Distribution Date: January 1, 2012  
DCP Submission Date: December 6, 2011

TO: PARTICIPANTS: ALL SWOG MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; ALSO, CTSU PARTICIPANTS AT CCOP INSTITUTIONS THAT ARE NOT AFFILIATED WITH SWOG AND NON-CCOP INSTITUTIONS AT ALBERT EINSTEIN CANCER CENTER, LEHIGH VALLEY HOSPITAL AND ST FRANCIS CANCER TREATMENT CENTER (for these institutions, patient enrollments will be conducted via the NCI Cancer Trials Support Unit [CTSU] and all data will be sent to the SWOG Data Operations Center as specified in the CTSU logistical Appendix 19.6.)

FROM: Kimberly F. Kaberle, Protocol Coordinator


REVISION #7

Study Coordinator: Catherine Van Poznak, M.D.  
Phone number: 734/936-9209  
E-mail: cvanpoz@med.umich.edu

IRB Review Requirements

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

( √ ) Expedited review allowed
(   ) No review required

REVISION #7

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

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

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

1. Title page: “Southwest Oncology Group” has been updated to “SWOG” above the title and in the participants list. The version date has been updated.
2. Section 7.2a, Page 10: In the formula, the units for serum creatinine have been corrected from "mg/mL" to "mg/dL".

3. Section 7.5d, Page 12: In the last sentence the references to Section 15.1d and 15.1e have been updated to 15.1e and 15.1f, respectively.

4. Section 7.5f, Page 12a: In the last sentence of the second paragraph, the reference to Section 15.1d has been updated to 15.1e.

5. Section 14.4e, Page 20: The references to Section 15.1d and 15.1e have been updated to 15.1e and 15.1f, respectively.

6. Section 14.5, Page 20: The reference to Section 15.1d has been updated to 15.1e.

7. Section 14.7, Page 20: The reference to Section 15.1d has been updated to 15.1e.

8. Section 15.1a, Page 21: References to “University of Colorado” have been removed. In the last sentence of this section, “SWOG Specimen Repository” has replaced “University of Colorado”.

9. Section 15.1b, Page 21: This section has been added to include a link to the SWOG specimen submission website. Subsequent sections have been renumbered accordingly.

10. Section 15.1c, Page 21: “Southwest Oncology Group Solid Tissue Bank” has been replaced with “SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division.” The contact information for Miguel Martinez has been removed and replaced with contact information for Filiz Muharrem.

11. Section 15.1f, Page 22-24: The previous section containing general specimen submission instructions has been deleted as all specimen submission instructions can be found on the SWOG specimen submission website referenced in Section 15.1b.

12. Model Consent Form, Page 33: This page contained two places where a change was made on “6/3/11”, this was a typographical error and has been corrected to “8/24/11”.

13. Model Consent Form, Pages 38 and 43: The location for the Solid Tumor Specimen Repository has been removed.

14. Section 19.6, Page 73: In the last bullet under “Registration/Randomization”, the reference to Section 15.1b has been changed to 7.5b2.

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

cc: Frank L. Meyskens, Jr., M.D. Joe Unger, M.S. 
Catherine Van Poznak, M.D. Danika Lew, M.A. 
Julie Gralow, M.D. Stephanie Edwards 
Mark M. Schubert, D.D.S., M.S.D. Laura Cannon – AG Mednet 
Robert A. Bagdarian, D.D.S., M.Ph., Ph.D. Kristen White – Novartis 
Lisa Hansen, R.N., M.S. Joseph Ciacciarelli – Novartis
Experience with both the ongoing enrollment to S0702 and recently reported results of other clinical trials have prompted revisions to S0702 to improve both accrual and representation of the prescribing habits of osteoclast inhibiting therapy by the medical community across the country.

Eligibility requirements have been modified to capture actual clinical practice across a representative cross-section of patients without imposing selection bias toward those with better dental care habits. Hence, the baseline dental exam is no longer mandatory, but
recommended in accordance with good medical practice. In addition the protocol has increased the amount of prior osteoclast inhibitor permitted prior to enrollment and this revision specifically addresses the newly FDA approved osteoclast inhibitor, denosumab. A revision of the study sample size was made based on ONJ data generated from prospective Phase III clinical trial adverse event reporting of ONJ which permits the patient sample size to be reduced from 7,000 to 3,500 patients. These changes, and others are outlined below and can be seen in the protocol, the appendices, Model Consent Form, and the case report forms.

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

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

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

The above-referenced protocol has been revised as follows:

**Fast Fact Sheet:** In the treatment section, changed "will" to "are advised to" for undergoing a dental evaluation every 6 months. Clarified 2nd eligibility box to state "Planned zoledronic acid treatment for metastatic bone disease." Clarified eligibility criteria, to be consistent with Section 5.0, for previous osteoclast inhibitor therapy for osteoporosis and metastatic bone disease (third and fourth eligibility points). The 90 day ibandronate, pamidronate, and zoledronic acid requirement has been changed to 180 days in the eligibility and ineligibility sections. The dental exam and dental imaging have been moved from "Prestudy Requirements" to "Prestudy Optional" and are now recommended. Added maximum number of previous bisphosphonate doses as "10", maximum number of total denosumab doses as "8", and maximum number of combination of IV bisphosphonates and denosumab as "12". Added denosumab to points 3 and 4 of eligibility and point 3 of ineligibility sections. Changed requirements for history and physical exams and Good Medical practice tests from "28" days to "42".

**Title page:** The title page reflects the current version date of 8/24/11. Specific non-CCOP CTSU institutions have been listed in the participants section.

**CTSU Information, Page 2a:** The following sentence has been removed: This trial is only available to CCOP Institutions.

**Schema, Page 3:** "Baseline Forms (Dental Contact Form, Dental Assessment Form)" has been removed from the Schema. The assessment is recommended, but submission of the forms is still required. "Baseline exam" has been updated to "Baseline Assessments".

**Section 2.0, Pages 4-5:** Added statement to second paragraph of Page 4 to clarify that FDA approved osteoclast inhibiting therapies include bisphosphonates and denosumab. Added background information on denosumab to Page 5. Updated reference numbers that were affected by additional references in bibliography.
Section 2.0, Pages 6-7: On Page 6, updated information about results from AZURE trial that were presented in December 2010. Added a paragraph above the "Study Population" section to include information about arrhythmias related to zoledronic acid treatment. Changed wording from "bisphosphonates" to "bisphosphonate therapy" and "bisphosphonates" to "osteoclast inhibitor" in the first paragraph of the study population section. In the third paragraph under "Study population", changed "starting" to "treated with" zoledronic acid. Updated last paragraph of the study population section from "bisphosphonate guidelines" to "ONJ guidelines". Included additional background information on denosumab in paragraphs 3 and 4 on Pages 6 and 7. Updated "Intravenous bisphosphonate" to "osteoclast inhibitor" in the correlatives section on Page 7. Updated reference numbers that were affected by additional references in bibliography.

Section 5.2, Page 8: Updated eligibility requirement to clarify that patients must be planning to receive zoledronic acid for metastatic bone disease within 30 days after registration. Updated wording from "bisphosphonate" to "osteoclast inhibition". Updated note to include maximum total doses of previous osteoclast inhibiting therapy, prior denosumab and combination treatments. An additional note was added to clarify that patients who have had osteoclast inhibiting therapy administered in doses used for metastatic bone disease or greater than the parameters set in this section are not eligible.

Section 5.2a, Page 8: Added header to clarify that criterion is related to prior osteoclast inhibition for low bone mass (osteoporosis or osteopenia). Added denosumab as drug patients may have previously received. Updated wording from "bisphosphonate" to "osteoclast inhibiting".

Section 5.2b, Page 8: Added header to clarify that criterion is related to prior osteoclast inhibition for metastatic bone disease (tumor involving bone). Added denosumab as drug patients may have previously received. Updated wording from "bisphosphonate" to "osteoclast inhibiting". The 90 day ibandronate, pamidronate, and zoledronic acid eligibility criterion has been changed to 180 days.

Section 5.2c, Page 8: This section has been removed and replaced with the following statement: "Prior osteoclast inhibiting therapy at higher dosing than outlined above at any time prior to registration is not allowed."

Section 5.9, Page 9: This section has been removed as the baseline dental exam is no longer a requirement; it has been moved to Section 7.2d (Page 10) with updated wording indicating assessment is recommended, not required. A reference to Section 14.4 has been added. Subsequent sections have been renumbered accordingly.

Section 7.2, Page 10: Updated to clarify that tests in the Good Medical Practice section are recommended and minor deviations from normal limits are acceptable if they do not affect patient safety. The tests are now recommended within 42 days instead of 28, or as specified.

Section 7.2a, Page 10: Changed the ">" symbol to "<" before 265 mcmol/L for serum creatinine.

Section 7.2d, Page 10: This section has been added to include information about the recommended dental exam. Subsequent sections have been renumbered accordingly.

Section 7.3, Page 10: The following sentence was added to provide clarification "Participants must be planning to receive zoledronic acid within 30 days of registration, but will not be made ineligible if other osteoclast inhibiting therapy is used or if osteoclast inhibiting therapy is delayed beyond 30 days."
Section 7.4, Page 10: The baseline dental exam is now recommended. This section has been moved to Page 11. A reference to Section 7.5e has been added.

Section 7.4, Page 11: Updated throughout to clarify that assessments are recommended and forms submissions are required.

Section 7.5a, Page 11: Added the following statement to the first paragraph: As per the zoledronic acid packet insert "patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates." Updated wording from "bisphosphonate" to "osteoclast inhibiting" in second paragraph. Updated reference numbers that were affected by additional references in bibliography. Updated fourth paragraph to clarify that the dental exam is recommended but not required. Updated the last sentence in the second paragraph to state: "Patients without dental care may participate in the study at the discretion of the clinical investigator" (previously non-compliant patients).

Section 7.5b.2, Pages 11-12: Added "When the patient has identified their oral health provider, then" to the beginning of this section. The fourth bullet has been un-nested for clarity. A note has been added to include information about regulatory requirements for patients who do not receive the recommended dental exam.

Section 7.5b.3, Page 12: A third bullet was added to instruct how to indicate if an evaluation was not performed by a dental professional on the case report forms.

Section 7.5b.4, Pages 12-13: This section has been changed to 7.5c. Subsequent sections on Pages 12-13 have been renumbered accordingly. The wording "(if available)" has been added to the first sentence.

Section 7.5e, Pages 12-12a: In first paragraph, updated to clarify that patients must be planning to receive zoledronic acid for metastatic bone disease. The reference to Section 5.11 has been changed to 5.10 due to renumbering in the eligibility section. For clarification, added the statement: "This study does not dictate subsequent osteoclast inhibiting therapy." In second paragraph, removed first sentence that states "Patients must be followed every 6 months for 3 years" and added information about filling out data forms for patients who did not receive a dental exam. In the last sentence of the third paragraph "Section 7.5e" has changed to "Section 7.5f". Information from Page 12 has been displaced to Page 12a. Added fourth paragraph to clarify that the Medical Assessment Form must be submitted at the required intervals.

Section 7.5f, Page 12a: Clarified in first and fourth sentences of the first paragraph that the dental assessment is recommended and clinical medical assessments are required. Instructions on how to fill out the ONJ Assessment form when patient is diagnosed with ONJ but has not seen a dentist have been added.

Section 7.5g, Page 13: Added paragraph to clarify when Medical Assessment Form is to be submitted for patients with suspected ONJ.

Section 7.5h, Page 13: This section has been added to include information on coordination of clinical and study visits. Subsequent sections have been renumbered accordingly.
Study Calendar, Page 14: The "β" footnote has been updated to reflect that the dental exam is recommended. "Required" has been changed to "recommended", and "imaging" was added in the "α" footnote. The "α" footnote was added to the prestudy column of the Dental Imaging row. The "Δ" footnote was updated to include "or to note that no dental provider is currently involved" at the end. Footnote "§" was added to clarify data submission and assessment timepoints for history and physical exam.

The "§" footnote indicates that the data is to be submitted on schedule (every 6 months) as outlined above. Physical exams are to be performed as clinically indicated, regardless as to whether this corresponds to a data submission timepoint. The forms are to be completed using the data collected at the time of the forms being due. Clinical (medical and dental) assessment intervals are not dictated by this study. Subsequent clinical assessments will be captured on subsequent CRFs.

Section 10.1, Page 15: "Bisphosphonate associated" has been removed from the last sentence of the paragraph about a suspected case of ONJ.

Section 11.0, Pages 15-17: Updated to include new statistical information for the new patient sample size of 3,500. Updated reference numbers that were affected by additional references in bibliography.

Section 11.1, Page 15: Clarified second sentence by adding "planning to receive" before zoledronic acid.

Section 11.4, Page 17: Updated feasibility information based on accrual changes in this revision.

Section 13.1, Page 18: Updated wording from "bisphosphonate" to "osteoclast inhibiting".

Section 13.3a, Page 18: Updated SWOG Operations Office phone number.

Section 14.3a, Page 19: Updated SWOG Operations Office phone number.

Section 14.4, Page 19: Changed submission requirements from 14 days to 7 days.

Section 14.5, Page 20: Updated wording from "bisphosphonate" to "osteoclast inhibiting".

Section 15.1a, Page 21: Updated to clarify that "with patient's consent, blood specimens must be submitted...". (Previously stated, "Blood specimens will be submitted...")

Section 15.1b, Page 21: Updated contact e-mail for Miguel Martinez.

Section 15.1f.1, Page 23: Updated contact e-mail for Miguel Martinez.

Section 15.2a, Page 24: The number of patients that will be registered to this study has been reduced from 7,000 to 3,500.

Section 15.2e, Page 25: This section has been added to include information about the process for submitting imaging if a patient is selected as a control.
Section 17.0, Pages 28-28a: References 17, 18, 33, and 34 have been added. Subsequent references have been renumbered accordingly. Page 28a was added to prevent extensive repagination.

Model Consent form, Page 32: Removed "are currently receiving or" from the last sentence in the second paragraph. In the "Why is this study being done?" section, added statement to clarify the type of cell affected by bisphosphonates. The number of patients for this study has been changed from 7,000 to 3,500 in the "How many people will take part in this study?" section.

Model Consent form, Page 33: In the "Before you begin the study..." section, the dental history and exam have been labeled as optional. Medical history and physical exam have been combined into one bullet. Optional blood work for research has been added to the list. A statement has been added to the last paragraph of this page to include that medical and dental history will be submitted with dental x-rays and scans. The second bullet of the "During the study" section has had "with zoledronic acid" removed, and the timing has been updated to "up to" 3 years. The following statement was added to the last paragraph: "This study asks permission to use information from all patients because it is unknown who will develop ONJ."

Model Consent form, Page 34: In the "How long will I be in the Study?" section, "approximately 3 years" has been changed to "up to three" years for patient participation in the study. In the side effects section, updated wording from "bisphosphonate" to "osteoclast inhibiting". Information has been added to clarify that the study is observational and the patient's treatment is not decided by the study, but by the patient and their physician. Added a statement to the benefits section to clarify that this information could help patients with bone metastases know more about ONJ in the future in the "Are there benefits to taking part in this study?" section.

Model Consent form, Page 35: Changed "career trials" to "clinical trials" in the information about CTSU as it was a typographical error. Clarified that patients will not receive study specific treatment on this study in the "What happens if I am injured because I took part in this study?" section.

Model Consent form, Page 37: Added the following sentence to the paragraph that starts with "Please note": "The collection of specimens lets the study answer more questions about osteoclast inhibiting therapy and ONJ."

Model Consent Form, Pages 40-41: The "Future Use of Specimens and Images" section has been divided into two sections titled "Future Use of Specimens" and "Future Use of Images" in order to clearly identify the patient’s consent. Questions regarding image use have been added specifically. Information from Page 40 has been displaced to Page 41.

Section 19.0, Page 62: Updated title of Section 19.1 from "bisphosphonate" to "osteoclast inhibitor".

Section 19.1, Pages 63-64: Updated title and headings to include "osteoclast inhibitor" instead of "bisphosphonate". Updated reference numbers that were affected by additional references in bibliography. Included an additional reference and guidelines at the end of the table.
Section 19.2, Pages 65-68: The number of patients for this study has been changed from 7,000 to 3,500. Included additional information on denosumab in second paragraph. Removed "bisphosphonate associated" from the definition of suspected and confirmed cases of ONJ. Removed "Suggested Staging and Management of ONJ" table and included an updated table. Added reference "3" to reference section; subsequent references have been renumbered accordingly. "In this letter" has been added to the last sentence on Page 65.

Section 19.3, Page 69: Added denosumab (Xgeva, Prolia) (osteoclast inhibitor, monoclonal antibody to RANKL) to this section.

Section 19.6, Page 73: The following sentence has been removed: "In order to participate in S0702, your site must be a CCOP member." Changed the box under prestudy requirements from "subjects must have planned treatment with zoledronic acid" to "all participants must be planning to receive zoledronic acid for metastatic bone disease within 30 days after registration".

S0702 Registration Worksheet (Form #6551): This form has been updated to include the new "Future Use of Specimens" and "Future Use of Images" consent questions (previously Form #21636).

S0702 Prestudy Form (Form #43194): This form has been updated to include information about denosumab and patient's history of arrhythmia (previously Form #41044).

S0702 Medical Assessment Form (Form #62856): This form has been updated to include denosumab and reporting of new onset of arrhythmias (previously Form #11945).

