a. Progression of disease or symptomatic deterioration (as defined in Section 10.5) **for patients being treated with higher dose (56 mg/m^2) carfilzomib**.

b. Completion of 12 cycles of low dose carfilzomib on Arm 1 or 12 cycles of high dose carfilzomib.

c. Unacceptable toxicity.

d. Patient is unable to dose-escalate to assigned dose (27 mg/m^2 or 56 mg/m^2) after 2 cycles of therapy.

e. Permanent discontinuation of carfilzomib.

f. Treatment delay for any reason > 4 weeks.

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

7.7 Discontinuation of Treatment

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

7.8 Follow-Up Period

All patients will be followed until death or 3 years after randomization, whichever occurs first.

8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 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 experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

c. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

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

e. If carfilzomib must be permanently discontinued the patient will be removed from protocol therapy. See below for specific dexamethasone pre-medication instructions in the event of permanently discontinuing dexamethasone.

8.3 Dose Reductions for Toxicity

a. Carfilzomib

If a patient experiences any Grade 3 or 4 non-hematologic toxicity or Grade 4 hematologic toxicity in Cycle 1 that is considered to be related to study treatment, the second cycle of treatment will be given with carfilzomib at 20 mg/m^2 prior to escalation to the respective treatment dose for subsequent cycles. If a patient cannot undergo the dose escalation to the treatment dose despite being at 20 mg/m^2 for 2 cycles, they will be removed from protocol therapy.

Patients experiencing ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity considered related to carfilzomib will have their treatment held until toxicity has resolved to Grade 2 or better. Supportive care should be administered per local institutional guidelines. When the toxicity has resolved, treatment will resume per the following guidelines:

- If the toxicity is resolved with supportive care prior to the next scheduled dose, carfilzomib treatment will be resumed at the same dose level.
- If the toxicity does not resolve until after the next scheduled dose, carfilzomib will be resumed at the next lower dose level as outlined in the dose reduction table below.

	Arm 1	Arms 2 and 3
Assigned Dose	*27 mg/m^2*	*56 mg/m^2*
Dose Level -1	20 mg/m^2	45 mg/m^2
Dose Level -2	15 mg/m^2	36 mg/m^2

- For patients whose drug toxicity does not resolve to Grade 1 or better (with the use of adequate supportive care) after 4 weeks of holding treatment, or who experience ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity at Dose Level -2 will be removed from protocol treatment.

b. Dexamethasone

In general, dose reduction of dexamethasone is not allowed. However, in the case of Grade 3 or 4 gastrointestinal bleeding, dexamethasone may be discontinued, depending on clinical judgment of the treating physician. In case of dexamethasone discontinuation, premedication guidelines as mentioned below should be used and carfilzomib therapy will continue. For other Grade 3 or 4 toxicities with dexamethasone (including Grade 3 or 4 hyperglycemia despite adequate treatment with anti-hyperglycemic measures including insulin) rather than discontinuing the drug, dose may be reduced by up to 50% if side effects persist despite administration of supportive care per local institutional standards.

If the dexamethasone cannot be administered even at a 50% dose reduction, pre-medication with dexamethasone 4 mg intravenously should be given prior to all doses of carfilzomib during Cycle 1 and prior to all carfilzomib doses during the first cycle of dose escalation to 27 mg/m^2 (Arm 1) or 56 mg/m^2 (Arms 2 and 3) to reduce the incidence and severity of any infusion reactions. Dexamethasone premedication (4 mg intravenously) will be reinstated if these symptoms develop or reappear during subsequent cycles.

8.4 Treatment Modification for Cardiopulmonary Events

Treatment modification for cardiopulmonary events is at the discretion of the treating physician. For the following events, it is suggested that the patient's treatment be held and their removal from protocol therapy should be considered:

a. Decrease in cardiac ejection fraction of 10% from baseline.

b. Development of NYHA Class III or IV heart failure (see Appendix 18.3).

c. Symptomatic cardiac arrhythmias other than isolated atrial fibrillation.

d. Clinically significant cardiac ischemia.

e. Pulmonary function testing is required and chest x-ray is strongly recommended in the event of Grade 3 or 4 dyspnea. The treating physician should consider holding treatment as outlined in Section 8.3; however dose modifications for dyspnea are at the discretion of the treating physician.

8.5 Dose Modifications Contacts

For treatment or dose modification questions, please e-mail S1304SC@swog.org and the first available Study Chair will respond. For emergency situations, sites may contact Dr. Sikander Ailawadhi at 904/953-7290, Dr. Muneer Abidi at 313/576-8711 or Dr. Suzanne Lentzsch at 646/317-4840.

8.6 Adverse Event Reporting

Toxicities (including suspected reactions) that meet the expedited reporting criteria as outlined in Section 16.0 of the protocol must be reported to the Operations Office, Study Chair and NCI via CTEP-AERS, and to the IRB per local IRB requirements.

9.0 STUDY CALENDAR

REQUIRED STUDIES [16, 19]	Pre-Study [2]	Cycle 1				C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	Prog [14]	FU [13]
		W1	W2	W3	W4	W5	W9	W13	W17	W21	W25	W29	W33	W37	W41	W45		
PHYSICAL																		
History and Physical Exam [1]	X	X				X	X	X	X	X	X	X	X	X	X	X		X
Weight and Performance Status	X	X				X	X	X	X	X	X	X	X	X	X	X		
Toxicity Notation	X	X		X		X	X	X	X	X	X	X	X	X	X	X		
LABORATORY STUDIES																		
CBC, Diff, Platelets [3]	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X
Bone Marrow Aspirate/Biopsy [4]	X																X	
Serum β2 Microglobulin	X																	
Complete Metabolic Panel [3,5]	X	X		X		X	X	X	X	X	X	X	X	X	X	X		X
Serum Uric Acid		X		X		X												
CK, CK-MB, and BNP or pro-BNP [6,15]		C1 D1					After C3			After C6			After C9			After C12	X	
Troponin T and/or Troponin I		C1 D1					After C3			After C6			After C9			After C12		
C-reactive protein	X					X	X	X	X	X	X	X	X	X	X	X	X	X
HIV/HepB/HepC Viral Load [7]	X																	

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REQUIRED STUDIES [16, 19]	Pre-Study [2]	Cycle 1				C2	C3	C4	C5	C6	C7	C8	C9	C10	C11	C12	Prog [17]	FU [13]
		W 1	W 2	W 3	W 4	W5	W9	W13	W17	W21	W25	W 29	W33	W37	W41	W45		
X-RAYS AND SCANS																		
Skeletal Survey [8]	X																X	
EKG [9,15]	X						p Tx			p Tx			p Tx			p Tx	X	
FDG-PET Scan [10]	X															X[18]		
ECHO [9,15]	X						p Tx			p Tx			p Tx			p Tx	X	
RESPONSE ASSESSMENT																		
Serum Protein Electrophoresis [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Quantitative Immunoglobulins [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
24 hour Urine for: Total Protein [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
24 hour Urine for: Protein Electrophoresis [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Serum and Urine Immunofixation Electrophoresis [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Serum Free Light Chains [11]	X					X	X	X	X	X	X	X	X	X	X	X	X	X
SPECIMEN SUBMISSION																		
Serum for Banking/Translational Medicine [12]	X																X	
Biopsy and Aspirate for Banking/Translational Medicine [12]	X																X	
Extramedullary Aspirate/Core [12]	X																X	
TREATMENT [14]																		
Dexamethasone		X	X	X		X	X	X	X	X	X	X	X	X	X	X		
Carfilzomib		X	X	X		X	X	X	X	X	X	X	X	X	X	X		

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Click here to view footnotes

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

Footnotes for Study Calendar:

1 To be performed on Day 1 (± 3 days) of each cycle. H&P should include CTCAE Grade assessment of neuropathy.
2 Labs and physical assessment on Cycle 1 Day 1 may be omitted if pre-study labs were performed within 4 days of Cycle 1 Day 1. Results of Day 1 labs are not required prior to starting treatment for each cycle. If lab results do show existence of adverse events, the treating physician should refer to Section 8.0, and otherwise continue treatment at their discretion.
3 Pre-study (within 14 days prior to registration), during Weeks 1 and 3, then every cycle or more often if clinically indicated.
4 Pre-study (within 28 days prior to registration) then as clinically indicated. Aspirate/biopsy is required at progression with patient consent.
5 Including magnesium, phosphate, sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, bilirubin, SGOT/SGPT, calcium, albumin, LDH.
6 To be performed at baseline (Day 1 of Cycle 1), after Cycles 3, 6, 9, and 12 and at completion of treatment for any reason (unless performed within previous 28 days). For patients who cross over, to be performed every 3 cycles based on previous date of measurement.
7 Tests required for patients known to be positive for HIV, HepB or HepC to determine viral load; optional for all others. Pre-study to be done within 28 days prior to registration, if required.
8 Pre-study to be done within 28 days of registration, and at the time of documented disease progression or as clinically indicated.
9 Pre-study (within 28 days prior to registration), then after completion of treatment on Cycles 3, 6, 9 and 12, and at completion of treatment for any reason (unless EKG or ECHO has been performed within previous 28 days). For patients who cross over, to be performed every 3 cycles based on date of previous measurement. Crossover patients do not need to repeat Cycle 1 Day 1 tests, as long as patient is starting Arm 3 treatment within 28 days of prior testing (at time of progression) and the previous test results did not show a significant change from baseline. See Section 15.3 for ECHO imaging information, and Appendix 18.2 for AG Mednet image submission instructions.
10 See Section 15.1 for PET imaging information, and Appendix 18.2 for AG Mednet image submission instructions.
11 Pre-study (within 14 days prior to registration), then on Day 1 (± 3 days) of Cycles 2-12, then monthly until disease progression, at disease progression and at all follow up visits.
12 See Section 15.2.
13 Every 3 months after removal from protocol therapy for up to 3 years after initial registration, or more often if clinically indicated. For study purposes, response assessments (SPEP, immunoglobulins, 24 hour urine, serum/urine IFE, and CRP) are no longer required after progression or removal from trial due to toxicity.
14 See Section 7.0.
15 See Section 8.5 for treatment modification for cardiopulmonary events.
16 Unless otherwise noted, all required studies are to be performed on Day 1 of the treatment cycle.
17 At the time of progression, patients on Arm 1 may cross-over to Arm 3, providing they meet the additional criteria outlined in Section 5.2.
18 For patients with extramedullary progression (EMP), a follow-up PET scan at the end of treatment or at the time of VGPR, whichever occurs earlier, is required. See Sections 15.1 and Appendix 18.2 for requirements.
19 For patients that crossover to Arm 3, return to Cycle 1, Day 1, and follow the same study calendar. Assessments completed at time of progression on Arm 1, do not need to be repeated on Arm 3 (crossover) C1, D1, provided that ANC, platelets, SGOT, SGPT, serum creatinine, SPEP, and lambda light chain assessments are accomplished within 14 days prior to registration to Arm 3. All other assessments may have been accomplished anytime within 28 days prior to registration to Arm 3 (i.e. at time of progression on Arm 1). Note: Per eligibility criterion 5.2b, at least 14 days and no more than 28 days must have elapsed between the last day of treatment on Arm 1 and registration to Arm 3.

10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Response Criteria

Multiple Myeloma:
For the purpose of establishing one set of criteria for both Phase II and Phase III multiple myeloma studies, the following definitions will be used. These definitions are based on the International Uniform Response Criteria for Multiple Myeloma.

a. **Measurable Disease**: Measurable, quantifiable protein criteria must be present. Acceptable protein criteria are:

- Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified by using densitometry on serum protein electrophoresis (SPEP).

AND / OR

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (≥ 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis (UPEP, see Section 10.2.b).

AND / OR

- Bone marrow plasma cells ≥ 30%

OR

- Patients who have both serum M protein levels < 1 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

Oligosecretory and Non-secretory Disease: Patients that do not meet the criteria for measurable disease above will be ineligible for this study.

b. **Objective Status:**

Stringent Complete Response (sCR):
- Meets all of the criteria for Complete Response (CR) and
- normal serum free light chain ratio and
- absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete Response (CR):
- Disappearance of all evidence of serum and urine M proteins on immunofixation electrophoresis studies ***and***
- < 5% plasma cells in bone marrow ***and***
- disappearance of any soft tissue plasmacytomas

Very Good Partial Response (VGPR):
- Meets all of the criteria for Partial Response (PR) ***and***
- Serum and urine M proteins detectable by immunofixation but not on electrophoresis ***or***
- ≥ 90% reduction in serum M protein and urine M protein < 100 mg/24 hrs.

Partial Response (PR):

- If the patient had soft tissue plasmacytomas present at baseline and they were assessed at this disease assessment: ≥ 50% reduction in size of soft tissue plasmacytomas (see Section 10.2.h) ***and***
- If the patient had ≥ 30% plasma cells in bone marrow at baseline and a bone marrow biopsy was done: ≥ 50% reduction in plasma cells ***and***
- ≥ 50% reduction in serum M protein and reduction in urine M protein ≥ 90% or to < 200 mg/24hr ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 50% decrease in the difference between involved and uninvolved serum free light chain levels

Stable Disease (STA):

- Patient does not meet criteria for Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression.

Progression (PROG): **Any one or more of the following:**

- Serum M protein increase ≥ 25% from lowest response level (or an increase of ≥ 1 g/dL if serum M protein was ≥ 5 g/dL at baseline), with an absolute increase of ≥ 0.5 g/dL or
- Urine M protein increase ≥ 25% from baseline (or lowest response level), with an absolute increase of ≥ 200 mg/24 hrs or
- If patient had serum M protein < 1 g/dL, urine M protein < 200 g/24 hrs, and an involved serum free light chain level ≥ 10 g/dL at baseline: ≥ 25% increase in the difference between involved and uninvolved serum free light chain level, with an absolute increase of ≥ 10 mg/dL or
- Bone marrow plasma cell percentage increase ≥ 25% from baseline (or lowest response level), with the absolute plasma cell % ≥ 10% or
- New bone lesions or soft tissue plasmacytomas, or definite increase in size of existing bone lesions or soft tissue plasmacytomas (see Section 10.2.h) or
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to multiple myeloma

NOTE: If a disease assessment indicates that a patient is experiencing a Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression, this should be confirmed by a second disease assessment (see Section 10.3). The second disease assessment may be done at any time.

10.2 Notes

a. "M protein" may also be known by the following synonyms: M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, M-component.

b. Urine M protein measurement is estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24 hour urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

c. Patients with 'measurable disease' in both the serum and urine (serum M protein ≥ 1g/dL and urine M protein ≥ 200 mg/24h) at baseline need to be followed by both SPEP and UPEP for response assessment.

d. Both serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP) must be conducted at timepoints indicated in Section 9.0. Patients with serum M protein ≥ 1 g/dL and/or urine M protein ≥ 200 mg/24h at baseline will be assessed for response based on SPEP and/or UPEP results only. Except for assessment of Stringent Complete Response, serum free light chain (FLC) assay response requirements are only applicable to patients who had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline. A normal serum free light chain ratio is required for all patients for a Stringent Complete Response.

e. To qualify for a Complete Response, both serum and urine immunofixation must be carried out and must be negative, regardless of the size of the baseline M protein in the serum or urine.

f. Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice. Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, and Stable Disease all require no known evidence of progressive or new bone lesions if radiographic studies were performed, but radiographic studies are not required to satisfy these response requirements.

g. The size of the soft tissue plasmacytomas is defined as the sum of the products of the cross-diameters of each plasmacytoma. The size of the bone lesions will be determined in a similar manner. A definite increase in the size is defined as a ≥ 50% increase (and at least 1 cm_2) of this sum.