S0702 Dental Contact Form (Form #16457): An option to indicate whether or not a dental assessment was performed has been added (previously Form #7219).

S0702 Dental Assessment Form (Form #38387): An option to indicate whether or not a dental assessment was performed has been added (previously form #63246).

S0702 ONJ Assessment Form (Form #33523): ONJ staging has been updated and an option to indicate whether or not a dental assessment has been performed has been added (previously Form #538).

New form numbers have been updated in the following Sections: 7.5a (Page 11), 7.5b and 7.5d (Page 12), 7.5e and 7.5f (Page 12a-13), 14.4 (Page 19), 14.5-14.9 (Page 20), and 18.2 (Page 29).

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

cc: Frank L. Meyskens, Jr., M.D.
Catherine Van Poznak, M.D.
Julie Gralow, M.D.
Mark M. Schubert, D.D.S., M.S.D.
Robert A. Bagramian, D.D.S., M.Ph., Ph.D.
Lisa Hansen, R.N., M.S.
Joe Unger, M.S.
Laura Cannon – AG Mednet
Danika Lew, M.A.
Stephanie Edwards
Miguel Martinez – SWOG Repository
Emily Demske – CTSU
Kristen White – Novartis
Joseph Ciacciarelli – Novartis
December 1, 2010

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

FROM: Patricia O’Kane, Protocol Coordinator


MEMORANDUM

Study Coordinator:
Phone number:
E-mail:

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 Dental Procedure Reimbursement Form, located on the S0702 abstract page of the SWOG website (http://swog.org), has been updated. The new version lists reimbursable costs with checkboxes so that institutions can indicate the procedure for which they seek reimbursement.

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

cc: Frank L. Meyskens, Jr., M.D.
Catherine Van Poznak, M.D.
Julie Gralow, M.D.
Mark M. Schubert, DDS, M.S.D.
Robert A. Bagramian, DDS, M.Ph., Ph.D.
Lisa Hansen, R.N., M.S.
Joe Unger, M.S.
Danika Lew, M.A.
Stephanie Edwards
Miguel Martinez – SWOG Repository
Emily Demske-CTSU
Solveig G. Ericson, M.D., Ph.D.-Novartis
Eliza Argonza-Aviles-Novartis
Lixian Jin, M.D., MPH - Novartis
Laura Cannon – AG Mednet
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU
FROM: Patricia O’Kane, Protocol Coordinator

MEMORANDUM

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.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

A patient brochure that can be used as a recruitment tool for S0702 is now available on the S0702 resource page. The S0702 resource page is located on the S0702 abstract page of the SWOG website (http://swog.org). A password is required (password=mandible) for access to that area of the website.

Institutions must obtain local IRB approval for the brochure prior to its use and distribution.

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

cc: Frank L. Meyskens, Jr., M.D.
Catherine Van Poznak, M.D.
Julie Gralow, M.D.
Mark M. Schubert, DDS, M.S.D.
Robert A. Bagramian, DDS, M.Ph., Ph.D.
Lisa Hansen, R.N., M.S.
Joe Unger, M.S.
Danika Lew, M.A.
Stephanie Edwards
Miguel Martinez – SWOG Repository
Emily Demske-CTSU
Solveig G. Ericson, M.D., Ph.D.-Novartis
Eliza Argonza-Aviles-Novartis
Lixian Jin, M.D., MPH - Novartis
Laura Cannon – AG Mednet
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU

FROM: Patricia O’Kane, Protocol Coordinator


REVISION #5

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.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

The above-referenced protocol has been revised as follows:

Title page: The title page reflects the current version date of 5/18/10.

Section 7.5a, Page 11: The form number for the Dental Assessment Form was updated from #93 to #63246.

Revision #4 memorandum, distributed May 1, 2010, neglected to list 2 changes that were made in the previous version of the protocol (version 3/15/10). The changes are as follows:

Section 7.5b.2, page 11: A note regarding the oral health assessment/provider was added at the bottom of page 11.

Section 7.5d, page 12a: Clarification of Reporting Periods on Dental and Medical Assessment Forms and Dentist Contact Form was added.

Please append this notice to the front of your protocol and insert the replacement pages for the Title page and page 11.
This memorandum serves to notify the NCI and Southwest Oncology Group Statistical Center.

cc: Frank L. Meyskens, Jr., M.D.
   Catherine Van Poznak, M.D.
   Julie Gralow, M.D.
   Mark M. Schubert, DDS, M.S.D.
   Robert A. Bagramian, DDS, M.Ph., Ph.D.
   Lisa Hansen, R.N., M.S.
   Joe Unger, M.S.
   Miguel Martinez – SWOG Repository
   Danika Lew, M.A.
   Stephanie Edwards
   Emily Demske-CTSU
   Solveig G. Ericson, M.D., Ph.D.-Novartis
   Eliza Argonza-Aviles-Novartis
   Lixian Jin, M.D., MPH - Novartis
   Elizabeth Jetton – AG Mednet
June 1, 2010

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

FROM: Patricia O’Kane, Protocol Coordinator


MEMORANDUM

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.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 alert investigators and CRAs to two new resource tools available for S0702.

In response to requests from study sites, a Frequently Asked Questions (FAQ) document is now available as a PDF on the S0702 web page. The S0702 web page is located on the S0702 abstract page of the SWOG website. Click on the S0702 Web Page and then scroll down to the link entitled “Dental, and other forms, information for study sites”. A password is required (password = mandible) for access to that area of the web site.

Also available in PDF is the S0702 Protocol Card, suitable for printing, folding, and carrying in a lab coat pocket as a quick reference screening tool.

For some centers, incorporating the pharmacy into the study team has helped identify patients who may be eligible for this important trial. Please consider S0702 whenever you think of starting a patient on zoledronic acid treatment.

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

cc: Frank L. Meyskens, Jr., M.D. Stephanie Edwards
    Catherine Van Poznak, M.D. Miguel Martinez – SWOG Repository
    Julie Gralow, M.D. Emily Dmske-CTSU
    Mark M. Schubert, DDS, M.S.D. Solveig G. Ericson, M.D., Ph.D.-Novartis
    Robert A. Bagramian, DDS, M.Ph., Ph.D. Eliza Argonza-Aviles-Novartis
    Lisa Hansen, R.N., M.S. Lixian Jin, M.D., MPH - Novartis
    Joe Unger, M.S. Elizabeth Jetton – AG Mednet
    Danika Lew, M.A.
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU
FROM: Patricia O’Kane, Protocol Coordinator

REVISION #4

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.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

The above-referenced protocol has been revised as follows:

Fast Fact Sheet: The Fast Fact Sheet has been updated to be consistent with eligibility criteria in the protocol.

Title page: The title page reflects the current version date of 3/15/10.

CTSU instructions, page 2a: The first bullet was revised as “The study protocol and all related forms and documents must be downloaded from the protocol-specific Web page of the members’ section of the CTSU Web site located at www.ctsu.org.”

At the bottom of page 2a, the second entry in the last box was changed to read “The members’ section of the CTSU Web site located at www.ctsu.org”.

Section 5.2, page 8: The bullet points were changed to Section 5.2a, b and c.

Section 5.2, page 8: The following note was added: “The sum of the IV bisphosphonate doses in Section 5.2a and 5.2b must not be greater than 4.”
Section 5.12, page 9: The following paragraph was added: “If the study candidate has had multiple tumors of the same basic origin, this may be counted as one malignancy. Examples: breast cancer (bilateral disease or multiple lesions), head and neck cancer (tongue and laryngeal).”

Section 7.5d, page 12: The second sentence of the second paragraph was revised as “The S0702 Medical Assessment Form (Form #11945) must be completed by the CRA, nurse or physician every 6 months.”

Section 7.5d, page 12: At the bottom of the second paragraph, the eighth sentence was revised as “The S0702 Dental Assessment Form (Form #63246) must be submitted at the required intervals. If the patient was non-compliant with the recommended dental follow-up, then the investigational medical team can indicate “No” dental evaluation has been performed during this reporting period.”

Section 7.5d, page 12: A third paragraph has been added to clarify the reporting periods to be recorded on the assessment forms. A sentence was added (fifth paragraph) to reference Appendix 19.7 which provides information about quantifying steroids.

Section 7.5d, page 12a: Clarification of Reporting Periods on Dental and Medical Assessment Forms and Dentist Contact Form was added.

Study Calendar, page 14: The word “Required” was removed from the first line of the Study Calendar. Under “PHYSICAL”, the word “Required” was removed from the Dental Exam heading, and a footnote (alpha “α”) was added to the Presudy “X” to indicate that the baseline dental exam is required. The following sentences were added to the corresponding “β” footnote: “It is the standard of care for patients receiving bisphosphonates to have regular dental exams throughout treatment. Patient treatment is not dictated by this protocol.”

Section 14.4d, page 20: This section was revised as: “Institutional surgical pathology report or equivalent documentation to support diagnosis of primary malignancy and reports from radiology, pathology, or other modality to support the diagnosis of bone metastases.”

Section 15.2d, page 25: The S0702 Image Transmittal Form (Form #33233) has been added to this section.

Section 16.0, page 26: The second paragraph under Adverse Events was revised as “The definitions of “serious adverse event” and “associated with the use of the drug” will be as per the FDA definitions in 21CFR314.80.

A fourth paragraph was added: “Associated with the use of the drug” is defined as: there is a reasonable possibility that the experience may have been caused by the drug.

Section 18.2g, page 29: The S0702 Image Transmittal Form (Form #33233) has been added to the list of forms and added to the protocol.

Section 19.0, page 62: This section now references Appendix 19.7.

Section 19.6, page 73: In the second and third paragraphs, “http://members.ctsu.org” was changed to “www.ctsu.org”.

Data Submission and Reconciliation, page 74: In point #1, “https://members.ctsu.org” was changed to “www.ctsu.org”.

Special Materials or Substudies, page 74: In the sentence above point #2, “CTSU Member Web site” was changed to “members’ section of the CTSU Web site”. 
Serious Adverse (AE) Reporting, page 75: In point #2, "https://members.ctsu.org" was changed to "www.ctsu.org".

Section 19.7, page 76: An appendix (19.7) has been added to help clarify how to quantify use of steroids.

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

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

cc: Frank L. Meyskens, Jr., M.D.  
    Catherine Van Poznak, M.D.  
    Julie Gralow, M.D.  
    Mark M. Schubert, DDS, M.S.D.  
    Robert A. Bagramian, DDS, M.Ph., Ph.D.  
    Lisa Hansen, R.N., M.S.  
    Joe Unger, M.S.  
    Miguel Martinez – SWOG Repository  
    Danika Lew, M.A.  
    Stephanie Edwards  
    Emily Demske-CTSU  
    Solveig G. Ericson, M.D., Ph.D.-Novartis  
    Eliza Argonza-Aviles-Novartis  
    Lixian Jin, M.D., MPH - Novartis  
    Elizabeth Jetton – AG Mednet
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU
FROM: Patricia O’Kane, Protocol Coordinator

REVISION #3
Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.edu

IRB Review Requirements
( ) Full board review required. Reason:
( ) Initial activation (should your institution choose to participate)
( ) Increased risk to patient
( ) Complete study redesign
( ) Addition of tissue banking requirements
( ) Study closure due to new risk information
(√) Expedited review allowed
( ) No review required

REVISION #3
The above-referenced protocol has been revised as follows:

Title page: The title page reflects the current version date of 9/21/09.

Model Informed Consent, page 40: The last sentence before the signature on page 40 that reads "I agree to have my specimens and imaging used for optional studies" was deleted. Patients make their choice regarding specimen use and imaging by answering the 3 questions on the top of page 40.

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

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

cc: Frank L. Meyskens, Jr., M.D. Danika Lew, M.A.
Catherine Van Poznak, M.D. Stephanie Edwards
Julie Gralow, M.D. Megan Rossmann-CTSU
Mark M. Schubert, DDS, M.S.D. Solveig G. Ericson, M.D., Ph.D.-Novartis
Robert A. Bagramian, DDS, M.Ph., Ph.D. Eliza Argonz-Aviles-Novartis
Lisa Hansen, R.N., M.S. Diep Tran, M.S., CCRA - Novartis
Joe Unger, M.S. Elizabeth Jetton – AG Mednet
Miguel Martinez – SWOG Repository
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU
FROM: Patricia O’Kane, Protocol Coordinator

REVISION #2

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.edu

IRB Review Requirements

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

(√) Expedited review allowed

( ) No review required

REVISION #2

The above-referenced protocol has been revised as follows:

Title page: The title page reflects the current version date of 7/21/09.

Section 7.5.b.3, page 11: The following text was added as a second bullet: “If a form is not fully or correctly completed, one attempt should be made to have the dental health provider clarify and complete the form, after which it should be noted in the Comments section of the form that this attempt has been made, and the form may be submitted.”

Section 7.5.c, page 12: The following was added as the second sentence of the paragraph: “NOTE: The patient-related outcomes assessment and questions regarding risk factors and patient history should be asked of the patient in order to complete this form.”

Section 7.5.d, page 12: The following was added as the third sentence of the second paragraph: “NOTE: The patient-related outcomes assessment questions should be asked of the patient in order to complete this form.”

The following was added as the seventh sentence of the second paragraph: “NOTE: If the form is not fully or correctly completed, one attempt should be made to have the dental health provider clarify and complete the form, after which it should be noted in the Comments section of the form that this attempt has been made, and the form may be submitted.”
Section 7.5.e, page 12: The following was added as the fourth sentence of the first paragraph: "Frequency of dental visits and clinical medical assessments will change to every 3 months."

The fifth sentence of the first paragraph was modified as: "Form requirements will consist of the S0702 ONJ Assessment Form (Form #538), and the S0702 Medical Assessment Form (Form #11945), every 3 months."

Section 9.0, Study Calendar, page 14: Phosphate, magnesium and electrolytes have been added to the laboratory tests that should be done at Prestudy for Good Medical Practice.

An entry for "Patient-Related Outcomes Assessment" was added above "Forms Submission" and is required at prestudy, and months 6, 12, 18, 14, 30 and 36.

The "π" footnote was revised to indicate that baseline dental films should be submitted within 28 days rather than 30 days of ONJ diagnosis.

A "®" footnote has been added next to the Patient-Related Outcomes Assessment entry as well as next to the S0702 Prestudy Form and S0702 Medical Assessment Form. The footnote reads: "Patient-related outcome assessments are included on the S0702 Prestudy Form and S0702 Medical Assessment Form, and should be asked of the patient prior to submission of these forms. The S0702 Prestudy Form also contains questions regarding risk factors and patient history that should be asked of the patient."

The following was added as a third sentence to the asterisk footnote: "Clinical medical assessments should be scheduled to match the forms submission schedules."

Section 14.6, page 20: "Within 30 days..." was changed to "Within 28 days..." in the heading of Section 14.6.

Form number changes

Form number changes have occurred in Section 7.5g, page 13, Section 14.4, page 19, Sections 14.5 through 14.9, page 20 and Section 18.2, page 29 as follows:

- S0702 Prestudy Form changed from Form 48068 to 41044
- S0702 Medical Assessment Form changed from Form 47673 to 11945
- S0702 Dentist Contact Form changed from Form 23043 to 7219
- S0702 Dental Assessment Form changed from Form 93 to 63246
- S0702 ONJ Assessment Form changed from Form 61115 to 538

Appendix 19.3, Page 69: Empty bullets have been deleted.

Appendix 19.4, Page 70: The title of the table has been changed from classes of "chemotherapies" to "systemic therapies" and revised to be in alphabetical order. Also, a typographical error has been corrected.

Two additional tables were added that include "Endocrine Therapies" and "Other" therapies with subclasses of WBC growth factor, RBC growth factor, and steroids.
Please append this notice to the front of your protocol and insert the replacement pages referenced above. Pages 12a and 71a were added to prevent extensive repagination.

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

cc: Frank L. Meyskens, Jr., M.D.
    Catherine Van Poznak, M.D.
    Julie Gralow, M.D.
    Mark M. Schubert, DDS, M.S.D.
    Robert A. Bagramian, DDS, M.P., Ph.D.
    Lisa Hansen, R.N., M.S.
    Joe Unger, M.S.
    Danika Lew, M.A.
    Stephanie Edwards
    Megan Rossmann-CTSU
    Solveig G. Ericson, M.D., Ph.D.-Novartis
    Eliza Argonza-Aviles-Novartis
    Diep Tran, M.S., CCRA - Novartis
    Elizabeth Jetton – AG Mednet
    Miguel Martinez – SWOG Repository
TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER INSTITUTIONS, CCOP INSTITUTIONS, AND AFFILIATE MEDICAL ONCOLOGISTS; CTSU
FROM: Patricia O'Kane, Protocol Coordinator

REVISION #1

Study Coordinator: Catherine Van Poznak, M.D.
Phone: 734/936-9209
E-mail: cvanpoz@med.umich.edu

IRB Review Requirements

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

( √ ) Expedited review allowed
( ) No review required

REVISION #1

The above-referenced protocol has been revised as follows:

Title Page, Participants: The title page has been revised to reflect that this study is supported by the NCI Cancer Trials Support Unit (CTSU). CCOP institutions not aligned with SWOG will now be able to participate through the CTSU mechanism. Non-CCOP institutions that are not SWOG institutions may not participate in this study.

Page 2a: Information regarding CTSU participation as well as CTSU contact information has been added. Page 2a was added to prevent extensive repagination.

Section 4.0, page 7: The words "such as" have been inserted into the text within the parentheses in the first sentence.

Section 7.5.b.2, page 11: In the second bullet, "Dental Contact Form" was changed to "Dentist Contact Form".

Section 7.5.b.3, page 11: The bulleted text has been revised as "The dental health provider is expected to return the forms to the registering institution within 10 days of evaluating the patient (or completing the form whether for a scheduled evaluation or for any assessment that occurs as clinically indicated)."
Section 7.5d, page 12: The second sentence of the first paragraph has been revised for clarity and now reads "Patients must be registered within 30 days prior to initiation of protocol-specified planned zoledronic acid treatment (see Section 5.2)."

Section 7.5d, page 12: The following has been added as the sixth sentence of the second paragraph: "The Dentist Contact Form should be submitted each time the Dental Assessment Form is submitted (i.e. every 6 months)."

Section 7.5e, page 12: The following sentence was added to the end of the first paragraph: "The Dentist Contact Form should be submitted each time the ONJ Assessment Form is submitted (i.e. every 3 months)."

Section 7.5g, page 13: The Dentist Contact Form has been added to the list of forms that are required at the 3 years post-registration timepoint.

Section 9.0, Study Calendar, page 14: Under Forms Submission, the "X" has been moved from the 1 month column to the Prestudy column for the Prestudy Form. A "∆" footnote has been added to the Dentist Contact Form to indicate that it should be submitted each time the Dental Assessment Form is submitted in order to capture a change in provider. X’s have been added to the 6, 12, 18, 24, 30, and 36 month columns.

Sections 13.1, page 18: Sections 13.1 was revised as: "Patients must be registered within 30 days prior to initiation of protocol-specified planned zoledronic acid treatment. (Note: Prior bisphosphonate therapy as noted in Section 5.2 is allowed)."

Section 14.4, page 19: The form # of the Dentist Contact Form was changed from #44900 to #23043.

Sections 14.5, 14.6, 14.7, 14.8, and 14.9, page 20: The data submission schedule was revised to include submission of the Dentist Contact Form (Form #23043) each time the Dental Assessment form or ONJ Assessment form is submitted.

Section 15.1b, page 21: "Class 9 label" was deleted from the list of items in the visit kits.

Section 15.2c, page 24: The AG Mednet URL has been updated in the second paragraph. Under the section entitled "Electronic Submission Set-up," the fourth sentence was revised as “AG Mednet will require the Desk Top Agent Order Form to be faxed directly to AG Mednet at 617/674-8125 or submitted online at the link provided.”

Section 18.2.d, page 29: A revision date was added next to the S0702 Dentist Contact Form (Form #23043). Note that the form number was changed from #44900 to #23043.

Model Informed Consent form, page 34: Under the section entitled "Can I stop being in the study?", the paragraph regarding the risks associated with stopping treatment was deleted as it does not apply to this registry study.

Model Informed Consent form, page 35: Under the section entitled "Will my medical information be kept private?", the CTSU has been added to the list of organizations allowed to review medical records. Please note that “CTSU” does not have to be added to the consent for institutions participating via SWOG.

Model Informed Consent form for Specimens and Imaging, page 40: In the paragraph that begins "If you decide to withdraw your specimens..." the last sentence was deleted as shipment of specimens back to the study doctor is not an option. The following sentence was added: "The remains of your sample or your imaging will then be destroyed."
**S0702 Dentist Contact Form:** The instructions were revised to indicate that this form should be submitted each time the S0702 Dental Assessment form or S0702 ONJ Assessment form is submitted after registration.

**Appendix 19.0, page 62:** The following text was added: "19.6 Cancer Trials Support Unit (CTSU) Participation Procedures".

**Appendix 19.6, pages 73-75:** CTSU participation procedures have been added in Appendix 19.6.

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

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

cc: Frank L. Meyskens, Jr., M.D.  
Catherine Van Poznak, M.D.  
Julie Gralow, M.D.  
Mark M. Schubert, DDS, M.S.D.  
Robert A. Bagramian, DDS, M.Ph., Ph.D.  
Lisa Hansen, R.N., M.S.  
Joe Unger, M.S.  
Danika Lew, M.A.  
Stephanie Edwards  
Megan Rossmann-CTSU  
Solveig G. Ericson, M.D., Ph.D.-Novartis  
Eliza Argonza-Aviles-Novartis  
Diep Tran, M.S., CCRA - Novartis  
Elizabeth Jetton – AG Mednet  
Miguel Martinez – SWOG Repository
December 15, 2008

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

FROM: Patricia O’Kane, Protocol Coordinator


STATUS NOTICE

Study Coordinator: Catherine Van Poznak, M.D.  
Phone number: 734/936-9209  
E-mail: cvanpoz@med.umich.edu

IRB Review Requirements

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

( ) Expedited review allowed

( ) No review required

ACTIVATION

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

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

cc: Frank L. Meyskens, Jr., M.D.
    Cathy Van Poznak, M.D.
    Julie Gralow, M.D.
    Mark M. Schubert, DDS, M.S.D.
    Robert A. Bagramian, DDS, M.Ph., Ph.D.
    Lisa Hansen, R.N., M.S.
    Joe Unger, M.S.
    Danika Lew, M.A.
    Stephanie Edwards
    Solveig G. Ericson, M.D., Ph.D.
    Eliza Argonza-Aviles
SOUTHWEST ONCOLOGY GROUP
PROTOCOL FAST FACT SHEET

THIS FORM HAS BEEN DESIGNED AS A RESOURCE ONLY AND IS NOT INTENDED FOR USE IN THE FULFILLMENT OF PATIENT REGISTRATION AND TREATMENT REQUIREMENTS

S0702

A PROSPECTIVE OBSERVATIONAL MULTICENTER COHORT STUDY TO ASSESS THE INCIDENCE OF OSTEONECROSIS OF THE JAW (ONJ) IN CANCER PATIENTS WITH BONE METASTASES STARTING ON ZOLEDRONIC ACID TREATMENT

Treatment Initiation: Within 30 days of registration*

Drugs provided: None

Treatment: Zoledronic acid IV

Patients are advised to undergo dental evaluation every 6 months. If ONJ develops, dental assessments will be performed every 3 months. Patients are followed for a total of 36 months.

*See eligibility criteria below

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Ineligibility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone metastasis from multiple myeloma, solid tumor, or other malignancy where bisphosphonate is indicated</td>
<td>History of osteonecrosis of the jaw</td>
</tr>
<tr>
<td>Planned zoledronic acid treatment for metastatic bone disease</td>
<td>Previous cancer treatment with radiation therapy to oral maxillofacial region for therapeutic intent</td>
</tr>
<tr>
<td>*History of osteoclast inhibitor therapy for osteoporosis or osteopenia:</td>
<td>&gt; 180 days prior IV ibandronate, pamidronate, zoledronic acid, or denosumab</td>
</tr>
<tr>
<td>- Permitted: up to 3 doses of IV ibandronate, pamidronate, zoledronic acid or denosumab (Prolia) in the past 3 years</td>
<td></td>
</tr>
<tr>
<td>- any prior oral bisphosphonate</td>
<td></td>
</tr>
<tr>
<td>*Osteoclast inhibitor therapy for metastatic bone disease</td>
<td>Prior malignancy except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, stage I or II cancer from which the patient is in complete remission, or any other cancer which the patient has been disease-free for 5 years. Multiple tumor of the same basic origin may be counted as one malignancy.</td>
</tr>
<tr>
<td>- up to 180 days of prior osteoclast inhibitor for metastatic bone disease (ibandronate, pamidronate, zoledronic acid or denosumab)</td>
<td></td>
</tr>
<tr>
<td>A total of no more than 10 doses of IV bisphosphonates or a total of 8 doses of denosumab are allowed. The combination of IV bisphosphonates and denosumab dosing may not be greater than 12 for any indication..</td>
<td></td>
</tr>
<tr>
<td>Zubrod performance status of 0 – 3</td>
<td></td>
</tr>
<tr>
<td>Willing to provide information regarding smoking history, alcohol consumption, pain assessments</td>
<td></td>
</tr>
<tr>
<td>Willing to provide access to prior and future dental information</td>
<td></td>
</tr>
<tr>
<td>Participation on other therapeutic or non-therapeutic trials OK</td>
<td></td>
</tr>
</tbody>
</table>

PRESTUDY REQUIREMENTS:
≤ 42 days of registration: History & physical exam

PRESTUDY SUGGESTED FOR GMP:
≤ 42 days of registration: serum creatinine, calculated creatinine clearance, corrected serum calcium, serum albumin, phosphorus, magnesium, electrolytes, complete blood count with platelet count and differential, pregnancy test for women of childbearing potential

PRESTUDY OPTIONAL:
Serum and whole blood submission
≤ 6 months before registration: Dental exam recommended
≤ 12 months before registration: Dental imaging recommended

*This form has been developed with the support of the SWOG Nurse Oncologist Committee
SWOG

A PROSPECTIVE OBSERVATIONAL MULTICENTER COHORT STUDY TO ASSESS THE INCIDENCE OF OSTEONECROSIS OF THE JAW (ONJ) IN CANCER PATIENTS WITH BONE METASTASES STARTING ZOLEDRONIC ACID TREATMENT

PARTICIPANTS: PARTICIPANTS: ALL SWOG MEMBER, CCOP, AND AFFILIATE MEDICAL ONCOLOGISTS; ALSO, CTSU PARTICIPANTS AT CCOP INSTITUTIONS THAT ARE NOT AFFILIATED WITH SWOG AND NON-CCOP INSTITUTIONS AT ALBERT EINSTEIN CANCER CENTER, LEHIGH VALLEY HOSPITAL AND ST FRANCIS CANCER TREATMENT CENTER (for these institutions, patient enrollments will be conducted via the NCI Cancer Trials Support Unit [CTSU] and all data will be sent to the SWOG Data Operations Center as specified in the CTSU logistical Appendix 19.6.)

STUDY COORDINATORS:

Catherine H. Van Poznak, M.D. (Medical Oncology)
University of Michigan Comprehensive Cancer Center
1500 E. Medical Drive
C346 Med Inn Building
Ann Arbor, MI 48109-0848
Phone: 734/936-9209
FAX: 734/615-2109
E-mail: cvanpoz@med.umich.edu

Julie R. Gralow, M.D. (Medical Oncology)
Seattle Cancer Care Alliance
825 Eastlake Ave E
MS G3-200
Seattle, WA 98109-1023
Phone: 206/288-7722
FAX: 206/288-2054
E-mail: pink@u.washington.edu

BIOSTATISTICIANS:

Joseph M. Unger, M.S. (Biostatistics)
Danika Lew, M.A.
Southwest Oncology Group Statistical Center
Fred Hutchinson Cancer Research Center
1100 Fairview Avenue North, M3-C102
PO Box 19024
Seattle, WA 98109-1024
Phone: 206/667-4623
FAX: 206/667-4408
E-mail: junger@fhcrc.org
E-mail: dlew@fhcrc.org

(Version Date: 12/06/11)
STUDY COORDINATORS (contd.):

Oral Medicine
Box 356370
School of Dentistry
University of Washington
Seattle, WA 98195-6370
Phone: 206/288-1331
FAX: 206/288-1332
E-mail: mschuber@Seattlecca.org

Robert A. Bagramian, D.D.S., M.Ph., Ph.D. (Epidemiologist)
University of Michigan
School of Dentistry
1011 N. University Ave, Room 3309
Ann Arbor, MI 48109-1078
Phone: 734/647-4239
FAX: 734/763-5503
E-mail: robtbagr@umich.edu

Lisa Hansen, R.N., M.S., AOCN (Nurse Coordinator)
Clinical Program Specialists
Legacy Good Samaritan Hospital
1015 NW 22nd Ave.
Portland, OR 97210
Phone: 503/413-6285
FAX: 503/413-6920
E-mail: lhansen@lhs.org
This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Institutions not aligned with SWOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the members’ section of the CTSU Web site located at www.ctsu.org.

- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.

- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.

- Data management will be performed by the Southwest Oncology Group. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to the Southwest Oncology Group Data Operations Center unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.

- **Data query and delinquency reports** will be sent directly to the enrolling site by the Southwest Oncology Group. Please send query responses and delinquent data to the Southwest Oncology Group Data Operations Center and do not copy the CTSU Data Operations.

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

---

**CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION**

<table>
<thead>
<tr>
<th>To submit site registration documents:</th>
<th>For patient enrollments:</th>
<th>Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone: 1-888/823-5923 Fax: 215/569-0206</td>
<td>CTSU Patient Registration Voice Mail: 1-888/462-3009 Fax: 1-888/691-8039 Hours: 9:00 am – 5:30 pm EST, Monday – Friday (excluding holidays) [Registrations received after 5:00 PM ET will be handled the next business day. For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301/704-2376 between 9:00 am and 5:30 pm.]</td>
<td>Southwest Oncology Group Data Operations Center Fax: 1-800/892-4007 [Please do not use a cover sheet for faxed data.] Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.</td>
</tr>
</tbody>
</table>

*For patient eligibility or treatment-related questions* Patient eligibility: contact the Southwest Oncology Group Data Operations Center at 206/652-2267 prior to registration. Treatment-related questions: contact the SWOG Study Coordinator.

*For questions unrelated to patient eligibility, treatment, or data submission* contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line: 1-888/823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The members’ section of the CTSU Web site is located at www.ctsu.org.

CTSU logistical information is located in Appendix 19.6.
Patients with metastatic bone disease initiating zoledronic acid (See Section 5.0)

Baseline Assessments

REGISTRATION:
Prestudy Form
Baseline Blood* Submission (optional)

Non-Protocol cancer and dental care as clinically indicated.

Protocol: Medical and Dental Forms submitted every 6 months.
Serum submitted every 6 months. (Optional)
Follow-up every 6 months (see Sections 7.0, 9.0, 14.0, and 15.0)

Patients Diagnosed with ONJ While On Study:
Switch to follow-up x3 months (see Sections 7.0, 9.0, 14.0, and 15.0)

Off Study at 3-Years After Registration

* Serum and white blood cells for DNA will be collected at this time point.
1.0 OBJECTIVES

1.1 The primary objective of this study is to prospectively assess the cumulative incidence of osteonecrosis of the jaw (ONJ) at 3 years in cancer patients with bone metastasis receiving zoledronic acid treatment.

1.2 Secondary Objectives

a. To describe the clinical presentation and natural history of ONJ.

b. To identify potential risk factors for the development of ONJ.

c. To estimate the cumulative incidence of ONJ at 3 years for different tumor types (breast cancer, multiple myeloma, prostate cancer, lung cancer and other cancers).

d. To investigate potential predictive and/or prognostic markers of increased risk for ONJ and/or to explore the potential mechanism of ONJ, the following correlative science resource banks will be established:

   - A specimen bank of serum for banking and whole blood for DNA analysis
   - A serial imaging bank of available x-rays, scans, CTs, and MRIs for ONJ cases, as well as for a set of non-ONJ controls

e. To better define the patient-related outcomes of ONJ in those patients who develop ONJ.

2.0 BACKGROUND

Bisphosphonates are analogues of pyrophosphate, an endogenous regulator of bone mineralization. This class of drugs has been extensively studied in the past three decades. The newest generation of bisphosphonates has a high binding affinity to hydroxyapatite in mineralized bone and acts as a potent inhibitor of osteoclastic activity. Other osteoclast inhibitors may work by an alternate mechanism, such as denosumab, which targets Receptor Activator Nuclear Factor Kappa B Ligand (RANKL). Bisphosphonates are widely used for the treatment of metabolic bone disorders associated with increased bone turnover such as osteoporosis, hypercalcemia of malignancy, metastatic bone disease and Paget’s disease. The two intravenous bisphosphonates approved for the treatment of metastatic bone disease in the U.S., pamidronate (FDA approved in 1995) and zoledronic acid (FDA approved in 2001), have demonstrated reductions in skeletal-related events in patients with metastatic bone involvement due to multiple myeloma and breast cancer. (1-5) Zoledronic acid is also effective in reducing skeletal-related events in metastatic prostate cancer, whereas pamidronate is not. Additionally, unlike pamidronate, zoledronic acid has shown efficacy in other solid tumor types including lung, renal, colorectal and bladder cancer. The use of bisphosphonates for metastatic bone disease results in reductions in pathological fractures, hypercalcemic crisis, spinal cord compression, and requirement for radiation therapy. In the U.S., zoledronic acid has approximately 80-85% of the total market share in cancer patients with bone metastases. Currently 6,000 metastatic cancer patients are started on monthly zoledronic acid per month in the U.S. (Novartis data). Approximately 2,000-2,500 are breast cancer patients, 1,200 are multiple myeloma patients, 1,000 are prostate cancer patients, 800 are lung cancer patients, and 800-1,000 are patients with other solid tumors.