10.3 Best Response

This is calculated from a sequence of Objective Status (see Section 10.1.b) evaluations

Stringent Complete Response (sCR): An objective status of Stringent Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Complete Response (CR): An objective status of Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Very Good Partial Response (VGPR): An objective status of Very Good Partial Response on at least two sequential disease assessments.

Partial Response (PR): An objective status of Partial Response on at least two sequential disease assessments.

Unconfirmed sCR (UsCR): One objective status of Stringent Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed CR (UCR): One objective status of Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed VGPR (UVGPR): One objective status of Very Good Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed PR (UPR): One objective status of Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Stable / No Response (STA): At least one objective status of Stable at least three weeks after registration, but not qualifying as any of the above. If radiographic studies were performed there should be no known progressive or new bone lesions.

Increasing Disease (INC): First objective status recorded (other than Unknowns or those before three weeks) of Progression, provided this occurs within eight weeks of registration.

Inadequate Assessment. Response Unknown (NASS): Progression greater than eight weeks after registration and either all objective statuses prior to registration are unknown or the only known objective statuses occurred less than three weeks after registration.

10.4 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.

10.5 Progression-Free Survival

From date of registration to date of first documentation of progression or symptomatic deterioration (as defined below), after having received the full-assigned Arm-specific dose of carfilzomib (27 mg/m^2 or 56 mg/m^2), or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

Symptomatic Deterioration: The global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

10.6 Performance Status

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

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 General Overview

The overall goal of this study is to determine and compare the progression-free survival (PFS) of two different doses of carfilzomib in combination with dexamethasone in multiple myeloma (MM) patients with relapsed and/or refractory disease. This study is based on a randomized Phase II design to determine whether the higher dose level of carfilzomib in combination with dexamethasone yields a better outcome as measured by PFS. Patients will be randomly assigned with equal allocation to one of the two dose levels of carfilzomib in combination with dexamethasone. The treatment arm with the lower carfilzomib dose will be denoted Arm 1 and the treatment arm with the higher carfilzomib dose will be denoted Arm 2.

11.2 Sample Size and Power Justification

Sixty-three eligible patients will be accrued to each treatment arm unless undue toxicity is encountered. The study anticipates an accrual of 72 eligible patients per year, based on recent ECOG accrual estimates for intergroup trials in this patient population. Thus 126 patients will be accrued in approximately 1.75 years. The study anticipates accruing an additional 14 patients to account for ineligibilities and withdrawal of consent for a total of 140 patients.

A median PFS of 9 months is anticipated in Arm 1, based on previous trials using this treatment combination in this patient group (Onyx, personal conversations). With 1.75 years of patient accrual and 1.5 years of follow-up 63 patients per arm results in a study with 90% power to detect a hazard ratio of 1.67, which corresponds to an increase in median PFS from 9 months to 15 months in Arm 2, the arm with the higher carfilzomib dose. These calculations are based on a one-sided stratified log rank test at level (alpha) of 0.1 and on the assumption that progressions are exponentially distributed.

11.3 Analysis of Primary Endpoint

Efficacy analysis will be performed on intent to treat basis. Progression-free survival will be assessed in each arm using the method of Kaplan Meier and compared between arms using the stratified long-rank test. Assuming exponential progression-free survival, uniform recruitment of 72 patients a year, an accrual period of 1.75 years and a follow-up period of 1.5 years, 100 progressions are expected to occur within 3.25 years. The analysis for the primary endpoint will be performed after 100 progressions have been observed, but no later than 2 years follow-up of the last patient.

11.4 Interim Analysis for Futility

An interim analysis for futility will be performed after approximately half the number of events has been observed. Based on the alternative hypothesis and the assumption that events are exponentially distributed, 50 progressions are expected to occur within 20 months or one year and 8 months. At this time the 96% confidence interval of the observed hazard ratio will be calculated based on the log-rank statistics. If the alternative hypothesis is within this confidence interval it will be concluded that the alternative hypothesis cannot be rejected and the study will continue as planned; otherwise the rejection of the alternative hypothesis would lead to early termination and the conclusion that dexamethasone in combination with the higher carfilzomib dose (Arm 2) is not better than dexamethasone in combination with the lower carfilzomib dose (Arm 1). The actual decision to terminate the study early will be made by the Data and Safety Monitoring Committee, and will consider toxicity and other endpoints. Since only futility is being tested the significance level alpha is not affected by this interim analysis. Also, the effect on overall power of the study is minimal.

11.5 Analysis of Secondary Endpoints

Secondary efficacy endpoints include response rate (PR or better) and overall survival (OS). All efficacy analyses will be performed on intent to treat basis. The response rate (sCR, CR, VGPR, PR) for each arm will be determined by the number of patients achieving a response as defined in Section 10.3 divided by the number of patients assessed for response in each arm and compared between arms using Fisher's exact test.

The response rate for patients who relapse on Arm 1 and cross-over to Arm 3 will also be determined in order to determine whether response can be re-captured for those patients by increasing the carfilzomib dose.

Overall survival will be assessed in each arm using the method of Kaplan Meier and compared using the stratified log-rank test.

11.6 Translational Medicine/Imaging Endpoints

GEP of the bone marrow plasma cells will be compared to that of an aspirate taken at the site of the EMP. Gene expression data will be log-transformed before any analysis. Exploratory analyses will be performed to examine the underlying distributions using boxplots, density plots, scatter plots, and so on. For differential expression analysis of the two sample types t-tests will be conducted upon tens of thousands of genes simultaneously. False discovery rate (FDR) will be used to control the average false positive proportions among selected genes. Genes will be ranked by their q-value and pathway analysis (www.ingenuity.com) will be conducted upon selected genes to ascertain biological plausibility and relevance to important molecular functionality.

Baseline PET images will be used to determine how many patients present with EMP. It is expected that 10-20% of patients (approximately 16-32 patients) will have EMP. For those patients, a second PET image will be taken when they achieve a VGPR or better, or at the end of their twelfth cycle of treatment, whichever is earlier. This second PET image will help determine response in those patients.

The main focus will be to determine the association of biochemical response with PET response for patients presenting with EMP at baseline. In this context a CR by PET will be defined by the disappearance of all focal lesions and the resolution of EMD. Univariate and multivariate logistic regression will be used to determine the impact of biochemical CR as defined in Section 10.1 on CR by PET. In the multivariate analysis adjustment for standard prognostic factors such as age, albumin, β-2 microglobulin, serum creatinine, CRP and LDH will be included.