FDA approved osteoclast inhibiting therapies include bisphosphonates and denosumab. Bisphosphonate therapy has generally been associated with good clinical tolerability. However, beginning in 2002, there have been reported cases of ONJ in cancer patients receiving intravenous bisphosphonates. (6-8) These patients presented with painful exposed necrotic bone in the mandible, maxilla or both. Treatment of this condition has proven to be difficult and often unsuccessful. Retrospective studies indicated that the time to onset of ONJ is longer with pamidronate than zoledronic acid (72 months vs. 18 months respectively). (9)
The Food and Drug Administration’s Oncologic Drugs Advisory Committee (ODAC) held a hearing March 4, 2005 to address safety concerns, particularly ONJ, in cancer patients receiving bisphosphonates. As presented at that hearing, a total of 875 cases of ONJ associated with pamidronate or zoledronic acid had been reported to Novartis, with an estimated worldwide exposure rate of 1.9 million for pamidronate and 1 million for zoledronic acid. (10) Approximately 20% of these cases had been exposed to pamidronate alone, 40% to zoledronic acid alone, and 40% had received some combination of both drugs. Also presented at the ODAC hearing was data from an ongoing retrospective chart review of ONJ and bisphosphonate exposure from M.D. Anderson, which was updated at the American Society of Clinical Oncology Annual Meeting 2006. (11) The update included data from 4,000 cancer patients receiving intravenous bisphosphonates. The frequency of ONJ was calculated by including patients from the pharmacy database: 16/1338 (1.2%) in breast cancer and 14/448 (3.1%) in multiple myeloma. The Memorial Sloan-Kettering experience indicates that the incidence of ONJ in patients with breast cancer at that institution is similar to that of M.D. Anderson’s, at approximately 1% in those with metastatic breast cancer. (12) A recent review of the literature by Woo, et al, indicated that the prevalence of osteonecrosis in patients with cancer is 6% to 10%. (13)

The risk of ONJ in patients with cancer treated with intravenous bisphosphonates appears to range between 1 to 10% depending on the specific bisphosphonate, total dose, duration of treatment, and dental history. (9, 11, 12, 14, 15) A longer duration of bisphosphonate therapy appears to be associated with an increased risk for developing ONJ. The risk appears to be increased from 1.5% among patients treated for 4 to 12 months to 7.7% for those treated for 27 to 48 months and may be higher with zoledronic acid as compared with pamidronate alone or pamidronate followed by zoledronic acid. (14, 9) A survey performed by the Australian Oral and Maxillofacial Surgeons identified the frequency of ONJ in patients with bone metastases treated with mainly intravenous zoledronate or pamidronate to be 1 in 87 to 114 (0.88% to 1.15%). If extractions were carried out, the calculated frequency of ONJ was 1 in 11 to 15 (6.67% to 9.1%). The median time to onset of ONJ appeared consistent with that of other studies, 12 months for zoledronate, and 24 months for pamidronate. (15) Using the Surveillance, Epidemiology, and End Results (SEER) program linked to Medicare claims Wilkinson, et al, correlated intravenous bisphosphonate use with an increased risk of jaw or facial bone surgery and the increased absolute risk of any jaw toxicity at 6 years was 5.48 events per 100 patients using intravenous bisphosphonates and 0.30 events per 100 patients not using such drugs. (16)

Denosumab, a monoclonal antibody targeting RANKL, dosed monthly at 120 mg subcutaneously, received FDA approval in 2010 for the prevention of skeletal related events in patients with bone metastases from solid tumors (but not multiple myeloma) [packet insert].

In Phase III clinical trials comparing monthly zoledronic acid 4mg intravenously to denosumab 120 mg subcutaneously in patients with metastatic bone disease the incidence of ONJ appears to be statistically similar between the two treatment groups. Among 5677 patients with ≥1 treatment dose, positively adjudicated ONJ occurred in 1.8% (52) denosumab and 1.3% (37) ZA patients (P=0.13). Patients received a median of 13 doses of denosumab and 11 doses of zoledronic acid. (17) In the Phase III study specific to women with metastatic breast cancer, ONJ occurred in 2% in those treated with denosumab and 1.4% in those treated with zoledronic acid (P=0.39). (18) These analyses demonstrated that denosumab is associated with ONJ; however, it does not provide a means of identifying specific individual risks of developing ONJ.

Through interrogation of the existing literature and by using clinical judgment, it is the best estimate of the current study's investigators that the incidence of ONJ is approximately 1-2%, in those individuals newly initiating intravenous bisphosphonate therapy for metastatic bone disease, acknowledging the likelihood that the risk of developing ONJ increases over time and with bone invasive procedures. Phase III clinical trials comparing monthly zoledronic acid to denosumab demonstrated that both osteoclast inhibitors were associated with a 1-2% risk of ONJ. (18)
This prospective observational study will help refine our understanding of the incidence and risk factors associated with ONJ in patients with metastatic bone disease receiving intravenous bisphosphonate therapy to decrease the risk of skeletal related events.

Patients Without Metastatic Bone Disease

The bisphosphonates are also used to treat benign conditions such as osteoporosis and Paget’s Disease of bone, and zoledronic acid is being explored in the adjuvant setting (Southwest Oncology Group Protocol S0307, Breast International Group AZURE trial, CALGB-79809, and Z-FAST). (19)

In AZURE, (BIG01/04, ISRCTN79831382), a study of 3,360 women undergoing adjuvant breast cancer care, one half of the study population was randomized to receive zoledronic acid monthly for 6 months, then every 3 months for 2 years, then every 6 months to complete a total of 5 years of therapy versus standard therapy. Data from the AZURE trial presented at the San Antonio Breast Cancer Symposium in December 2010 demonstrated that there were 13 confirmed (0.83%; 95% CI 0.38%, 1.28%) cases of osteonecrosis of the jaw (ONJ) in the zoledronic acid arm. (SABC Symposium abstract 2010). The Southwest Oncology Group Clinical trial S0307 (NCT00127205) is investigating the effects of zoledronic acid, oral ibandronate and oral clodronate on the risk of recurrence and has incorporated dental follow up into the protocol to prospectively gather information regarding ONJ. The HORIZON study, examining zoledronic acid for the treatment of postmenopausal osteoporosis (N=3889) reported one case of ONJ in both the placebo and zoledronic acid arm within the 3 year study period. (20) The FDA approved the use of zoledronic acid 5 mg (Reclast®) dosed annually for postmenopausal osteoporosis in August 2007, and had approved zoledronic acid 5 mg (Reclast®) in April 2007 for the treatment of patients with Paget’s disease of the bone. These studies and this FDA labeling indication for the use of high potency nitrogen-containing bisphosphonates for benign conditions, emphasize the need to better understand the risks, management and pathogenesis of ONJ. Our study population consists of patients with metastatic bone disease receiving zoledronic acid as this is the patient subset with the highest reported incidence of ONJ and is likely to lend the most insight into the disease process.

Treatment with zoledronic acid may be associated with arrhythmias. (34) The case report forms of this study will capture reports of arrhythmias and clinical teams are advised to report adverse events as outlined in Section 14.0.

Study Population

Although no definite causal relationship has been established between ONJ and exposure to bisphosphonate therapy, there is an increasing concern regarding the association of ONJ with osteoclast inhibitor therapies. The actual incidence of ONJ in patients with metastatic bone disease receiving osteoclast inhibition therapy and in the general population has not been established. More importantly, risk factors predisposing to this clinical condition have only loosely been described.

Through retrospective case reporting the risk factors for bisphosphonate associated ONJ in patients with cancer have been suggested to include: specific bisphosphonate used (nitrogen-containing intravenous formulation), dental trauma (extractions, surgery involving the jaw bones, or periodontal surgery involving bone), demographics (age, race, cancer- with multiple myeloma and breast cancer having a greatest risks), comorbid diagnoses, medication or behavior (chemotherapy, corticosteroid therapy, diabetes, tobacco abuse, alcohol use, poor oral hygiene). (7, 22-26) Cases of ONJ have been reported in patients receiving the osteoclast inhibitor denosumab (STOPEK).

Consequently, this prospective observational study is designed to define the incidence, associated risk factors, clinical presentation and natural history of ONJ in patients with bone metastasis treated with zoledronic acid treatment. The study proposed here focuses on zoledronic acid as the study drug due to the greater number of reported cases of ONJ associated with zoledronic acid, the apparent shorter time to onset of ONJ, the substantially more common use of zoledronic acid (compared to pamidronate) in cancer patients in the U.S., and the fact that zoledronic acid is used in multiple tumor types, unlike pamidronate which is approved only for metastatic breast
cancer and multiple myeloma. Denosumab has been shown to have an incidence of ONJ, similar to zoledronic acid when used to treat bone disease. Denosumab was FDA approved in December 2010 for the management of metastatic bone disease for solid tumors. The off-protocol ONJ experience of denosumab is undefined. The focus of this study will be zoledronic acid. Data on the use of zoledronic acid and other osteoclast inhibitors will be collected.

A number of management recommendations to aid the clinician in addressing the phenomenon of ONJ have been generated based on case reports and consensus statements, as outlined in Appendix 19.1. (13, 22-25, 27-31) However these guidelines have been generated in the absence of prospectively gathered data and the validity of such recommendations have been criticized for their lack scientific rigor. (29) That being said, they will serve as the foundation on which this observational study will incorporate dental assessments, and this study will generate much needed data on the true incidence of ONJ as well as risk factors associated with this condition and response to our present management practices. Of note, the ONJ guidelines universally recommend pretreatment (or early in the course of therapy) dental exam and many guidelines/experts include recommendations for dental imaging. (12, 22-24)

Correlatives

The pathogenesis of ONJ is unknown and, to date, there are no patient specific characteristics known to aid in individualized risk assessment. This observational study is in a unique position to establish a repository of specimens, images and clinical data that could be used for a wide variety of investigations.

The frequency of ONJ being diagnosed in patients with metastatic bone disease receiving osteoclast inhibitor therapy has been estimated between 1-10%. The relatively infrequent occurrence of ONJ, and the heterogenous data collection, variability of patients and systemic therapies has limited the ability to perform case control studies.

This observational study will uniformly generate a repository of germline DNA, serial serum specimens, and imaging of bone of the jaw along with a well annotated clinical database. This study will permit case – control correlative investigations to be performed as well as potentially fostering translational studies by having developed a bank of serum, white blood cells for DNA, and dental imaging. The study specimens and film materials will be banked and made available for correlative science investigations (of independent funding and separate clinical trial).

Patients diagnosed with ONJ will remain on study and have additional assessments including follow up forms every 3 months and evaluation by the oral health care provider. Recent imaging studies capturing the jaw (bone scan, dental films) obtained for clinical indications will be requested for the image bank.

Inclusion of Women and Minorities:

This study is designed to include women and minorities, but is not designed to measure differences of intervention effects.

3.0 DRUG INFORMATION

There is no drug information for this study.

For information relating to bisphosphonate, please refer to the Packet Insert.

4.0 STAGING CRITERIA

There are no cancer staging criteria for this study other then all patients must have been diagnosed with metastatic bone disease (such as multiple myeloma with osseous lesions or solid tumors metastatic to bone).

A staging and grading system for those affected by ONJ is included in the Appendix 19.2.
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 Prestudy Form and submit to the Data Operations Center in Seattle (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. If Day 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 Participant must have bone metastasis from multiple myeloma, solid tumors, or other malignancy for which intravenous bisphosphonate has clinical indications in the treatment of metastatic bone disease.

—— 5.2 All participants must be planning to receive zoledronic acid for metastatic bone disease within 30 days after registration. (NOTE: Osteoclast inhibition therapies will continue thereafter as clinically indicated.) Patients previously treated with osteoclast inhibiting therapy are eligible if the following criteria apply:

a. Prior osteoclast inhibition for low bone mass (osteoporosis or osteopenia):

   Patients may have previously received at most 3 doses of osteoclast inhibiting therapy with denosumab, IV ibandronate, pamidronate, or zoledronic acid for low bone mass (osteopenia or osteoporosis) within 3 years prior to registration

   Prior oral bisphosphonate therapy at osteoporosis or osteopenia dosing at any time prior to registration is allowed. Prior exposures to other medications used to treat low bone mass at osteoporosis or osteopenia dosing are permitted.

b. Prior osteoclast inhibition for metastatic bone disease (tumor involving bone):

   Patients may have previously received osteoclast inhibiting therapy with denosumab, ibandronate (oral or IV cancer dosing), pamidronate, or zoledronic acid to treat metastatic bone disease within 180 days prior to registration. Patients receiving these regimens for metastatic bone disease prior to 180 days before registration are not eligible.

c. Prior osteoclast inhibiting therapy at higher dosing than outlined above at any time prior to registration is not allowed.

NOTE: The sum of prior IV bisphosphonate doses in Sections 5.2a and 5.2b must not be greater than 10. The sum of prior denosumab doses in Sections 5.2a and 5.2b must not be greater than 8. The total of both IV bisphosphonate and denosumab used for any indication must not be greater than 12 doses.

—— 5.3 Participants must not have a pre-existing diagnosis of ONJ.

—— 5.4 Participants must not have a history of radiation to the maxillofacial area administered for therapeutic intent in the treatment of cancer.

—— 5.5 Participants must have a Zubrod performance status of 0-3 (see Section 10.2).

NOTE: Participants who may be acutely ill from spinal cord compromise, hypercalcemia of malignancy or other process may be study candidates once the acute condition has been addressed and performance status improves to 0-3.
5.6 Participants must be willing and physically able to comply with the study procedures and assessments.

5.7 Patients must be offered the option to submit blood for banking and DNA analysis, as specified in Section 15.0.

5.8 Participants must be willing to provide information on history, including tobacco and alcohol use, symptoms, and pain assessment.

5.9 Participants must be willing to provide access to prior and future dental information.

5.10 Participants can concurrently participate in other therapeutic and non-therapeutic clinical trials.

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

If the study candidate has had multiple tumors of the same basic origin, this may be counted as one malignancy. Examples: breast cancer (bilateral disease or multiple lesions), head and neck cancer (tongue and laryngeal).

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

5.13 At the time of patient registration, the treating institution's name and ID number must be provided to the Data Operations Center in Seattle in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the database.
6.0 **DESCRIPTIVE FACTORS**

Patients will be described by type of disease: breast cancer versus multiple myeloma with osseous lesions versus prostate cancer versus lung cancer versus other tumors.

7.0 **STUDY PLAN**

7.1 For study related questions, please contact Dr. Van Poznak at 734/936-9209, or Dr. Gralow at 206/288-7722.

7.2 **Good Medical Practice**

The following pre-study tests are recommended within 42 days, or as specified below, prior to registration in accordance with good medical practice. Results of these tests do not determine eligibility and minor deviations from normal limits would be acceptable if they do not affect patient safety in the clinical judgment of the treating physician. If there are significant deviations in these tests that could impact on patient safety, it is highly recommended that the registering investigator discuss the patient with the Study Coordinator prior to registering.

a. Serum creatinine < 3.0 mg/dl or < 265 mcmol/L and creatinine clearance as calculated by the Cockcroft-Gault formula ≥ 30 mL/min. Creatinine for dosing of zoledronic acid is recommended to be obtained within 14 days of dosing.

   Cockcroft-Gault Formula:
   \[
   \text{Crcl} = \frac{(140-\text{age (years)} \times \text{weight (kg)} \times 0.85 \text{ for female patients})}{(72 \times \text{serum creatinine (mg/dL})}
   \]

b. Adjusted serum calcium (> 7 mg/dl), albumin (Albumin is required to calculate adjusted serum calcium. Any albumin value is considered acceptable.), phosphate (> 2 mg/dl), magnesium (> 0.8 mg/dl) and electrolytes (reflective of patients volume status), or within standard institutional parameters for administration of intravenous bisphosphonate.

c. CBC with differential platelet count (total WBC ≥ 3.0 K/mm³, hemoglobin (hgb) ≥ 10.0 g/dL, platelets ≥ 100,000/mm³, other values based on institutional standards or within standard institutional parameters for administration of intravenous bisphosphonate.

d. Patients are recommended to undergo a baseline dental exam, although it is not required. The dental exam should occur within 6 months prior to registration. The baseline dental exam should include: dental history, dental exam, periodontal exam and dental imaging. Panoramic x-ray is the preferred imaging technique, although other imaging modalities such as intraoral films (small films), bite wings, x-rays films and/or digital files may be appropriate for some individuals. Dental imaging within 12 months prior to registration is acceptable. The S0702 Dentist Contact Form and S0702 Dental Assessment Form (related to the baseline dental exam) are recommended to be completed by the Dental Health Professional and returned to the registering institution prior to registration. If baseline dental exam is not done, this is to be noted on the form and returned (see also Sections 7.5a and 14.4).

e. Negative pregnancy test if the patient is of childbearing potential.

NOTE: Pregnant and lactating women should not receive bisphosphonates.

7.3 Cancer and dental care should be performed as clinically indicated. Participants must be planning to receive zoledronic acid within 30 days of registration, but will not be made ineligible if other osteoclast in inhibiting therapy is used or if osteoclast inhibiting therapy is delayed beyond 30 days. See Section 7.5 for general guidelines.
7.4 A baseline dental exam is recommended within 6 months prior to registration. After registration, the study follow-up plan consists of required forms submission every 6 months for 3 years (see Sections 9.0 and 14.0 for recommended scheduled assessments and required forms submission). For patients diagnosed with ONJ while on study, recommended assessments switch to every 3 months until 3 years after registration (see Section 9.0 and 14.0 for recommended scheduled assessments and required forms submission) (see also Section 7.5e).

7.5 General Guidelines

a. Dental Assessment

As per the zoledronic acid packet insert, patients should maintain good oral hygiene and should have a dental examination with preventive dentistry prior to treatment with bisphosphonates. Patients with multiple myeloma and bone metastasis of solid tumors should be advised to take an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of Vitamin D daily. This recommendation may be tailored to the individual patient.

Compliance with dental recommendations may vary with the clinical situation. Maintaining oral hygiene is an important component of health maintenance and takes on a larger role in patients who may experience bone marrow suppression and oral complications of cancer therapy. (22, 23) Present standard of care includes a dental exam prior to initiating osteoclast inhibiting therapy. (13,22,23, 28,30) The use of dental imaging (panoramic radiographic examinations) is often advised within the present guidelines. (22,23) If a study patient is not compliant with dental assessments, this will be documented by checking the box indicating no dental exam was performed on the Dental Assessment Form (Form #38387). Patients without dental care may participate in the study at the discretion of the clinical investigator.

Invasive dental procedures involving the bone would ideally occur prior to initiating osteoclast inhibiting therapy. Minimally invasive approaches to manage the oral health condition are recommended for patients on osteoclast inhibiting therapy. Any clinically indicated dental procedure will be permitted and patients may remain on study. The course of dental and medical care will be captured on study related reporting forms.

It is recommended, but not required that patients undergo standard dental examinations and care while on study. (See http://www.nlm.nih.gov/medlineplus/ency/article/001957.htm for more information). Financial assistance will be available for dental exams for patients with financial need and without dental insurance who would not have access to dental care by any other means. Please see the Funding Memorandum provided on the protocol abstract page of the SWOG website for S0702 for reimbursement instructions.

b. Prior to Registration (Instruction to sites)

1. Obtain S0702 study consent and Health Insurance Portability and Accountability Act (HIPAA) authorization for study participation. Include patient's authorization to allow the Dental Health Professional to receive and release information as per established policies of the enrolling institution.

2. When the patient has identified their oral health provider, then the institution provides the Dental Health Professional with

   • a copy of the "Letter to the Dental Health Professional" (Appendix 19.2)
   • the S0702 Dentist Contact Form and
   • the S0702 Dental Assessment Form related to the baseline exam
   • the HIPAA authorization for receipt/release of information

The release of information forms are per the individual study sites established practice.
NOTE: Patients may utilize the oral health provider of their choice and for some patients this may include a combination of specialties, such as general dentistry, periodontist, endodontist, oral surgeon, etc. These and other oral health specialists may be appropriate to address the Dental Assessment Form (Form #38387). To assure the provider is appropriately identified, the Dentist Contact Form (Form #16457) is to be used for each Dental Assessment Form (Form #38387) submission. Similarly, a newly involved oral health provider is to be given the Letter for Dental Health Provider (Appendix 19.2).

NOTE: For patients who do not receive the recommended dental care, they should also complete the S0702 HIPAA authorization, including the potential to allow communications with Dental Health Professionals, as the course of oral care may change during the time on study. Should such an individual seek dental care during the course of the study, then the institution is to provide the Dental Health Professional with

- a copy of the "Letter to the Dental Health Professional" (Appendix 19.2)
- the S0702 Dentist Contact Form and
- the S0702 Dental Assessment Form related to the baseline exam
- the HIPAA authorization for receipt/release of information

The release of information forms are per the individual study sites established practice.

3. The registering institution is responsible for the collection of the forms from the Dental Professional
   - The dental health provider is expected to return the forms to the registering institution within 10 days of evaluating the patient (or completing the form whether for a scheduled evaluation or for any assessment that occurs as clinically indicated).
   - If a form is not fully or correctly completed, one attempt should be made to have the dental health provider clarify and complete the form, after which it should be noted in the Comments section of the form that this attempt has been made, and the form may be submitted.
   - If an evaluation has not been performed by a Dental Professional, then the study team is to identify this by checking the "No" box on the case report forms in relationship to whether a dental examination has been performed during this reporting period.

c. Register Patient.
d. Initial Assessment

The S0702 Prestudy Form (Form #43194) must be completed and submitted for all patients at prestudy. NOTE: The patient-related outcomes assessment and questions regarding risk factors and patient history should be asked of the patient in order to complete this form. A baseline phlebotomy should be performed to obtain blood for banking. See Section 15.1e and 15.1f for blood submission requirements.

e. On Study Assessments

Patients will undergo therapy with zoledronic acid as clinically indicated. Patients must be planning to receive zoledronic acid for metastatic disease (see Section 5.2). Patients will receive medical and dental care as clinically indicated at the discretion of the patient’s health care providers. As stated in Section 5.10, patients may concurrently participate in other clinical trials. This study does not dictate subsequent osteoclast inhibiting therapy.
The **S0702** Medical Assessment Form (Form #62856) must be completed by the CRA, nurse or physician every 6 months. NOTE: The patient-related outcomes assessment questions should be asked of the patient in order to complete this form. The **S0702** Dental Assessment Form (Form #38387) must be completed by the office of the dental professional performing the dental assessment, unless no dental assessments have been done. In which case, the CRA will mark the box indicating that no dental assessment was performed during this reporting period. Communication with the dental team is at the discretion of the registering institution. The dental health provider is expected to return the forms to the registering institution within 10 days of the evaluation. NOTE: If the form is not fully or correctly completed, one attempt should be made to have the dental health provider clarify and complete the form, after which it should be noted in the Comments section of the form that this attempt has been made, and the form may be submitted.

The **S0702** Dental Assessment Form (Form #38387) must be submitted at the required intervals. If the patient was non-compliant with the recommended dental follow-up, then the investigative medical team can indicate “No” dental evaluation has been performed during this reporting period. The **S0702** Dentist Contact Form (Form #16457) should be submitted each time the Dental Assessment Form is submitted (i.e. every 6 months). If no dental provider is involved in the patient's care, this should be noted in the Dental Contact Form and submitted. The **S0702** ONJ Assessment Form (Form #33523) is submitted per Section 7.5f.

The **S0702** Medical Assessment Form must be submitted at the required intervals. The clinical care dates will be recorded on the form and reflect the most recent medical assessment. The study does not dictate follow up.

Clarification of Reporting Periods on Dental and Medical Assessment Forms and Dentist Contact Form

For the initial prestudy submission of these forms, please use the actual date of prestudy dental exam for Reporting Period Start Date. The date of registration should be used as the Reporting Period End Date for the initial prestudy submission of these forms, and as the Reporting Period Start Date for the first on-study submission.

At each 6 month assessment, serum should be obtained for banking. See Section 15.1d for serum submission requirements.

Please refer to Appendix 19.7 for information about how to quantify use of steroids for forms reporting.

**f. Cases of ONJ**

If an oral lesion is suspected for or confirmed to be ONJ by a health care provider assessment, it is recommended that the patient have a dental evaluation which involves dental exam and dental imaging as clinically indicated. For the patient in this situation, the survey forms will change from "screening" to "ONJ lesions". The frequency of study assessments will change from every 6 months to every 3 months until 3 years after registration. Frequency of recommended dental visits and required clinical medical assessments will change to every 3 months. Form requirements will consist of the **S0702** ONJ Assessment Form (Form #33523), and the **S0702** Medical Assessment Form (Form #62856) every 3 months. The **S0702** Dentist Contact Form (Form #16457) should be submitted each time the ONJ Assessment Form is submitted (i.e. every 3 months). If ONJ is diagnosed by the medical team and the patient has not had dental care, please mark the corresponding box on the ONJ form and submit.

For patients with suspected or confirmed ONJ, serum will also be requested every 3 months rather than every 6 months. See Section 15.1e.
On-study oncology assessment with the **S0702** Medical Assessment Form (Form #62856) must be completed every 3 months.

1. Suspected or confirmed ONJ is defined in Section 10.1
2. Image Collection

For patients diagnosed with confirmed ONJ, relevant dental and medical images must be submitted to the AG Mednet, as outlined in Section 15.2. The required images include the baseline dental imaging (panoramic radiograph and/or X-rays), any follow-up dental images obtained up to and including the ONJ diagnostic dental images, and any baseline or on-study scans (CT, MRI, bone scans, skeletal surveys) of the head and neck obtained between prestudy and diagnosis of ONJ. Any follow-up dental or medical scans performed after diagnosis of ONJ up to 3 years after registration will also be required to be submitted.

For patients without ONJ, relevant dental and medical images may be requested for submission to the AG Mednet at a future time point.

g. Resolution of Suspected ONJ

If a patient with suspected ONJ has complete resolution of the suspected ONJ lesion without developing confirmed ONJ as evaluated by serial monitoring, and if clinically indicated, dental follow-up form submission may be changed from every 3 months (ONJ Assessment Form) back to every 6 months (Dental Assessment Form). If the patient develops confirmed ONJ, the ONJ Assessment Form would be used.

In patients with suspected ONJ the Medical Assessment Form submission interval changes from every 6 to every 3 months. In those with suspected ONJ who do not go on to develop confirmed ONJ, the Medical Assessment Form submission frequency will return to every 6 months.

h. Coordination of Clinical and Study Visits

Patients are to be cared for as clinically indicated, including the frequency of all medical visits. The submission of study forms is to occur as per Section 14.0. Recognizing that the timing of the clinical assessments may not align precisely with dates of form submission, please submit the forms as per protocol using the last clinical assessment dates and data. For those patients that have consented for donation of blood specimens, the blood specimens should be collected and shipped as per study calendar plus or minus 30 days.

i. Off Study

At 3 years after registration, submit a final **S0702** Medical Assessment Form (Form #62856) and **S0702** Dental Assessment Form (Form #38387) (along with the **S0702** Dentist Contact Form [Form #16457]) for patients without ONJ. For patients who developed ONJ, submit a final **S0702** Medical Assessment Form (Form #62856) and a **S0702** ONJ Assessment Form (Form #33523) (along with the **S0702** Dentist Contact Form [Form #7219]). Submit the **S0702** Off Protocol Notice (Form #16689) for all patients.

7.6 **Criteria for Removal from Study:**

a. If a medical condition arises which in the opinion of the treating investigator precludes patient’s participation in this study, the patient will then be removed from study.

b. Completion of 3 years on study.

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

7.7 All reasons for discontinuation of study must be documented in the **S0702** Off-Protocol Notice (Form #16689).

7.8 Patients will be followed for a maximum of 3 years after registration.

8.0 **TOXICITIES TO BE MONITORED AND DOSAGE MODIFICATIONS**

There are no dose modifications or toxicities associated with this study.
### Required Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Month</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History &amp; Physical Exam</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Exam</td>
<td>Xa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Laboratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBC/Differential/Platelets/Hemoglobin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, albumin</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Creatinine</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine Clearance (calculated)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy Test</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphate, magnesium, electrolytes</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>X-Rays/Scans</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Imaging</td>
<td>Xa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Specimens</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum for banking (optional)</td>
<td>£</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whole blood for DNA analysis/banking (optional)</td>
<td>Ω</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Patient-Related Outcomes Assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Forms Submission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0702 Prestudy Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0702 Medical Assessment Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0702 Dental Contact Form</td>
<td>Δ</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0702 Dental Assessment Form</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S0702 ONJ Assessment Form</td>
<td>◊</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Study Calendar

- Results of these tests do not determine eligibility but are suggested at Prestudy for Good Medical Practice (see Section 7.2).
- Patients are recommended to undergo standard dental examinations and care while on study (see Appendix 19.1). It is the standard of care for patients receiving bisphosphonates to have regular dental exams throughout treatment. Patient treatment is not dictated by this protocol. Medical and dental assessment forms are submitted every 6 months until diagnosis of ONJ (if diagnosed), then every 3 months until 3 years from the time of registration.
- The baseline dental exam and imaging are recommended.
- Participants who develop ONJ will submit their baseline dental films (capturing the jaw) within 28 days of ONJ diagnosis. See Section 15.2.
- Serum will be drawn for banking at baseline and every 6 months until the end of study. If ONJ is diagnosed during study, the serum banking interval must switch to every 3 months until off protocol.
- Whole blood will be drawn at baseline only.
- If ONJ is diagnosed during study, submit the S0702 ONJ Assessment Form within 30 days of detection of ONJ, and then every 3 months until off protocol.
- Submit the S0702 Medical Assessment Form every 6 months until either ONJ is detected or until off protocol. If ONJ is diagnosed during study, the interval for submission of the S0702 Medical Assessment Form must switch to every 3 months until off protocol. Clinical medical assessments should be scheduled to match the form submission schedule.
- S0702 Dental Assessment Form should be submitted every time the S0702 Dental Assessment Form or the S0702 ONJ Assessment Form (for those with ONJ) is submitted in order to capture a change in provider or to note that no dental provider is currently involved.
- Patient-related outcome assessments are included on the S0702 Prestudy Form and S0702 Medical Assessment Form, and should be asked of the patient prior to submission of these forms. The S0702 Prestudy Form also contains questions regarding risk factors and patient history that should be asked of the patient.
- The data is to be submitted on schedule (every 6 months) as outlined above. Physical exams are to be performed as clinically indicated, regardless as to whether this corresponds to a data submission timepoint. The forms are to be completed using the data collected at the time of the forms being due. Clinical (medical and dental) assessment intervals are not indicated by this study. Subsequent clinical assessments will be captured on subsequent CRFs.
10.0 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

10.1 Primary Endpoint:

The primary endpoint is the diagnosis of confirmed ONJ. Diagnosis will be defined as follows:

**A suspected case of ONJ:** is defined as an area of exposed bone in the maxillofacial region that had been identified by a health care provider and had been present for less than 8 weeks in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region. Suspected cases of ONJ should receive follow-up evaluation to determine whether they ultimately meet the definition of a confirmed case.

**A confirmed case of ONJ:** is defined as an area of exposed bone in the maxillofacial region that had been identified by a health care provider and had been present for 8 weeks or more in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region.

10.2 Performance Status: Patients will be graded according to the Zubrod performance status scale.

<table>
<thead>
<tr>
<th>POINT</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>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.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled; cannot carry on any self-care; totally confined to bed or chair.</td>
</tr>
</tbody>
</table>

11.0 STATISTICAL CONSIDERATIONS

11.1 The primary goal of this study is to estimate the cumulative incidence rate of confirmed ONJ associated with zoledronic acid at 3 years in patients with bone metastases. We plan to accrue 3,500 patients planning to receive zoledronic acid. According to recent reports, the median time to onset of ONJ among patients receiving zoledronic acid is 18 months according to Durie, et al, (range, 4-35 months) and 18 months according to Maerevoet, et al, (range, 4-22 months). Based on these data, in this study patients will be followed for a total of 3 years to allow sufficient assessment time for detection of ONJ. The anticipated dropout rate over 3 years is 30% (where dropout, for the purposes of analysis, is defined as not achieving 3 years of follow-up for any reason). Under this scenario, a conservative estimate of the confidence interval (as calculated from the exact binomial in patients with complete follow-up) is shown in the table below for different rates of assumed incidence. Note that because the assumed incidence differs substantially from 50%, the confidence intervals are not symmetric.
A sample size of 3,500 will allow us to estimate the confidence interval to within ± 26% (based on the upper bound of 95% confidence interval) of the assumed incidence (the "relative accuracy"), if the assumed incidence is at least 2.0%. The estimate of 2.0% is based on Stopeck, et al (2010), adjusted for longer follow-up. The relative accuracy will improve with higher incidence, as shown in the table. The estimates below are conservative as they are based on the assumption of no information from the 30% of patients estimated to drop out. The cumulative incidence of ONJ at 3 years will be estimated to account for censoring.

<table>
<thead>
<tr>
<th>Assumed Incidence (p)</th>
<th>95% confidence interval about p</th>
<th>Relative accuracy [(95% CI upper bound – p)/p]</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.0%</td>
<td>1.59% - 2.52%</td>
<td>.26</td>
</tr>
<tr>
<td>3.0%</td>
<td>2.48% - 3.62%</td>
<td>.21</td>
</tr>
<tr>
<td>4.0%</td>
<td>3.40% - 4.70%</td>
<td>.18</td>
</tr>
<tr>
<td>5.0%</td>
<td>4.33% - 5.77%</td>
<td>.15</td>
</tr>
</tbody>
</table>

11.2 Secondary Objectives

a. Secondary objectives include disease-specific estimates of the confirmed cumulative incidence at 3 years of ONJ. Because disease-specific subsamples will be smaller than the overall sample size, relative accuracy will be limited. As shown in the table below, the relative accuracy will differ depending on the proportion of patients in the disease subset and the assumed incidence.

<table>
<thead>
<tr>
<th>Relative Accuracy</th>
<th>Proportion in disease subset</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONJ Incidence</td>
<td>50%</td>
</tr>
<tr>
<td>2%</td>
<td>.45</td>
</tr>
<tr>
<td>3%</td>
<td>.38</td>
</tr>
<tr>
<td>4%</td>
<td>.31</td>
</tr>
<tr>
<td>5%</td>
<td>.27</td>
</tr>
</tbody>
</table>

Given historical data from Novartis, the anticipated proportion of patients by disease type is breast, 37%; myeloma, 20%; prostate cancer, 17%; lung cancer, 13%; and other solid tumors, 13%.

b. In addition to estimating overall and disease-specific incidence, we will explore the association of baseline factors with cumulative incidence of confirmed ONJ. As an example, with 3,500 patients and 30% dropout (defined as in 11.1), for a given binary factor with 50% in each subgroup, and the anticipated 3 years of accrual with 3 additional years of follow-up, if the ONJ cumulative incidence at 3 years is 2%, there will be adequate power (≥ 80%) to detect a risk ratio of ≥ 2.32 between the poor and good performing groups. The minimum detectable risk ratio with adequate power will depend on the proportion in subgroups (as defined by the factor of interest) and the cumulative incidence, and are shown in the table below. These estimates are conservative as they are based on the assumption of no information from the 30% of patients estimated to drop out.