In order to evaluate whether there is a difference in the incidence of clinically relevant cardiovascular toxicity, between treatment arms (normal- versus high-dose carfilzomib), where a clinically relevant cardiovascular toxicity is defined as the clinical development of any of the following toxicities per Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0) of Grade 2 or higher: congestive heart failure, dyspnea, edema, or arrhythmia, a decrement in left ventricular ejection fraction on echocardiogram > 10% from baseline (per central review) or to less than 53% absolute, or an increase in global longitudinal strain (GLS) by > 15% from baseline (per central review), the proportion of patients experiencing cardiovascular toxicity at any time while on study will be compared between the two treatment arms. *(33)* Assuming a clinically relevant cardiovascular toxicity rate of 8% in the control arm, a binomial test with a one-sided significance level of 0.1 and 63 eligible patients in each arm has 79% power to detect a difference of 15% between arms. Furthermore, a multivariate Cox Proportional Hazards model estimating time-to-clinically significant cardiovascular toxicity will be developed using a stepwise selection procedure and will consider potentially relevant baseline factors including patient demographic data, comorbid conditions, clinical data, echocardiography and serum biomarkers, where a clinically significant cardiotoxicity is defined as Grade 2 or greater cardiac toxicity per CTCAE v4.0, following subclinical myocardial dysfunction, as defined by abnormalities in LV strain (an increase of GLS > 15%) and/or in serum biomarker levels (NTproBNP, BNP, CKMB, Troponin T, or Troponin I levels that are greater than the upper limit of normal from the reference range of the testing laboratory). All patients who are eligible and who have been assessed for toxicity will be included in the above described analyses. Additionally, the timing and onset of clinically significant cardiotoxicity from the onset of the earliest occurrence of subclinical myocardial dysfunction will be evaluated using cumulative incidence analysis. All patients who are eligible, who have been assessed for toxicity, and who have developed a subclinical abnormality will be included in this analysis.

All these analyses will be exploratory and hypothesis-building as there are not enough patients to perform meaningful hypothesis testing. However, this will be a unique opportunity to study this subset of patients.

11.7 Toxicity Stopping Rule

After 20 patients have been accrued to each arm and treated for at least two cycles of therapy the rate of unacceptable toxicity will be determined in each arm and compared between arms. Unacceptable toxicities in this context are defined as any Grade 3 or higher non-hematologic toxicity or any Grade 4 or higher hematologic toxicity. If the proportion of patients experiencing an unacceptable toxicity is significantly higher in Arm 2 (the arm with the larger carfilzomib dose) than in Arm 1 (the arm with the lower carfilzomib dose) a recommendation will be made to close the study to further accrual. With 20 patients per arm there is at least 83% power to detect a difference of 40% between arms. These calculations are based on the assumption that the number of patients experiencing an unacceptable toxicity as defined above are binomially

distributed and a one-sided significance test of 0.1. The DSMC will be responsible for decisions regarding possible termination and/or early reporting of the study, and any major study amendments.

11.8 Toxicity Monitoring

All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. With 72 patients per study arm, the probability of any particular toxicity can be estimated within ±14% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more within one of the treatment arms is very likely to be observed in at least one patient (probability ≥ 96%).

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

In addition to the above DSMC review, toxicity and accrual monitoring during the randomized Phase II portion will be done routinely by the Study Chair, Study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the Study Statistician and Study Chair. Accrual reports are generated weekly and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Serious Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer and Study Chair monitor toxicities on an ongoing basis.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

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

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet to CTEP.

a. CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>.

For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

b. CTEP Associate Registration Procedures

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.).

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

c. CTSU Registration Procedures

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

1. Downloading Site Registration Documents:

   Site registration forms may be downloaded from the **S1304** protocol page located on the CTSU members' website.
   - Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
   - Click on the Protocols tab in the upper left of your screen
   - Click on the SWOG link to expand, then select **S1304**. Click on the Site Registration Documents link.

2. Requirements for S1304 Site Registration:

   - CTSU IRB Certification (for sites not participating via the NCI CIRB)
   - CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

3. Submitting Regulatory Documents:

   Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

4. Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

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

13.4 Registration Procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is integrated with the CTSU Enterprise System for regulatory and roster data and, at the time of patient registration, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.

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

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. Questions should be directed to the CTEP Associate Registration Help Desk by e-mail at ctepreghelp@ctep.nci.nih.gov.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

  1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

  2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

d. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

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

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

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

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, you must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.gov/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

c. Institutions participating through the Cancer Trials Support Unit (CTSU) please refer to the CTSU Participation Table.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS AFTER INITIAL REGISTRATION (STEP 1):

Submit the following:

S1304 Onstudy Form

FDG-PET and ECHO Images (see Appendix 18.2). Retrospective ECHO image submission will also be requested for all patients.

PET Report

Specimens for TM and Banking (see Section 15.2)

b. WITHIN 14 DAYS FOLLOWING EACH TREATMENT CYCLE:

Submit the following:

S1304 Treatment Form

Adverse Event Form

Follow-up Tumor Assessment Form for Multiple Myeloma

c. AFTER COMPLETION OF CYCLES 3, 6, 9 AND 12 (including crossover to Arm 3):

Submit the following:

S1304 Cardiac Assessment Form

ECHO Images (see Appendix 18.2) (For crossover patients, ECHOs must be submitted every 3 cycles from the date of previous measurement.) Retrospective ECHO image submission will also be requested for all patients.

d. WITHIN 7 DAYS OF ACHIEVING VGPR OR BETTER:

Submit the following:

FDG-PET and ECHO Images (see Appendix 18.2). Retrospective ECHO image submission will also be requested for all patients.

PET Report

e. WITHIN 14 DAYS OF FIRST PROGRESSION/RELAPSE (ARMS 1 AND 2):

Submit the following:

Follow-up Tumor Assessment Form for Multiple Myeloma (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

Specimens for TM and Banking (see Section 15.2)

f. WITHIN 14 DAYS OF CROSSOVER REGISTRATION (STEP 2):

Submit the **S1304** Step 2 Eligibility Form

g. WITHIN 14 DAYS OF SECOND PROGRESSION/RELAPSE (ARM 3):

Submit the following:

Follow-up Tumor Assessment Form for Multiple Myeloma (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse.

Specimens for TM and Banking

h. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the following:

Off Treatment Notice

S1304 Treatment Form

Adverse Event Form

(for patients with extramedullary disease) FDG-PET Image, unless submitted for VGPR (see Appendix 18.2)

ECHO Images (see Appendix 18.2). Retrospective ECHO image submission will also be requested for all patients.

S1304 Cardiac Assessment Form (if ECHO is performed)

i. EVERY 3 MONTHS AFTER OFF TREATMENT FOR UP TO 3 YEARS FROM INITIAL REGISTRATION:

Submit the Follow-up Form

j. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death **and a final** Follow-Up Form (if the patient was off protocol treatment) documenting death information.

15.0 SPECIAL INSTRUCTIONS

15.1 FDG-PET Imaging (mandatory)

A standard FDG-PET scan will be obtained for all patients at the time of study entry and patients who have evidence of extramedullary progression (EMP) will have a second PET scan at the end of treatment or at the time of achieving a VGPR or better response, whichever occurs earlier. Note: The baseline PET scan may have been obtained as part of standard of care (prior to patient informed consent) provided that it was obtained within 28 days prior to registration. The follow up PET scan should occur at least 2 weeks after the last dose of study treatment received.

The funding of the second PET scan will be provided by the sponsor for the first 30 patients. Upon confirmation of receipt of the first 30 scans, a memorandum will be sent investigators advising that no further patients should have PET scans submitted and that sites may remove the extra PET scan from their local consent forms.

Images will be submitted for central review via AG Mednet as outlined in Appendix 18.2 and will be reviewed by the PET Coordinator as outlined in Section 11.6.

Sites should obtain the AG Mednet Desktop Agent at the time of IRB approval (see Appendix 18.2). Note that users must request access for this trial even if AG Mednet is being used for another SWOG trial.

FDG-PET studies will be acquired per standard clinical protocol. All studies will be performed as PET/CT, with inclusion of a dose-optimized CT study for attenuation correction and localization. The following scan parameters will be recorded at each site: administered activity (mCi), localization time (min), and injection site. Scans will include the whole body, from the vertex of the skull to the feet in order to include the entire skeleton.