<table>
<thead>
<tr>
<th>Risk Ratio Proportions in poor vs. good performing groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative Incidence</td>
</tr>
<tr>
<td>2%</td>
</tr>
<tr>
<td>3%</td>
</tr>
<tr>
<td>4%</td>
</tr>
<tr>
<td>5%</td>
</tr>
</tbody>
</table>
Multivariate modeling of ONJ risk will be performed incorporating both the patient status (ONJ vs. no ONJ) and the time to event, using Cox regression modeling.

Baseline factors will include (but not be limited to) corticosteroid therapy, radiotherapy, pre-existing dental disease, prior dental procedures, concomitant infections, oral trauma, alcohol use, smoking history, cancer history, and comorbid diseases.

c. Most cases of "suspected" ONJ are anticipated to be confirmed by follow-up. However, a sensitivity analysis of overall and disease-specific cumulative incidence, as well as of exploratory analyses of baseline factors and cumulative incidence, will be performed on the combined endpoint of confirmed plus suspected ONJ, if the number of "suspected" cases of ONJ at study conclusion is > 10% of all cases.

d. The incidence of ONJ in subgroups of patients according to their amount of actual zoledronic acid received (dose-response) will be estimated.

e. The association between patient-related outcomes and confirmed incidence will be explored, in a similar fashion as other baseline factors.

f. The clinical presentation and natural history of ONJ will be analyzed in a descriptive fashion.

11.3 The imaging bank will be utilized to conduct a case-control study for investigation of potential predictive and/or prognostic markers of increased risk for ONJ and/or exploring the potential mechanism of ONJ. The design and hypotheses specifications for this substudy are unknown at the time of protocol initiation, and will depend in part on the number of ONJ cases found. Images for ONJ cases will be routinely collected; information on the availability of images for non-ONJ cases will also be collected prospectively. Given the number of cases anticipated, a case of control ratio of 1:1 is projected.

11.4 Feasibility

Based on prior accrual, as well as expected changes to eligibility under the study revision enacted on March of 2011 ongoing accrual to this study is expected to be about 70-75 patients/month, with accrual completion occurring in about 3 years from study revision. In assessing accrual feasibility following study revision, we will allow 6 months for IRB approval of the revised study before steady study-wide accrual is assumed to be reached. Feasibility will be assessed at 1.5 years after study revision. If monthly average accrual in quarters 5-6 after study revision is < 50% of projected accrual, efforts will be made to increase accrual over the succeeding 6 month period. If after 2 years, monthly accrual remains < 50% of projected accrual, study closure will be considered.

11.5 There is no formal data and safety monitoring committee for this study. Monitoring of study conduct and accrual for feasibility will be performed routinely by the Study Coordinator, Study Statistician, and the Disease Committee Chair. Accrual reports are generated weekly.

12.0 DISCIPLINE REVIEW

There will be no formal discipline review for this study.
13.0 REGISTRATION GUIDELINES

13.1 Patients must be registered within 30 days prior to initiation of protocol-specified planned zoledronic acid treatment. (Note: Prior osteoclast inhibiting therapy as noted in Section 5.2 is allowed).

13.2 For either phone or web registration, the individual registering the patient must have completed the appropriate Southwest Oncology Group Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

The individual registering the patient must also be prepared to provide the treating institution's name and ID number in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered into the data base. Patients will not be registered if the IRB approval date has not been provided or is > 365 days prior to the date of registration.

13.3 Registration procedures - Southwest Oncology Group Institutions

a. You may register patients from Member, CCOP and approved Affiliate institutions to this study using the SWOG Registration program. To access the Registration program go to the SWOG Web site (http://swog.org) and click on the Logon link to go to the SWOG Members Area logon page (https://swog.org/visitors/logon.asp). This Web program is available at any time except for periods listed under Down Times. Log on as an Individual User using your SWOG Roster ID Number and individual web user password. Help for the logon process may be found at https://swog.org/visitors/logonhelp.asp. After you have logged on, click on the Clinical Trials link and then the Patient Reg link to go to the Entry Page for the Patient Registration program. If you are a Registrar at an institution with Internet access you are encouraged to register this way. For new users, the link to a "Starter Kit" of help files may be found by clicking on Starter Kit link at the logon page.

To register a patient the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN to the institution where a registration is occurring, and
3. You are granted permission to use the Patient Registration program at that institution.

For assistance with points 1 and 2 call the SWOG Operations Office at 210/614-8808. For point 3 you must contact your Web User Administrator. Each SWOG institution has one or more Web User Administrators who may set up Web Users at their institution and assign permissions and passwords to these users. For other password problems or problems with the Patient Registration program, please e-mail webreghelp@crab.org. Include your name, Roster ID Number, and telephone number, when the problem occurred, and exactly what you were doing.

b. If the Web Reg program is not used, the registration must be done by phone.

Member, Affiliate and CCOP Institutions

Registration by phone of patients from member, affiliate and CCOP institutions must be done through the Southwest Oncology Group Data Operations Center in Seattle by telephoning 206/652-2267, 6:30 a.m. to 4:00 p.m. Pacific Time, Monday through Friday, excluding holidays.
14.0 **DATA SUBMISSION SCHEDULE**

14.1 Data must be submitted according to the protocol requirements for **ALL** patients registered including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master forms are included in Section 18.0 and (with the exception of the sample consent form and the Registration Worksheet) must be submitted to the Data Operations Center in Seattle. Data from approved SWOG institutions must be submitted on-line via the Web; see Section 14.3a for details. Exceptions to online data submission are patient-completed (e.g. Quality of Life) forms and source documents (e.g. pathology/operative/lab reports).

14.3 Data Submission Procedures.

a. Data Submission Procedures for SWOG Institutions

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

To submit data via the web the following must be done (in order):

1. You are entered into the Southwest Oncology Group Roster and issued a SWOG Roster ID Number,
2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed, and
3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to submit data for that institution.

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

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

14.4 **WITHIN 7 DAYS OF REGISTRATION**:

Submit the following:

a. **S0702** Dentist Contact Form (Form #16457)
b. **S0702** Dental Assessment Form (Form #38387)
c. **S0702** Prestudy Form (Form #43194)
d. Institutional surgical pathology report or equivalent documentation to support diagnosis of primary malignancy and reports from radiology, pathology or other modality to support the diagnosis of bone metastases.

e. Submit blood and serum specimens as described in Sections 15.1e and 15.1f.

14.5 WHILE ON PROTOCOL, EVERY 6 MONTHS FOR THREE YEARS OR UNTIL ONJ IS DETECTED:

Submit copies of the S0702 Medical Assessment Form (Form #62856) documenting treatment information for cancer and details of osteoclast inhibiting therapy, the S0702 Dental Assessment Form (Form #38387) and the S0702 Dentist Contact Form (Form #16457).

Submit serum as described in Section 15.1e.

14.6 WITHIN 28 DAYS OF DETECTION OF ONJ:

Submit S0702 ONJ Assessment Form (Form #33523)

Submit the S0702 Dentist Contact Form (Form #16457)

Submit Dental Imaging and radiology report as described in Section 15.2.

14.7 FOR THOSE WITH SUSPECTED OR CONFIRMED ONJ, EVERY 3 MONTHS WHILE ON PROTOCOL:

Submit S0702 Medical Assessment Form (Form #62856), the S0702 ONJ Assessment Form (Form #33523) and the S0702 Dentist Contact Form (Form #16457).

NOTE: In the situation of the resolution of suspected ONJ lesion without development of ONJ, the S0702 Dental Assessment Form (Form #38387) is to be used for the submission every six months for the duration of study participation, unless the patient develops new or recurrent suspected ONJ or develops confirmed ONJ. The S0702 Dentist Contact Form (Form #16457) is to be submitted each time the S0702 Dental Assessment Form (Form #38387) is submitted.

Submit serum as described in Section 15.1e and dental and other films as described in Section 15.2.

14.8 WITHIN 14 DAYS OF REMOVAL FROM PROTOCOL FOR PATIENTS WITHOUT SUSPECTED OR CONFIRMED ONJ:

Submit a copy of the S0702 Off-Protocol Notice (Form #16689) along with the final copies of the S0702 Medical Assessment Form (Form #62856), S0702 Dental Assessment Form (Form #38387) and the S0702 Dentist Contact Form (Form #16457).

Patients will not be followed beyond the duration of the 3 year study period.

14.9 WITHIN 14 DAYS OF REMOVAL FROM PROTOCOL FOR PATIENTS WITH SUSPECTED OR CONFIRMED ONJ:

Submit a copy of the S0702 Off-Protocol Notice (Form #16689) along with the final copies of the S0702 Medical Assessment Form (Form #62856) and S0702 ONJ Assessment Form (Form #33523) and the S0702 Dentist Contact Form (Form #16457).

Patients will not be followed beyond the duration of the 3 year study period.

14.10 WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit a copy of the Notice of Death (Form #49467) if death occurs during the 3 year study period.
15.0 SPECIAL INSTRUCTIONS

15.1 Specimen Banking and Correlative Studies

a. **Institutions must seek additional patient consent to submit and bank the following specimens:**

1. Serum for banking.

2. Whole blood for DNA analysis and banking

With patient's consent blood specimens must be submitted to the SWOG Specimen Repository, where they will be banked for future translational medicine studies. Additionally, the SWOG Specimen Repository will perform DNA preparation from whole blood.

b. **Specimen submission instructions**

Specimen submission instructions can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/STSpecimens.asp), or via the link on the **S0702** protocol abstract page on the SWOG website (www.swog.org).

c. **Visit kits**

Prior to registration, institutions should order blood collection kits by contacting the SWOG Specimen Repository-Solid Tissue, Myeloma and Lymphoma Division.

- Contact: Filiz Muharrem
- Phone: 614/355-2805
- E-mail: filiz.muharrem@nationwidechildrens.org

Anticipate need and allow time for shipment (2 – 3 days).

Each **S0702** blood collection kit contains:

- The collection tubes (10 mL red-top serum tube and 10 mL EDTA lavender top whole blood tube)
- Cryovials 1.8 mL
- Cool Pack (U-tek)
- Specimen transfer pipettes
- Biohazard label
- UN3373
- Dry ice label
- Specimen Submission Form
- Fed Ex Airbill
- Instruction Sheet
- Absorbent Sheets
- Specimen transport bag with biohazard label (6x10)

d. **General directions for collecting and processing specimens**

- Prior to phlebotomy, make sure participant’s paper work includes SWOG study number (**S0702**), and SWOG patient ID number.
- Prepare collection material and make sure the ID of the participant to be drawn matches the demographics on the requisition of the draw.
- Seat the participant for at least five minutes prior to blood collection.
e. Serum collection:

Serum will be drawn for banking at baseline and at 6, 12, 18, 24, 30 and 36 months. For patients who developed suspected or confirmed ONJ on protocol, the frequency of serum collections will increase to every 3 months until end of study.

1. Collect one Serum Separator (SST Vacutainer® tube) preferably under fasting conditions.

2. Label specimen with SWOG study number (S0702), SWOG patient ID number, and other institutional requirements.

3. Allow the red-top tube to clot for 20-30 minutes at room temperature. Centrifuge the red top for 20 minutes at 3000 rpm.

4. Distribute even aliquots of serum to the cryovials provided using the transfer pipet provided.

5. Label cryovials with SWOG study number (S0702) and SWOG patient ID number.

6. At the local site, the specimen is stored at -70°C prior to shipment on dry ice.

7. Place the cryovials in the provided specimen transport bag; place the provided absorbent sheet into the bag; place the bag in a Styrofoam container with 3 lbs dry ice; place container into a shipping box.

8. A copy of the Shipment Packing List produced by the Specimen Tracking System should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. Seal the shipping box. Place the provided biohazard, UN3373 and dry ice labels to the outside of the shipping box. Fill out the sender information on the provided preprinted FedEx air bill and attach the air bill to the top of the shipping box. Retain a copy of the air bill.

f. Whole blood:

10 mL whole blood will be drawn at baseline for all patients. A portion of each of these samples will be used for DNA analysis. With additional patient consent, the remaining portion of the sample will be banked for future research.

1. Collect one EDTA (lavender top) Vacutainer® tube preferable under fasting conditions. Mix sample by gentle inversion, 4-5 times. Do not shake.

2. Label specimen with SWOG study number (S0702), SWOG patient ID number, and other institutional requirements.

3. Wrap the lavender-top tube in the provided absorbent sheet and place into the provided specimen transport bag, and place the bag in the refrigerator at 4°C until ready to ship. Place specimen above in Styrofoam container with a cold pack provided (DO NOT SHIP ON DRY ICE).
4. A copy of the Shipment Packing List produced by the Specimen Tracking System should be printed and placed in the pocket of the specimen bag if it has one, or in a separate resealable bag. Seal the shipping box. Fill out the sender information on the provided preprinted FedEx air bill and attach the air bill to the top of the shipping box. Retain a copy of the air bill.
15.2 Instructions for Submission of Dental Imaging

a. Baseline dental scan(s) (such as, panoramic radiograph, X-rays, bone scans, CT, MRI, skeletal survey or PET scan) capturing the jaw must be submitted within 30 days of ONJ diagnosis for patients who develop ONJ on study. (NOTE: Similar imaging will be requested of participants who are selected as match case controls.) Please note that of the 3,500 patients to be enrolled on this study, we estimate 100-200 ONJ cases and an equal number of control cases.

b. For ONJ cases, subsequent images of the area affected by ONJ must be submitted within 30 days of their performance.

c. Electronic submission of dental imaging is to be used if the dental image capturing the jaw (such as panoramic radiograph, x-rays, bone scans, CT, MRI, skeletal survey or PET scan) is available in any digital format (i.e., JPEG, DICOM, GIF, TIFF, etc).

The electronic images must be submitted electronically via the AG Mednet service provided by SWOG. Specific information about the imaging workflow and instructions for the imaging portion of this study can be found at http://www.agmednet.com/doc/TrialUserGuide.pdf.

Electronic Submission Set-up

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

Note: The person responsible for activating the desktop agent should be involved in submitting the exams as the Desktop Agent requires specific log-in verification. All questions regarding AG Mednet agent use should be directed to 888-9AGMEDNET, and hit 2 for the support option.

Sites should contact AG Mednet at the time that it is known they will be required to submit an image for S0702, so that the Desktop Agent program specific to S0702 can be activated to allow the image submission. This contact is needed even if you are using AG Mednet for another SWOG trial.
Electronic Image Submission Process

When submitting images, you will be required to follow the S0702 Image Submission protocol, which includes completing a transmittal form and de-identifying the exam. First import the exam from a CD or file system, PACS, or directly from the scanner. Select the exam in your Desktop Agent worklist, assign it to the S0702 trial.

To complete the Transmittal Form, select the form under the tasks column. Instructions for the form will be sent to your site at enrollment. The data from that transmittal form will be automatically integrated with the trial databases.

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

The final task in your workflow after completing the transmittal form and de-identification is to upload the exam and associated information to SWOG. This can be completed by selecting upload exam in the task list.

All questions regarding Ag Mednet Agent use, transmittal forms, de-identification or image submission through AG Mednet should be directed to 888.9AGMEDNET, and hit 2 for the support option.

d. If the images are only available on film and you cannot locally digitize the film, the film images can be sent by mail to the Cancer Research and Biostatistics (CRAB) for digitization and de-identification. CRAB will then submit the de-identified images to AG Mednet and return the original films to the site.

In these cases, the S0702 Image Transmittal Form (Form #33233) must be completed by the site and a hard copy of the Transmittal Form will be sent to CRAB with the films. Mail to:

Cancer Research Biostatistics (CRAB)
1730 Minor Avenue, Suite 1900
Seattle, WA 98101-1468
Attn: S0702 Coordinator

e. If a patient has been selected as a control and imaging is to be submitted, the same S0702 image transmittal form should be submitted. However, only 2 options for image time points are relevant to check off on the form: baseline (within 12 months of study entry) and follow up (while on study).

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).
Adverse Events

Institutions should use the FDA MedWatch guidelines at http://www.fda.gov/medwatch to voluntarily report a serious adverse event that is associated with the use of an FDA-regulated drug such as zoledronic acid.

The definitions of “serious adverse event” and “associated with the use of the drug” will be as per the FDA definitions in 21CFR314.80:

“Serious adverse drug experience” is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate 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.

“Associated with the use of the drug” is defined as: there is a reasonable possibility that the experience may have been caused by the drug.

For this study, serious adverse experiences (defined above) should be reported to the FDA using the MedWatch form. In parallel, Novartis Pharmaceutical Corporation will collect similar adverse experience data related to zoledronic acid via their SAE Fax Cover Form included in Appendix 19.5, which should be completed in addition to the MedWatch Form.
17.0 BIBLIOGRAPHY


18.0 MASTER FORMS SET

18.1 The Model Informed Consent Form is included in this section, preceded by "Notes for Local Institution Consent Form Authors" and "Notes for Local Investigators." The study - as well as the local consent form meeting the guidelines noted in these documents - must be reviewed and approved by the Institutional Review Board prior to registration of patients on this study.