PET/CT scans will be interpreted qualitatively and semiquantitatively. Qualitative analysis of the baseline PET/CT scans will be performed for the presence, number, and location of sites of medullary and extramedullary disease. Follow up PET/CT scans will be analyzed qualitatively to determine response (CR, PR, SD, PD) as defined by standard criteria. For response assessment, PET/CT studies will also be analyzed semiquantitatively using maximum standardized uptake values (SUVmax) normalized to body weight. Response will be determined based on previously published guidelines whereby >20% decrease in SUVmax is considered indicative of response, and a >30% increase in SUVmax is considered indicative of progression. *(21)* SUV measurements will also be analyzed as a continuous variable and correlated with response. For SUV analysis, up to 5 reference lesions will be selected.

15.2 Translational Medicine and Banking (optional for patient)

Specimens for translational medicine and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division, Lab #201):

a. With patient's consent bone marrow biopsy core specimens must be submitted at the following times (see Section 9.0):

   1. Pretreatment (within 28 days prior to Step 1 registration)

   2. Progression (including second progression for patients who cross over to Arm 3)

b. With patient's consent serum and bone marrow aspirate specimens must be submitted at the following times (see Section 9.0):

1. Pretreatment (within 28 days prior to to Step 1 registration)

2. Progression (including second progression for patients who cross over to Arm 3)

c. Note that in addition to regular aspirate and biopsy core submission, submission of aspirate/core from extramedullary disease site is also required with patient consent.

If extramedullary site specimen is an aspiration, process as if the sample were a bone marrow aspiration. If this is a biopsy, process the sample as if it were a core biopsy of the iliac crest.

d. Specimen collection and submission instructions can be accessed on the SWOG Specimen Submission webpage, (http://swog.org/Members/ClinicalTrials/Specimens/MyelSpecimens.asp).

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

15.3: ECHO Imaging (mandatory)

A standard echocardiogram will be obtained for all patients at 28 days prior to registration, then after completion of treatment on Cycles 3, 6, 9, and 12, and at time of completion of treatment for any reason (unless echocardiogram had been performed within the previous 28 days). For patients who cross over to Arm 3, ECHOs will be performed every 3 cycles, based on the date of previous measurement.

The development of significant cardiotoxicity by echocardiography is defined as a decrease in the LVEF of > 10 percentage points, to a value < 53% (normal reference value for 2 dimensional echocardiography (2DE) or >15% increase in global longitudinal strain (GLS) from baseline.

Images will be submitted for central review at Oregon Health and Science University via AG Mednet (as outlined in Appendix 18.2). De-identified echocardiograms will be copied to CD in standard DICOM format and mailed to the coordinating site for further analysis. Each echocardiogram will undergo 2D speckle-tracking deformation imaging using EchoInsight®, a vendor-independent analysis package. Apical 4-, 3-, and 2-chamber views will be traced manually for calculation of segmental strain and GLS of the left ventricle (LV). The apical view of the right ventricle (RV) will similarly be analyzed for assessment of RV free-wall strain. The parasternal short axis view at the level of the papillary muscles will be analyzed for circumferential and radial strain. Subsequent to strain analysis, each echocardiogram will undergo further analysis for standard 2DE calculation of volumetric LV ejection fraction (LVEF) using the Simpson's biplane method of discs. Right ventricular function will be further quantified using RV fractional area change (FAC), tricuspid annular plane excursion (TAPSE), and RV S' velocity.

ECHO Images will also be subsequently compared to mandatory cardiac monitoring test results, including: EKG, CK, CK-MB, BNP and/or pro-BNP as well as troponin testing that were submitted in accordance with Sections 7.5g and 9.0 at 6 time points for EKG, ECHO, CK, CK-MB, BNP and/or NTpro- BNP (10 in the event of crossover to Arm 3) and 5 time points for troponin testing (9 in the event of crossover to Arm 3).

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.

Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purpose 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 prescribe 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 using the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS web-based application located at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to the SWOG Operations Office by telephone at 210-614-8808 or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

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.

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(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agent(s) used in this study is carfilzomib. 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 Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Carfilzomib

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 or Section 16.1f.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

May 5, 2011

f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Late Phase 2 and Phase 3 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within 5 **calendar days** submit the following to the SWOG Operations Office by fax to 210/614-0006 or mail to the address below:

- 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 Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below also require expedited monitoring for this trial:

- ≥ Grade 3 acute coronary syndrome
- ≥ Grade 3 cardiac arrest
- ≥ Grade 3 heart failure
- ≥ Grade 3 myocardial infarction

NOTE: If any of these events occur at < Grade 3 but are felt to be clinically significant in the judgment of the treating investigator, they should also be reported in an expedited manner.

- Should pregnancy be reported in association with Section 16.1h, any lactation exposure should also be reported.

g. 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.

SWOG requires all secondary malignancies that occur following treatment with an agent under a Non-NCI IND to be reported via CTEP-AERS. Three options are available to describe the event.

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

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

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ae_guidelines.pdf.

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 by fax to 210/614-0006 or mail to the address below:

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

   SWOG
   ATTN: SAE Program
   4201 Medical Drive, Suite 250
   San Antonio, Texas 78229

   NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

h. **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 at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm .

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 FDG-PET and ECHO Image Submission Guidelines

18.3 New York Heart Association Classifications

18.4 Temperature Excursion Disposition Form

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 16.1f of the protocol.

An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

18.2 FDG-PET and ECHO Image Submission Guidelines

a. **Instructions for Electronic Submission of Digital FDG-PET Images via AG Mednet**

Digital images must be submitted electronically via the AG Mednet service provided by SWOG. (Please note that while AG Mednet service is provided by SWOG, SWOG will not be responsible for the cost of the FDG-PET imaging).

b. **Electronic Submission Set-Up**

Upon IRB approval, you can begin the process to use the AG Mednet Desktop Agent. To request access, email agmednetadmin@swog.org and provide the following information:

- Contact Name
- Email Address
- Phone Number
- Site Name
- NCI Site Code
- Address
- Trial Name
- Trial ID
- Date

c. **Registration via the AG Mednet Portal**

1. If your site is qualified to participate in the trial, the SWOG Trial Administrator will invite you to the trial via the AG Mednet Portal. When you are added, you will receive a welcome email notification prompting you to register in the portal: https://portal.agmednet.net.

2. Complete the 3 pages of registration information. This includes creating your own username and password and a challenge question and answer.

3. When you are finished with registration, the portal will display a "Registration Complete" page. At this point you now have access to the trial. After you download the Desktop Agent, you will be able to login with your new username and password. You will also receive a registration confirmation email notification.

d. **Download the Desktop Agent and Login**

All participating sites need to download the AG Mednet Desktop Agent. The AG Mednet Desktop Agent can be accessed from a networked PC with *Java 6 or 7 plugin* installed. This plug-in ensures AG Mednet will run within the web browser. It is likely that you already have Java 6 or 7 installed. If you do not have Java 6 or 7 installed, downloading the Desktop Agent automatically downloads the most recent version of Java.

1. Launch your web browser and type in the following URL. This will download the AG Mednet Desktop Agent to your system: https://portal.agmednet.net/Desktop-Agent.

2. Type in your user name and password.

3. Click “Launch”.

NOTE: This will place an icon on your desktop so, for future submissions, you can click on the “AG Mednet” icon, and it will automatically launch and request your user name and password when clicked.

e. **Submission (DICOM Exam)**

1. Use the buttons to navigate your computer to find an exam to send. You may choose the DICOM-formatted images that you would like to upload, or select the DICOMDIR file to import the entire exam. Click on Import Exam to bring the files into the Desktop Agent.

2. Click on the **Exam List** tab. Click on the “+” sign next to the exam to show the series. Click on the “+” sign next to the series to show the images (i.e. Instances) in that series. Right click on the images to delete them. You may delete single instances/ images, series, or the entire exam.

3. Select the exam you would like to send from the Available Exams. Click on the Assign Exam to Trial button. From the window that appears, click on the Assign Trial button.

4. In the Available Tasks for Selected Exam section, select Pixel De-Identification. Click on Do Task button. Use the cross-hair to select pixels containing patient identifying information. These pixels will be obscured in the de-identified image exam.Click on the De-Identify Images button.

5. Select De-Identification. Click on Do Task button. Instructions for each task appear in the guidance window. Complete the required tasks in the Exam De-Identification window, and then click on the De-Identify button. A progress window will appear and alert you when de-identification is complete.

6. Select Transmittal Form. Click on Do Task button. Complete the form. Mandatory fields are outlined in red. (Note that not all fields are mandatory.) Click on the Print button to print a copy for your records. Complete by clicking on the Save button. A window will alert you when saving is complete.

7. Select Upload Exam, then click on Do Task button. A progress bar will appear in the exam list. Do not exit the Desktop Agent during the upload or exam transfer will be paused. You can click on the 'i' button under Info for information on the exam upload progress.

8. A pop-up window in the Desktop Agent will appear letting you know that the exam has been successfully uploaded. You will also receive an email confirming the exam has been successfully uploaded. The e-mail includes a link for you to view the submission details on the AG Mednet Portal.

*In most cases, a DICOMDIR file will be generated by scanners. However, if this is not the case, please use the “shift” key to manually select all files from the folder where the images are stored. “Import Exam” can then be clicked. The process is then the same as where a DICOMDIR file exists.

Note: The person responsible for activating the desktop agent should be involved in submitting the exams as the Desktop Agent requires specific log-in verification. All questions regarding AG Mednet use should be directed to 888-9AGMEDNET, or support@agmednet.com (1 business day turnaround).

18.3 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

18.4 Temperature Excursion Disposition Form

Instructions: Please complete the form completely and accurately. Return copy of form to clinicaltrials@biologicsinc.com or fax to 650/266-0135.

Site Information:

Site Number:	Date:
PI Full Name:	
Protocol Number:	
Site Name:	
Site Address:	
City:	
State:	Country:
Full Name of Person Reporting Incident:	
Telephone of Person Reporting Incident:	
E-mail of Person Reporting Incident:	
Site contact person (if not the above):	

Temperature Excursion Details:

Study Drug Name:	Shipment Reference No.: (*if excursion occurred in-transit – carrier or depot shipment of reference)*
Lot Number:	Quantity of Vials:

Type of Temperature Excursion	Temperature Excursion Date	Temperature Excursion Duration (hr, min, sec)	Excursion Temperature Extreme Low	Excursion Temperature Extreme High	Monitor/ Temperature Charts Attached?
☐ Storage ☐ Shipment					
☐ Storage ☐ Shipment					
☐ Storage ☐Shipment					

If monitor/chart readings not available – please detail reason:_____

_____

_____

Detailed Site Comments Regarding Incident – (Required)

1. Cause of Excursion:_____
2. When was it identified?:_____
3. Corrective action taken:_____
4. Other additional items:_____

Informed Consent Model for S1304

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	64.9 (targeted above 55)
Flesch-Kincaid Grade Level	8.1 (targeted below 8.5)

- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is

through the SWOG Data Operations Office or directly through the other group), as well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at at *https://pubs.cancer.gov/ncipl/detail.aspx?prodid=P105*or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Testing Two Doses of Carfilzomib with Dexamethasone for Relapsed or Refractory Myeloma

S1304, "A Phase II Randomized Study Comparing Two Doses of Carfilzomib (NSC-756640) with Dexamethasone for Multiple Myeloma Patients with Relapsed or Refractory Disease"

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 multiple myeloma that is either refractory (has not responded to prior treatment) or is relapsed (has come back after prior treatment).

What is the usual approach to my relapsed/refractory myeloma?

To treat relapsed or refractory myeloma doctors usually use the drug dexamethasone with another approved anti-cancer treatment drug.

What are my other choices if I do not take part in this study?

Your other choices may include:

- **You may choose to have the usual approach described above**
- **You may choose to take part in a different study, if one is available**
- **You may choose to get comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.**
- **Or you could decide not to be treated**

Talk to your doctor about your choices before you decide if you will take part in this study.

Why is this study being done?

The purpose of this study is to find out what effects, good and/or bad, adding the drug carfilzomib to regular treatment with dexamethasone has on you and your disease. We would like to compare a higher dose of carfilzomib to the lower dose that is usually used to find out which is better. The lower dose of carfilzomib is approved for treatment of your cancer. The higher dose is experimental. Therefore, carfilzomib is experimental for this study.

How many people will take part in the study?

There will be about 140 people taking part in this study.

What are the study groups?

This study has two main study groups. Group 1 will get dexamethasone with the study drug carfilzomib at the lower dose and Group 2 will get dexamethasone with the study drug carfilzomib at the higher dose.

A computer will randomly put you in a study group. This is done because no one knows if one study group is better, the same, or worse than the other group. Neither you nor your doctor can choose which group you will be in.

One cycle of study treatment lasts 28 days. No matter which group you are in you will get dexamethasone into your vein by IV on Days 1, 2, 8, 9, 15 and 16. Then you will rest on Days 17-28. You will get up to 12 cycles of treatment.

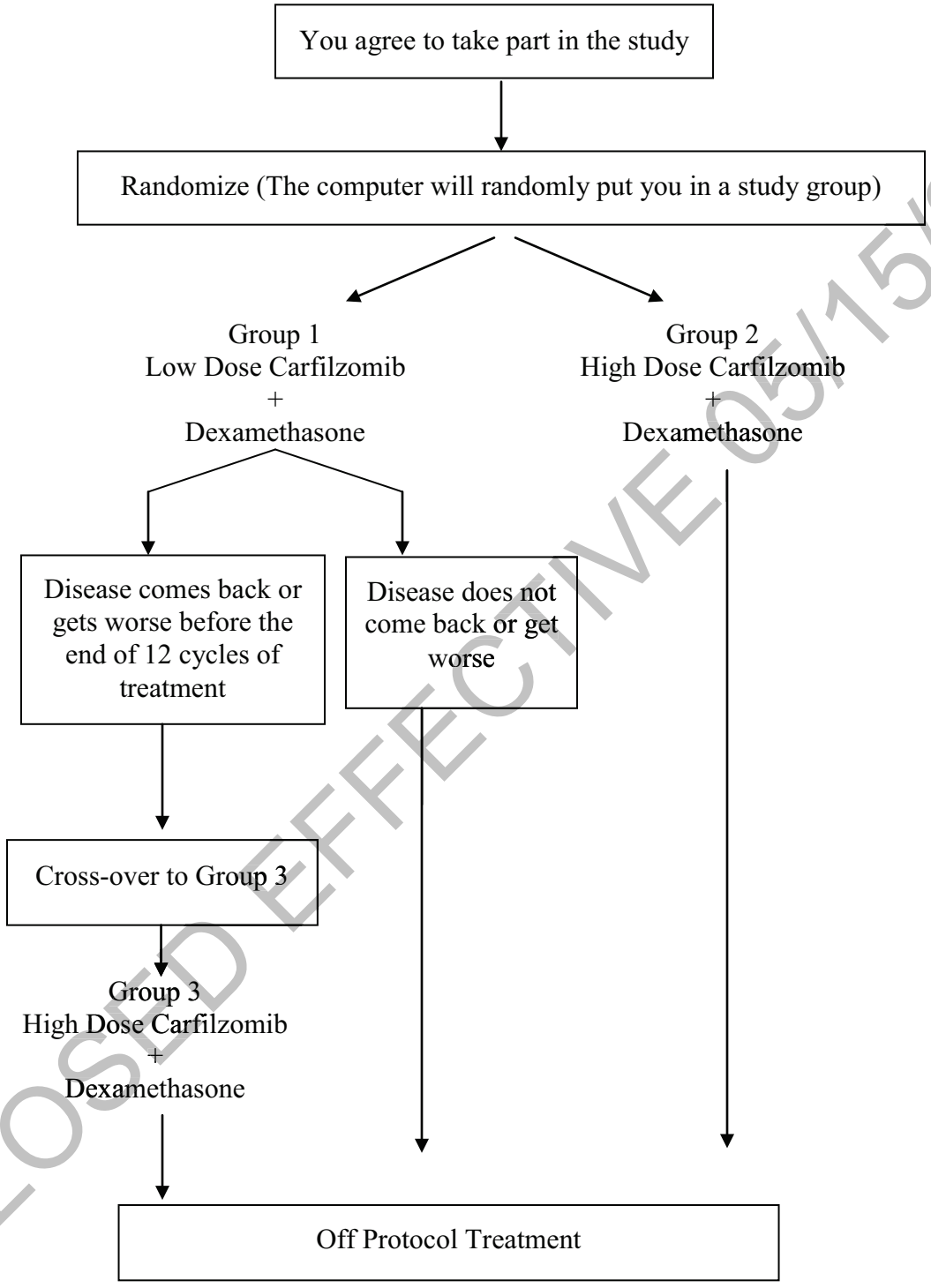
If you are in Group 1 you will get low dose carfilzomib given into your vein by IV on the same days that you get dexamethasone.