18.2 This section includes copies of all data forms which must be completed for this study. These include:

a. **S0702** Registration Worksheet (Form #6551) (Revised 10/1/2011)
b. **S0702** Prestudy Form (Form #43194) (Revised 10/1/2011)
c. **S0702** Medical Assessment Form (Form #62856) (Revised 10/1/2011)
d. **S0702** Dentist Contact Form (Form #16457) (Revised 10/1/2011)
e. **S0702** Dental Assessment Form (Form #38387) (Revised 10/1/2011)
f. **S0702** ONJ Assessment Form (Form #33523) (Revised 10/1/2011)
g. **S0702** Image Transmittal Form (Form #33233) (Revised 5/1/2010)
h. **S0702** Off-Protocol Notice (Form #16689)
i. Notice of Death (Form #49467) (9/1/03)
Informed Consent Model for **S0702**

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:*

This model informed consent form has been reviewed by the DCT/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the Southwest Oncology Group Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the Southwest Oncology Group Operations Office.

<table>
<thead>
<tr>
<th>Readability Statistics:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flesch Reading Ease</td>
</tr>
<tr>
<td>Flesch-Kincaid Grade Level</td>
</tr>
</tbody>
</table>

- 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 the Southwest Oncology Group.

The "Southwest Oncology Group" 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 the Southwest Oncology Group. This includes consent forms for studies where all patients are registered directly through the Southwest Oncology Group Data Operations Office, all intergroup studies for which the registration is being credited to the Southwest Oncology Group (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 the Southwest Oncology Group.
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: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at http://cissecure.nci.nih.gov/ncipubs/details.asp?pid=1035 or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.

- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.
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 cancer that has spread to the bone are planning to receive zoledronic acid as a part of your treatment. (8/24/11)

Who is doing this study?

The Southwest Oncology Group (SWOG) is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of almost four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

Zoledronic acid falls under a category of drugs called bisphosphonates. Bisphosphonates are a type of drug that inhibit cells in the bone called osteoclasts. (sentence added 8/24/11) Osteoclast inhibitors are sometimes given to patients who have cancer that has spread to their bones because it can lower the chances of getting fractures and reduces bone pain. (8/24/11) Usually, zoledronic acid is well tolerated by patients, but there has been an increase in the number of reported cases of osteonecrosis of the jaw (ONJ). Symptoms associated with ONJ are swelling of the soft tissue around the jaw, infection, loosening of teeth, drainage, and exposed jaw bone. There is concern about the association of ONJ with bisphosphonate therapy.

The purpose of this study is to learn how often ONJ occurs in patients who are being treated with zoledronic acid during a three year time period after starting treatment. This study will also identify risk factors associated with ONJ. (8/24/11)

How many people will take part in the study?

About 3,500 people will take part in this study nationally.
What will happen if I take part in this research study?

This is not a treatment study. This study involves collecting information about your treatment with zoledronic acid and collecting information about your general health and medical history, oral health and dental history and pain assessment through questionnaires. Most importantly, we will collect information about ONJ if it occurs and what kind of treatment you receive for ONJ. Your medical and dental care will be directed by your health care team.

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

• Medical history and physical exam (8/24/11)
• Bloodwork (standard for zoledronic acid) (8/24/11)
• Optional dental history and dental exam (may include dental x-rays) (8/24/11)
• (deleted 8/24/11) (delete date corrected 12/6/11)
• Optional bloodwork for research (added 8/24/11)

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be asked to provide information regarding your treatment, medical history, physical examinations and dental evaluations.

Every six months for up to three years… (8/24/11)
You will be asked to provide

• Information regarding current treatment for metastatic bone disease
• Information about any health problems you are having
• Information about your medical history, treatments and physical exam
• Information regarding your oral health, dental history and exams and pain assessment

If at any time you are diagnosed with osteonecrosis of the jaw (ONJ)
Every three months for up to three years, you will be asked to provide (8/24/11)

• Information regarding current treatment for ONJ
• Information about any health problems you are having (8/24/11)
• Information regarding oral complications and recent dental procedures
• Updated information on your medical history, physical exam, and treatment
• Submission of dental x-rays and scans

Even if you do not develop ONJ, you may be selected as a "control" to have your dental x-rays and scans compared to patients who do get ONJ. In this case, you will be asked provide your medical and dental history with the submission of dental x-rays and scans. (8/24/11) (date corrected 12/6/11) This study asks permission to use information from all patients because it is unknown who will develop ONJ. (added 8/24/11)
How long will I be in the study?

You will be asked to take part in the study for up to three years. (8/24/11) After you are finished with the study, you do not have to come to the clinic for reasons relating to the study.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or if you decide to stop.

(paragraph deleted 2/9/09)

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the study?

You will receive care as directed by your healthcare team. (8/24/11) This study does not give treatment, that is for you and your doctor to decide on together. (added 8/24/11) This is an observational study. (added 8/24/11) Therefore there should be no side effects associated with this study. (8/24/11) The goal of the study, however, is to observe and record the potential dental side effect of ONJ associated with your osteoclast inhibiting treatment. (8/24/11) A list of side effects that may occur with the osteoclast inhibiting treatment can be provided to you by the clinic or physician administering the osteoclast inhibiting therapy. Osteoclast inhibiting therapy is part of routine care in treating patients whose cancer has spread to the bone. (8/24/11)

Are there benefits to taking part in the study?

Taking part in this study may not directly benefit you. We do know that the information from this study will help doctors learn more about relationship between bisphosphonates and osteonecrosis of the jaw. This information could help patients with bone metastases know more about ONJ in the future. (8/24/11)

What other choices do I have if I do not take part in this study?

Your other choices may include:

- Taking part in another study

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.
Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The Southwest Oncology Group
- Novartis Pharmaceuticals
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- The Cancer Trials Support Unit (CTSU), a service sponsored by the National Cancer Institute (NCI) to provide greater access to clinical trials (added 2/9/09) (8/24/11)

What are the costs of taking part in this study?

You and/or your health/dental plan/insurance company will need to pay for some of the costs of associated with this study like regular a physical exam and dental health screening. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. If you do not have dental insurance coverage, discuss this with your study team.

The parts of the research consisting of keeping research records will be paid by those organizing and conducting the research. The research requires that you receive certain standard medical tests and examinations. These standard tests and examinations will be charged in the usual way.

Dental exams, dental x-rays and care will be billed to you and/or your health/dental plan/insurance. If you do not have dental insurance coverage, discuss this with your study team.

The fees associated with shipping and storing of the study-associated blood and imaging is covered within the study.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute’s Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

There is no risk of injury because you will not receive study specific treatment on this study. (8/24/11)

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.
We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

You may be in the study and yet decline to have blood or films stored for future research. Further, if you first decide to have these samples stored for research, but later change your mind, you may do so by giving written notice of this to (principal investigator) at the (participating institution). The remains of your sample will then be destroyed. Your decision will not affect your care.

Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor __________________ [name(s)] at ________________ [telephone number].

For questions about your rights while taking part in this study, call the __________________ [name of center] Institutional Review Board (a group of people who review the research to protect your rights) at ________________ (telephone number). [Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

*You may also call the Operations Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only). [*Only applies to sites using the CIRB.]*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at http://cancer.gov/

- For NCI’s clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI’s general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.
I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Signature

Print name of participant

Date

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. The collection of specimens lets the study to answer more questions about osteoclast inhibiting therapy and ONJ. (added 8/24/11) You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies. You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Optional DNA and Future Contact for Protocol
1. If you agree, with your additional permission, whole blood will be collected at the time of your initial visit and will be sent to a lab for DNA analysis and the leftover blood will be kept at a central storage lab for use in future research.

   DNA testing may be done on my initial blood sample.
   
   Yes        No

Occasionally, researchers working with the Southwest Oncology Group (SWOG) may have another research idea that relates to people who were on a SWOG study. In some cases, to carry out the new research, we would need to contact participants in a particular study. You can agree or not agree to future contact by circling "yes" or "no".

2. 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
Consent Form for Future Use of Specimens and Imaging for Research

About Using Specimens and Imaging for Research

If you agree, blood and dental images (and/or images of the jaw bone) will be stored indefinitely and may be used in research to learn more about cancer, ONJ and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

Optional Blood Collection for Future Research

If you agree to the optional study, with your additional permission, blood samples will be collected when you enter the study and every 6 months while you are on study (or every 3 months if you are diagnosed with ONJ) and will be sent to a central storage lab for use in future research.

(Optional section deleted 12/6/11)

Optional Image Collection for Future Research

Dental imaging consists of panoramic, intraoral films, small films, bite wings, x-ray films and/or digital files. Imaging of the jaw may include x-rays, bone scans, CT scans, PET scans or MRI.

If you develop ONJ or even if you do not develop ONJ, you, your medical oncology team or your dental health provider may be asked to submit electronic copies of any of your dental (and/or jaw) imaging that has been done since you agreed to take part in this study. This is done so that the investigators can learn about the disease by comparing scans of persons with and without ONJ.

Electronic copies of your dental images and/or images of your jaw bone will be kept at:

Cancer Research and Biostatistics
1730 Minor Ave., Suite 1900
Seattle, WA 98101-1468
Phone: 206/652-2267
Fax: 206/652-4612
Email: information@crab.org
Website: http://www.crab.org/

The research that may be done with your specimens and images are not designed specifically to help you. It might help people who have ONJ and other diseases in the future.
Reports about research done with your specimens and images will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep your specimens and images for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens and imaging can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or imaging. Then any specimen that remains and/or the images will no longer be used for research.

In the future, people who do research may need to know more about your health. While the Southwest Oncology Group may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes tissue is used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records. None of these genetic studies would be of direct benefit to you, but could help us learn about other ways to better treat ONJ.

Your specimens and images will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

Benefits

The benefits of research using specimens and images include learning more about what causes cancer, ONJ and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Risks related to blood tests include bruising, bleeding, infection and pain at the blood draw site.

Making Your Choice

Giving blood and access to bone imaging (example: dental X-rays) for future research is up to you. **You may show whether you want to have these samples and imaging collected and stored by circling "yes" or "no" and signing the consent.** If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB’s phone number.
No matter what you decide to do, it will not affect your care.

**Future Use of Specimens** *(section updated 8/24/11)*

a. My specimens (including any leftover DNA specimen and the "every 6 month" blood specimen) may be kept for use in research to learn about, prevent, treat or cure cancer or ONJ.

   Yes    No

b. My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes    No

c. Someone may contact me in the future to ask me to allow other uses of my specimens.

   Yes    No

**Future Use of Images** *(section updated 8/24/11)*

d. My images may be kept for use in research to learn about, prevent, treat or cure cancer or ONJ.

   Yes    No

e. My images may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

   Yes    No

f. Someone may contact me in the future to ask me to allow other uses of my images.

   Yes    No

If you decide to withdraw your specimens from a Southwest Oncology Group Specimen Repository in the future, or if you decide to withdraw your x-rays and/or scans from the imaging repository in the future, a written withdrawal of consent should be submitted through your study doctor to the Southwest Oncology Group Operations Office. *(sentence deleted 2/9/09)* The remains of your sample or your imaging will then be destroyed. *(added 2/9/09)*

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237) or TTY: 1-800-332-8615

You may also visit the NCI Web site at [http://cancer.gov/](http://cancer.gov/)

- For NCI’s clinical trials information, go to: [http://cancer.gov/clinicaltrials/](http://cancer.gov/clinicaltrials/)
- For NCI’s general information about cancer, go to [http://cancer.gov/cancerinfo/](http://cancer.gov/cancerinfo/)
You will get a copy of this form. If you want more information about this study, ask your study doctor.

I have been given a copy of all _____ [insert total of number of pages] pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. (sentence deleted 9/21/09)

Signature __________________________________________

Print name of participant __________________________________

Date ________________________________________________
Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by the Southwest Oncology Group. Your doctor does not work for the Southwest Oncology Group, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact the Southwest Oncology Group and request samples for their studies. The Southwest Oncology Group reviews the way that these studies will be done, and decides if any of the samples can be used. The Southwest Oncology Group gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. The Southwest Oncology Group will not send your name, address, phone number, social security number or any other identifying information to the researcher.

Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to the Southwest Oncology Group. If more information is needed, the Southwest Oncology Group will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go 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?

Sometimes, health records have been used against patients and their families. For example, insurance companies may deny a patient insurance or employers may not hire someone with a certain illness (such as AIDS or cancer). The results of genetic research may not apply only to you, but to your family members too. For disease caused by gene changes, the information in one person's health record could be used against family members.

How am I protected?

The Southwest Oncology Group is in charge of making sure that information about you is kept private. The Southwest Oncology Group will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

(section deleted 12/6/11)

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).
A Prospective Observational Multicenter Cohort Study to Assess the Incidence of Osteonecrosis of the Jaw (ONJ) in Cancer Patients with Bone Metastases Starting Zoledronic Acid Treatment

**SOUTHWEST ONCOLOGY GROUP**

**S0702 REGISTRATION WORKSHEET**

**Activation Date:** December 15, 2008

**Last Amended Date:** November 1, 2011

**Registration Step:** 1

**INSTRUCTIONS:** All of the information on this Registration Worksheet and the Protocol Eligibility Section must be answered appropriately for a patient to be considered eligible for registration. This Registration Worksheet must be entirely filled out and referred to during the registration. **Do NOT submit this worksheet as part of the patient data.**

### For SWOG Institutions:
- **Registrar's SWOG Roster ID Number:**
- **SWOG Investigator Number:**
- **SWOG Treating Institution Number:**

Check that IRB approval is current for this institution prior to registering. Registrations are not allowed if the IRB approval is expired.

### For Non-SWOG Institutions:
- **Registering Group:**
- **Investigator Name:**
- **Institution Name:**
- **NCI Institution Number:**
- **IRB Approval Date:**
- **Participating Group Patient ID:**

### SWOG Patient ID Status:
- **New Patient**
- **Previous Patient:**

If the patient has a SWOG Patient ID assigned by a prior registration or Specimen Tracking, choose “Previous Patient” and use that number.

- **Date Informed Consent Signed:**
- **Date HIPAA Authorization signed:** (Not required if Country of Residence is not USA)
- **Projected Start Date of Treatment:**

### Patient’s Information:
- **Patient’s Name:** (Full names preferred, initials OK)
- **Patient’s Date of Birth:**

### Country of Residence:
- **US (USA)**
- **CA (Canada)**
- **Other:**

- **If USA, Patient Social Security Number:**
- **ZIP Code:**

- **If Canada, Social Insurance Number:**
- **Postal Code:**

Both Social Security Number and Social Insurance Number are desired, but optional. Do not enter invalid numbers in either field.

### Patient’s Race (select all that apply):
- **White**
- **Native Hawaiian or Other Pacific Islander**
- **American Indian or Alaska Native**
- **Black or African American**
- **Asian**
- **Unknown**

### Patient’s Ethnicity:
- **No (not Spanish)**
- **Yes, Mexican**
- **Yes, Puerto Rican**
- **Yes, Cuban**
- **Yes, Central American**
- **Yes, South American**
- **Yes, NOS**
- **Yes, Other:**
- **Unknown**

### Method of Payment:
- **Private insurance**
- **Veterans-sponsored**
- **Military or Veterans-sponsored, NOS**
- **Medicare**
- **Medicare and Private insurance**
- **Medicaid**
- **Medicaid and Medicare**
- **Self Pay (no insurance)**
- **No means of payment (no insurance)**
- **Unknown**
- **Other:**

### Patient Gender:
- **Female**
- **Male**

---

*continued on next page*
Stratification Questions

Type of cancer (select one): □ Breast □ Multiple Myeloma □ Prostate □ Lung □ Other tumor type

Indicate how the patient answered the following questions on the consent form
If this is not the EXACT WORDING on the consent form, phone in the registration and tell the registrar how the wording was changed.

- My specimens (including any leftover DNA specimen and the "every 6 month" blood specimen) may be kept for use in research to learn about, prevent, treat, or cure cancer or ONJ. □ Yes □ No
- My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer’s disease, or heart disease). □ Yes □ No
- Someone may contact me in the future to ask me to allow other uses of my specimens. □ Yes □ No
- My images may be kept for use in research to learn about, prevent, treat, or cure cancer or ONJ. □ Yes □ No
- My images may be kept for use in research about other health problems (for example: diabetes, Alzheimer’s disease, or heart disease). □ Yes □ No
- Someone may contact me in the future to ask me to allow other uses of my images. □ Yes □ No
- 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
- DNA testing may be done on my initial blood sample. □ Yes □ No

Has the Southwest Oncology Group Registration Worksheet been completed entirely and is the patient eligible according to the current version of protocol section 5.0? □ Yes □ No

Comments (notes from Confirmation of Registration):

SWOG Patient ID: □ □ □ □ □ □ □

Expectations Notes:

Other Notes:
**SOUTHWEST ONCOLOGY GROUP**

**S0702 PRESTUDY FORM**

---

**Patient Initials**

(L, F M)

---

**Participating Group:** Group Name/Study No./Patient ID

---

**Physician**

---

**Institution / Affiliate**

---

**Instructions:** Submit this form within 7 days of registration. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an **X** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

---

### PATIENT AND DISEASE DESCRIPTION

**Zubrod performance status:**  
- [ ] 0  
- [ ] 1  
- [ ] 2  
- [ ] 3

**Date of initial diagnosis of cancer:**

---

**Date of diagnosis of bone disease:**

---

**Has the patient been diagnosed with osteonecrosis of the jaw?**  
- [ ] Yes  
- [ ] No

**Has the patient had any prior skeletal related events?**  
- [ ] Yes  
- [ ] No

If Yes, select all that apply:

- [ ] Fracture  
- [ ] Radiation to bone  
- [ ] Surgery to bone  
- [ ] Spinal cord compression  
- [ ] Hypercalcemia of malignancy

**Has the patient had any prior facial bone fracture other than nose?**  
- [ ] Yes  
- [ ] No

If Yes, what year?  