If you are in Group 2 you will get high dose carfilzomib given into your vein by IV on the same days that you get dexamethasone.

For both Groups, carfilzomib will be given at a lower dose for the first cycle. The full dose will be given starting with the second cycle if your side effects aren't too great.

If you are in Group 1 getting low dose carfilzomib and your disease comes back or gets worse, your doctor may switch you to high dose carfilzomib instead (Group 3). Treatment for Group 3 will be given just like for Group 2. If you get treatment in Group 3, you could get up to another 12 cycles of treatment with dexamethasone and high dose carfilzomib.

Another way to find out what will happen to you during this study is to read the chart below. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in this study?

The amount of time you will be on treatment depends on which study group you are in and how your disease responds to treatment. For both groups, you will be asked to take the dexamethasone and carfilzomib for up to 12 months. If you are in Group 1 (low dose carfilzomib + dexamethasone) you will be asked to take the study treatment at a higher dose for up to an additional 12 months if your disease starts to come back or get worse. After you are finished taking study treatment, the study doctor will ask you to visit the office for follow-up exams for 3 years from the time you started treatment. At the follow up visits you will have a physical exam, blood tests, and urine tests. Your doctor may give you other tests or procedures if they think they are needed.

What extra tests and procedures will I have if I take part in this study?

Before you start the study:

You will need to have the following extra tests to find out if you can be in the study:

- Blood tests to check the heart

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 extra tests and procedures. They are not part of the usual approach for your type of cancer.

During the study:

- PET scan (to check for fractures and spots of myeloma in your body) after you finish treatment. *(4/23/14)*
- EKG and ECHO and blood tests to check the heart after Cycles 3, 6, 9, and 12 and/or when you finish treatment

What risks can I expect from taking part in this study?

If you choose to take part in this study, there is a risk that you may:

- **Lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **Be asked sensitive or private questions which you normally do not discuss**

The treatment used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**

- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

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

Study Group 1 and Group 2 will both get treated with dexamethasone and carfilzomib.

Possible Side Effects of Dexamethasone

COMMON, SOME MAY BE SERIOUS In 100 people receiving dexamethasone, more than 20 may have:
• **Sores or ulcers in the stomach and throat. If you already have sores or ulcers they may get worse.** • **Inflammation of the pancreas** • **Weight gain around the stomach** • **Puffiness (especially in the face)** • **Retaining of salt and fluids which could cause an increase in blood pressure** • **A possible rise in the blood sugar, and problems with the level of potassium in the blood** • **Muscle weakness** • **Brittle bones** • **Menstrual changes** • **Mood swings** • **Depression** • **Trouble with sleeping** • **Changes in personality** • **Increased risk of infections** • **Increased risk of blood clots**

OCCASSIONAL, SOME MAY BE SERIOUS
In 100 people receiving dexamethasone, from 4 to 20 may have:
• **Itching, and other allergic reactions (including severe allergic reactions)** • **Convulsions, and dizziness.**

POSSIBLE, SOME MAY BE SERIOUS
• **If you are more prone to heart disease, you may experience heart failure.** • **Dexamethasone may interact with several medications. Please be sure to tell your study doctor of any other medicine, including over-the-counter medicines, vitamins, and herbal products that you may be taking. Vaccines may not work as well while you are using dexamethasone. You should talk with your doctor before getting flu shots or other vaccines.**

Possible Side Effects of Carfilzomib

COMMON, SOME MAY BE SERIOUS
In 100 people receiving carfilzomib, more than 20 may have:
• **Anemia which may require blood transfusion** • *(moved to Occasional, Some May be Serious 7/27/15)* • **Lower number of blood cells that help to clot blood** • **Constipation, diarrhea, nausea, vomiting** • **Tiredness** • **Fever** • **Infection of the upper respiratory tract** • *(deleted 4/6/15)* • *(added 12/22/14)(moved to Occasional, Some May be Serious 7/27/15)* • **Headache** • **Cough** • **Shortness of breath** • **Swelling of arms and/or legs**

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving carfilzomib, from 4 to 20 may have:

- **High or low blood pressure** *(updated 12/22/14)*
- **Inability of the heart to adequately pump blood to supply oxygen to the body** *(added 7/27/15)*
- **Chest pain** *(added 7/27/15)*
- **Loss of appetite**
- **Weakness**
- **Chills**
- **Rash, itching dry skin, redness of the skin, excessive perspiration** *(added 12/22/14) (updated 4/6/15)(updated 7/27/15)*
- **Pain, including: joint pain, pain in arms and/or legs, abdominal pain, back pain, muscle pain** *(updated 7/27/15)*
- **Lung/respiratory tract infection** *(updated 12/22/14)*
- *(removed 7/27/15)*
- **Muscle spasms and weakness** *(updated 4/6/15)(updated 7/27/15)*
- **Dizziness**
- **Difficulty sleeping or falling asleep**
- **Numbness, tingling, burning sensations** *(updated 7/27/15)*
- **Kidney failure which can lead to dialysis**
- **Anxiety**
- *(removed 7/27/15)*
- **Blurred vision** *(updated 4/6/15)*
- *(removed 7/27/15)*
- **Urinary tract infection** *(added 12/22/14) (updated 4/6/15)*
- **Kidney failure or impairment** *(added 12/22/14)*
- *(removed 7/27/15)*
- **Dehydration** *(added 4/6/15)*
- **Bronchitis** *(added 7/27/15)*
- **Nose bleed** *(added 4/6/15)*
- **Increased or decreased blood levels of sugar, potassium or calcium** *(added 4/6/15)(updated 7/27/15)*
- **Decreased blood levels of phosphate, magnesium, sodium, or a blood protein called albumin** *(added 4/6/15) (updated 7/27/15)*
- **Lower number of white blood cells that help fight infection** *(added 7/27/15)*
- **Increased blood level of creatinine (a substance normally eliminated by the kidneys in the urine)** *(added 4/6/15)*
- **Increased blood level of uric acid, a waste material from food digestion** *(added 3/12/15)*
- **Increased blood level of liver enzymes** *(added 3/12/15)*

RARE, AND SERIOUS

In 100 people receiving carfilzomib, 3 or fewer may have:

- **Fever with low white blood cell count** *(added 12/22/14)*
- **Reduced blood flow to the heart or loss of some of the heart's function** *(moved to Occasional, Some May Be Serious and re-worded 7/27/15)*
- **Heart attack**
- **Heart weakness that leads to build up of fluid in the lungs and surrounding body tissues**
- **Inflammation (swelling and redness) of the sac around the heart** *(added 12/10/2015)*
- **Fluid in the sac around the heart** *(added 12/10/2015)*
- **Extremely high blood pressure, severe chest pain, severe headache, confusion, blurred vision, nausea, vomiting, or severe anxiety, which may be signs of a condition known as hypertensive crisis** *(added 7/27/15)*
- **Build up of fluid in the lungs, scarring of lung tissue, inflammation of the lungs, or sudden failure of the respiratory system that prevents oxygen from getting into the lungs and blood that may be life-threatening** *(updated 7/27/15)*
- **High blood pressure of the blood vessels in the lungs**
- **Liver failure**
- **Hole in the stomach or bowel** *(added 12/10/2015)*
- **Rapid tumor breakdown as a consequence of therapy which can cause salts and the uric acid in the blood to rise quickly and can be life-threatening**
- **Bacterial infection in the bloodstream or body tissues**
- **Bleeding within the skull**
- **Blood clots in the legs or lungs**
- **Infusion reactions (which can occur during or shortly after carfilzomib infusion), including flushing or feeling hot, fever, shakes, nausea, vomiting, weakness, shortness of breath, swelling of the face, pain in the muscles or joints, tightness or pain in the chest, and low blood pressure**
- **Allergic reaction including total body rash, hives, and difficulty breathing**
- *(deleted 4/6/15)*
- **Tiredness, infection, and easy bruising or bleeding which may be symptoms of a blood condition known as Myelodysplastic syndrome/Acute Myeloid Leukemia (MDS/AML)** *(updated 7/27/15)*
- **Irregular heartbeat, kidney failure or abnormal blood test results which may be associated with Tumor Lysis Syndrome, which can be caused by the rapid breakdown of tumor cells.** *(added 7/27/15)*
- **Posterior reversible encephalopathy syndrome (PRES): abnormal changes in the brain that can cause a collection of symptoms including headache, confusion, seizures, and vision loss, and is associated with MRI findings** *(added 12/22/14)*
- **Cataract** *(added 4/6/15)*
- **Bleeding, bruising, weakness, confusion, fever, nausea, vomiting and diarrhea, and acute kidney failure, which may be signs of a blood condition known as Thrombotic Microangiopathy (including Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome (TTP/HUS)** *(added 7/27/15)*

RARE, AND SERIOUS In 100 people receiving carfilzomib, 3 or fewer may have: (contd.)
• **Failure of multiple organs** *(added 4/6/15)* • **Stroke (or lack of blood flow to an area of the brain)** *(added 7/27/15)* • **Flu-like symptoms** *(added 7/27/15)* • **Loss or impairment of your voice** *(added 4/6/15)* • **Toothache** *(added 7/27/15)* • **Increase in a protein called c-reactive protein, which is a substance produced by the liver that increases inflammation throughout the body** *(added 4/6/15)* • *(added 4/6/15)(removed 7/27/15)*

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: You should not get pregnant, breastfeed, or father a baby while in this study. The drugs used in this study could be very damaging to an unborn baby. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study.

Will I benefit from this study?

Taking part in this study may or may not make your health better. While doctors hope this study will be more useful against cancer compared to the usual treatment, there is no proof of this yet. *(4/23/14)* We do know that the information from this study will help doctors learn more about this study as a treatment for cancer. This information could help future cancer patients. *(4/23/14)*

Can I stop taking part in this study?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest
- If new information becomes available
- If you do not follow the study rules
- If the study is stopped by the sponsor, IRB or FDA

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

The carfilzomib will be supplied at no charge while you take part in this study. The cost of getting the carfilzomib ready and giving it to you is not paid by the study sponsor so you or your

insurance company may have to pay for this. It is possible that the carfilzomib may not continue to be supplied free while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

The blood tests to check the heart throughout the study, the EKGs, the ECHOs throughout the study and the extra PET scan (if needed) will be paid for by the study sponsor. *(added 4/23/14) (updated 12/22/14) (updated 3/12/15)*

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of managing any side effects. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

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.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. There are organizations that may inspect your records. These organizations are required to make sure your information is kept private. Some of these organizations are:

- The study sponsor and any drug company supporting the study.
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study,
- The Food and Drug Administration and the National Cancer Institute in the U.S., and similar ones if other countries are involved in the study.
- The Cancer Trials Support Unit (CTSU), a service sponsored by the NCI to provide greater access to clinical trials. *(added 3/12/15)*

- SWOG *(added 3/12/15)*
- The Alliance for Clinical Trials in Oncology *(added 3/12/15)*
- The ECOG-ACRIN Cancer Research Group *(added 3/12/15)*
- NRG Oncology *(added 3/12/15)*
- The NCIC-CTG/NCIC Clinical Trials Gorup *(added 3/12/15)*
- AG Mednet, the service that will transmit your PET/ECHO images *(updated 12/10/2015)*

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

Where can I get more information?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

This section is about optional studies you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. You will not get health benefits from any of these studies. The researchers leading this optional study hope the results will help other people with cancer in the future.

The results will not be added to your medical records, nor will you or your study doctor know the results.

You will not be billed for these optional studies. You can still take part in the main study even if you say 'no' to any or all of these studies. If you sign up for but cannot complete any of the studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

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. Optional Sample Collections for Laboratory Studies and/or Biobanking for Possible Future Studies

Researchers are trying to learn more about cancer, diabetes, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems.

Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect bone marrow biopsy and aspirate for research on how the genes in your myeloma change.

The researchers also ask your permission to store and use your samples and health information for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking". The Biobank is being run by SWOG and supported by the National Cancer Institute.

WHAT IS INVOLVED?

If you agree to take part, here is what will happen next:

1) About 4 teaspoons of bone marrow aspirate and 1-2 inches of biopsy core will be collected (usually from your hip) at the same time as the bone marrow taken to test your disease before treatment and if your disease comes back or gets worse. If you have myeloma in other areas of your bones your doctor will also take a tissue sample from that spot. About 2 teaspoons of blood will also be taken (usually from your arm).
2) Your blood and bone marrow will be used in one or both of the following ways, depending on what you choose.
   a) Your sample and some related information will be sent to a researcher for use in the genes study described above.
   b) If there is blood or bone marrow left after these tests, your blood or bone marrow and some related information may be stored in the Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up.

3) Qualified researchers can submit a request to use the materials stored in the Biobanks. A science committee at the clinical trials organization, and/or the National Cancer Institute, will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
4) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
5) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

WHAT ARE THE POSSIBLE RISKS?

1) The most common risks related to drawing bone marrow are back pain, tiredness, stiffness, and bleeding at the collection site. There are also rare side effects from the anesthesia that your doctor will discuss with you.
2) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
3) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
4) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

HOW WILL INFORMATION ABOUT ME BE KEPT PRIVATE?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your samples are sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. Any Biobank and SWOG staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom SWOG sends your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

WHAT ARE THE POSSIBLE BENEFITS?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

ARE THERE ANY COSTS OR PAYMENTS?

There are no costs to you or your insurance. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

WHAT IF I CHANGE MY MIND?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used. Samples or related information that have already been given to or used by researchers will not be returned.

WHAT IF I HAVE MORE QUESTIONS?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option (*include only applicable questions)*:

SAMPLES FOR FUTURE RESEARCH STUDIES:

My samples and related information may be kept in a Biobank for use in future health research.

YES NO

This is the end of the section about optional studies.

My Signature Agreeing to Take Part in the Main Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the main study and any additional studies where I circled 'yes'.

Participant's signature (or authorized legal representative) _____

Date of signature_____

Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).