---

Was surgery required?  
- [ ] Yes  
- [ ] No

---

**Please read the following questions to the patient and record her/his responses on the form.**

**Tobacco use:**

- **Cigarettes:** Have you smoked ≥100 cigarettes in your lifetime?  
  - [ ] Yes  
  - [ ] No

If Yes, are you smoking now?  
- [ ] Yes  
- [ ] No

Have you ever used other types of tobacco?  
- [ ] Yes  
- [ ] No

**Alcohol use:** In the last three months, how often did you usually have an alcoholic drink?  

- [ ] Never or < 1/month  
- [ ] 1-3/mo  
- [ ] 1/wk  
- [ ] 2-4/wk  
- [ ] 5-6/wk  
- [ ] 1/day  
- [ ] 2-3/day  
- [ ] 4-5/day  
- [ ] 6/day

---

### CURRENT ZOLEDRONIC ACID USE

**Is the patient currently receiving zoledronic acid treatment?**  
- [ ] Yes  
- [ ] No

If Yes, reason for receiving zoledronic acid treatment:

- [ ] For treatment of metastatic bone disease
- [ ] For treatment of low bone mass (osteopenia or osteoporosis)

Other reason, specify:  

---

**Date of zoledronic acid treatment start:**

---

If No, date of planned start of zoledronic acid treatment:

---

**Indication for initiating zoledronic acid:**  
- [ ] Hypercalcemia  
- [ ] Decrease risk of skeletal related events

**Planned dosing interval while on study:**  
- [ ] q 3-4 wks  
- [ ] q 5-8 wks  
- [ ] q 9-12 wks  
- [ ] > 12 wks

**Anticipated duration of zoledronic acid use:**  
- [ ] < 1 yr  
- [ ] 1-2 yrs  
- [ ] >2 yrs  
- [ ] Indefinitely

---

*continued on next page*
Did the patient receive any other prior osteoclast inhibiting therapy (other than zoledronic acid within the first 6 months prior to registration)?  

<table>
<thead>
<tr>
<th></th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
</table>

If Yes, indicate reason for receiving other osteoclast inhibiting therapy (select all that apply):

- For treatment of metastatic bone disease
- For treatment of low bone mass (osteopenia or osteoporosis)

<table>
<thead>
<tr>
<th>Date of first dose:</th>
<th>Date of last dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indicate type(s) received (select all that apply):**

- Other IV bisphosphonate, specify: 
  - Average dose amount: mg/dose
  - Number of doses: 
- Other oral bisphosphonate, specify: 
  - Average dose amount: mg/dose
  - Number of doses: 
- Denosumab
  - Average dose amount: mg/dose
  - Number of doses: 

- For treatment of low bone mass (osteopenia or osteoporosis)

<table>
<thead>
<tr>
<th>Date of first dose:</th>
<th>Date of last dose:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Indicate type(s) received (select all that apply):**

- Other IV bisphosphonate, specify: 
  - Average dose amount: mg/dose
  - Number of doses: 
- Other oral bisphosphonate, specify: 
  - Average dose amount: mg/dose
  - Number of doses: 
- Denosumab
  - Average dose amount: mg/dose
  - Number of doses: 

**PRIOR ADJUVANT/INDUCTION THERAPY**

Select all types of adjuvant therapy that were previously received:

- Surgery to the primary site Date: 
- Radiation therapy
  - Specify site: 
  - Total dose: cGy
  - Year completed: 
- Systemic therapy*
  - Alkylating agents
  - Anti-angiogenics
  - Antibiotics/anthracyclines
  - Anti-HER2
  - Antimetabolites
  - Biologics
  - Mitotic inhibitors/microtubule agents/taxanes
  - Monoclonal antibodies
  - Myeloablative therapy requiring stem cell or bone marrow transplant
    - If Yes: Autogeneic
    - Allogeneic
  - Endocrine therapy
  - Targeted agents
  - Other, specify: 

* Refer to Appendix 19.4 of the protocol for explanations of the systemic therapy categories

continued on next page
**SOUTHWEST ONCOLOGY GROUP**  
**S0702 PRESTUDY FORM**

Patient Initials (L, F M)  

- **SWOG Patient ID**: [ ] [ ] [ ]  
- **SWOG Study No.**: S0702  
- **Registration Step**: 1

---

### PRIOR THERAPY FOR ADVANCED/METASTATIC DISEASE

Select all types of therapy for advanced/metastatic disease that were previously received.

- Radiation therapy
  - Specify site:  
    - Total dose: [ ] [ ] [ ] cGy  
    - Year completed: [ ] [ ] [ ]
  - Specify site:  
    - Total dose: [ ] [ ] [ ] cGy  
    - Year completed: [ ] [ ] [ ]
  - Specify site:  
    - Total dose: [ ] [ ] [ ] cGy  
    - Year completed: [ ] [ ] [ ]

- Systemic therapy*  
  - If Yes, select all that apply:
    - Alkylating agents
    - Anti-angiogenics
    - Antibiotics/anthracyclines
    - Anti-HER2
    - Antimetabolites
    - Biologics
    - Mitotic inhibitors/microtubule agents/taxanes
    - Monoclonal antibodies
    - Myeloablative therapy requiring stem cell or bone marrow transplant  
      - If Yes:  
        - Autogeneic
        - Allogeneic
    - Endocrine therapy
    - Targeted agents
    - Other, specify: __________________________

* Refer to Appendix 19.4 of the protocol for explanations of the systemic therapy categories

- If Yes, indicate number of lines of systemic therapy (excluding adjuvant) received: [ ]

- If Yes, was the majority of prior therapy a combination including 2 or more anticancer agents?  
  - Yes
  - No

---

### OTHER THERAPY

- Has the patient ever received steroids (> the equivalent of 5 mg prednisone daily)?  
  - (Refer to Appendix 19.7 of the protocol for information on steroids)
    - No
    - Yes, but not currently receiving
    - Yes, receiving currently

  - If Yes, duration:
    - < 6 mos
    - ≥ 6 mos

- Red Cell Growth factor support:  
  - None
  - < 6 mos
  - ≥ 6 mos

- White Cell Growth factor support:  
  - None
  - < 6 mos
  - ≥ 6 mos

* Refer to Appendix 19.4 of the protocol for examples of these therapies

- Has the patient received any prior radiation to the maxillofacial area for therapeutic intent in the treatment of cancer?  
  - Yes
  - No

  - If Yes, radiation start date: [ ] [ ] [ ] / [ ] [ ] [ ]  
    - Radiation stop date: [ ] [ ] [ ] / [ ] [ ] [ ]

  - Total cGy (if known): [ ] [ ] [ ] [ ] [ ]

- Has the patient received any radioisotope therapy for metastatic bone disease?  
  - Yes
  - No

---

*continued on next page*
COMORBID CONDITIONS  (Select all that apply):

Current history:
- Auto-immune disease
- Chronic infection (including HIV/AIDS)
- Coagulopathy or blood clotting problems
- Diabetes
- Malnutrition
- Osteoporosis or osteopenia
- Paget's disease of bone or metabolic bone disease
- Renal failure or renal insufficiency

Has the patient had any arrhythmias requiring treatment (medical or surgical)?  Yes  No

PATIENT-RELATED OUTCOMES ASSESSMENT

Please ask the patient to provide ratings for the following questions. We are monitoring pain and other problems that a patient with cancer has experienced in her/his mouth or jaw including oral infections. Ask the patient to consider an AVERAGE rating for the 3-month period prior to joining the study.

1. Please rate your pain by selecting the one number that best describes your pain on the AVERAGE.

   - 0 No pain
   - 10 Pain as bad as you can imagine

2. Please rate how your oral health has interfered with your eating on AVERAGE.

   - 0 Has not interfered
   - 10 Completely interfered

3. Please rate how oral health has interfered with how you smile on AVERAGE.

   - 0 Has not interfered
   - 10 Completely interfered

4. Please rate how oral health has interfered with how you speak on AVERAGE.

   - 0 Has not interfered
   - 10 Completely interfered

5. Please rate how your oral health has interfered with your overall quality of life on AVERAGE.

   - 0 Has not interfered
   - 10 Completely interfered

Comments:
Patient Initials: (L, F M)  
11/1/2011  

SOUTHWEST ONCOLOGY GROUP  
S0702 MEDICAL ASSESSMENT FORM  
Page 1 of 3  

Has the patient had any skeletal related events since the time of the last assessment (record only new events occurring since last assessment)?

<table>
<thead>
<tr>
<th>Participating Group: Group Name/Study No./Patient ID</th>
<th>Physician</th>
</tr>
</thead>
</table>

Instructions: Please complete this form every 6 months after registration until first diagnosis of suspected or confirmed osteonecrosis of the jaw (ONJ) or 36 months post-registration, whichever occurs first. If suspected or confirmed ONJ is diagnosed, submit this form every 3 months after diagnosis until 36 months post-registration. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section. Place an X in appropriate boxes. Circle AMENDED items in red and write AMENDED across top of form.

<table>
<thead>
<tr>
<th>Reporting Period Start Date:</th>
<th>Reporting Period End Date:</th>
</tr>
</thead>
</table>

SWOG Study No. S0702  
Registration Step 1  

Date of last clinical assessment:  
Date of last contact or death:  
Vital Status: Alive  
Dead  
(Submit Notice of Death)

Has the patient’s cancer progressed since the previous assessment?  
No  
Yes

If Yes, date of most recent cancer progression:  

SCANS COMPLETED
Indicate any scans completed since last assessment, with date of latest assessment (select all that apply):

<table>
<thead>
<tr>
<th>CT of head</th>
<th>Date:</th>
</tr>
</thead>
<tbody>
<tr>
<td>MRI of head</td>
<td>Date:</td>
</tr>
<tr>
<td>Bone scan (including head)</td>
<td>Date:</td>
</tr>
<tr>
<td>Skeletal survey or x-ray of skull/face</td>
<td>Date:</td>
</tr>
<tr>
<td>Other head and neck imaging, specify:</td>
<td>Date:</td>
</tr>
</tbody>
</table>

Skeletal-Related Events
Has the patient had any skeletal related events since the time of the last assessment (record only new events occurring since last assessment)?  
Yes  
No

If Yes (select all that apply):

| Fracture | Radiation to bone | Surgery to bone | Spinal cord compression | Hypercalcemia of malignancy |

Arrhythmias
Has the patient had any new onset arrhythmias requiring medical or surgical treatment since the time of the last assessment (record only new events occurring since last assessment)?  
Yes  
No

ZOLEDRONIC ACID
Did the patient receive zoledronic acid since the last evaluation?  
Yes  
No

If Yes, number of doses:

| Dosing interval: q 3-4 wks | q 5-8 wks | q 9-12 wks | > 12 wks |

Since last evaluation, date of first dose received:  
Date of last dose received:  

continued on next page  
62856  
11/1/2011
**OTHER OSTEOCLAST INHIBITOR THERAPY**

Did the patient receive any osteoclast inhibiting therapy other than zoledronic acid since the last evaluation?  
☐ Yes  ☐ No  

If Yes, indicate type(s) received (select all that apply):

- Number of doses received: 
- Dosing interval:  
  - Daily  
  - Weekly  
  - Monthly  
- Denosumab  
  - Number of doses received:  

Reason for administering osteoclast inhibiting therapy other than zoledronic acid (select all that apply):

- Toxicity  
- Patient preference  
- Physician preference  
- ONJ diagnosed  
- Logistics  
- Other, specify:

---

**CANCER THERAPIES**

List all cancer therapies received since the last evaluation:

- Surgery  
  - Site:  
  - Date:
- Radiation therapy  
  - Specify site:  
  - Total dose: cGy
- Systemic therapy* If Yes, select all that apply:
  - Alkylating agents  
  - Anti-angiogenics  
  - Antibiotics/anthracyclines  
  - Anti-HER2  
  - Antimetabolites  
  - Biologics  
  - Mitotic inhibitors/microtubule agents/taxanes  
  - Monoclonal antibodies  
  - Myeloablative therapy requiring stem cell or bone marrow transplant  
  - If Yes:  
    - Autogeneic  
    - Allogeneic  
  - Endocrine therapy  
  - Targeted agents  
  - Other, specify:

* Refer to Appendix 19.4 of the protocol for explanations of the systemic therapy categories

---

**OTHER THERAPY**

Has the patient received steroids (> the equivalent of 5 mg prednisone daily) since the last evaluation?  
(Refer to Appendix 19.7 of the protocol for information on steroids)

☐ No  ☐ Yes, but not currently receiving  ☐ Yes, currently receiving

Has the patient received Red Cell Growth Factor support since the last evaluation?  
☐ Yes  ☐ No

Has the patient received White Cell Growth Factor support since the last evaluation?  
☐ Yes  ☐ No

* Refer to Appendix 19.4 of the protocol for examples of these therapies

---

continued on next page
PATIENT-RELATED OUTCOMES ASSESSMENT

Please ask the patient to provide ratings for the following questions. We are monitoring pain and other problems that a patient with cancer has experienced in her/his mouth or jaw including oral infections. Ask the patient to consider an AVERAGE rating for the period between the last time this form was completed and the current visit.

1. Please rate your pain by selecting the one number that best describes your pain on the AVERAGE.
   - [ ] 0 No pain
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Pain as bad as you can imagine

2. Please rate how your oral health has interfered with your eating on AVERAGE.
   - [ ] 0 Has not interfered
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Completely interfered

3. Please rate how oral health has interfered with how you smile on AVERAGE.
   - [ ] 0 Has not interfered
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Completely interfered

4. Please rate how oral health has interfered with how you speak on AVERAGE.
   - [ ] 0 Has not interfered
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Completely interfered

5. Please rate how your oral health has interfered with your overall quality of life on AVERAGE.
   - [ ] 0 Has not interfered
   - [ ] 1
   - [ ] 2
   - [ ] 3
   - [ ] 4
   - [ ] 5
   - [ ] 6
   - [ ] 7
   - [ ] 8
   - [ ] 9
   - [ ] 10 Completely interfered

Comments:
**SOUTHWEST ONCOLOGY GROUP**

**S0702 DENTIST CONTACT FORM**

<table>
<thead>
<tr>
<th>SWOG Patient ID</th>
<th>SWOG Study No.</th>
<th>Registration Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] [ ] [ ] [ ]</td>
<td>S0702</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reporting Period Start Date:</th>
<th>11/1/2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reporting Period End Date:</td>
<td>11/1/2011</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Institution / Affiliate</th>
<th>Physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>_______________________</td>
<td></td>
</tr>
</tbody>
</table>

**Participating Group:** Group Name/Study No./Patient ID

| [ ] [ ] [ ] | [ ] [ ] [ ] |

**Instructions:** Please complete and submit this form within 7 days of registration and then each time the S0702 Dental Assessment Form or S0702 ONJ Assessment Form is submitted post-registration. For the initial prestudy submission of this form, please use the actual date of prestudy dental exam for Reporting Period Start Date, if available, otherwise use the **day before** the date of registration. The date of registration should be used as the Reporting Period End Date for the initial prestudy submission of this form, and as the Reporting Period Start Date for the first on-study submission. All dates are **MONTH, DAY, YEAR**. Explain any blank fields or blank dates in the **Comments** section. Place an [X] in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** across top of form.

**Has the patient been seen by a dental provider during this reporting period?**

- [ ] Yes (please fill in the contact information below)

- [ ] No, but contact information for patient's dental provider has been reported on a previous form submission

- [ ] No, patient has no dental provider

<table>
<thead>
<tr>
<th>Dentist name:</th>
<th>___________________________</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Dentist phone number:</th>
<th>[ ] [ ] - [ ] [ ] - [ ] [ ] [ ] (extension, if appropriate) x [ ] [ ]</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Dentist fax number:</th>
<th>[ ] [ ] - [ ] [ ] - [ ] [ ] [ ] (extension, if appropriate) x [ ] [ ]</th>
</tr>
</thead>
</table>

**Dentist email:** ___________________________

**Dentist office address:** ___________________________

**Comments:**
In order to participate in this study, the participant has already signed a HIPAA-related release allowing you to provide the information requested on this form. If you have any questions about this, please contact the participant's study investigator.

Has a dental examination been performed during this reporting period? ☐ Yes ☐ No

If Yes, date of exam: __/__/____
(Note: If multiple dental exams have been performed during this reporting period, enter the date only from the most recent exam.)

If No, no other information is required. Please submit this form.

### DENTAL HISTORY
(complete only at time of baseline dental exam)

How many dental cleanings occurred in the last 2 years? ☐ 0 ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ > 4

Has the patient had prior oral surgery? ☐ Yes ☐ No

If Yes, indicate number of extractions: ☐ 1-3 ☐ > 3 Date of last extraction: __/__/____

Has the patient had prior periodontal treatments? ☐ Yes ☐ No

If Yes, indicate extent of prior treatments: ☐ Minor ☐ Intermediate ☐ Extensive

Has the patient had prior endodontic treatments? ☐ Yes ☐ No

If Yes, indicate extent of prior treatments: ☐ Minor ☐ Intermediate ☐ Extensive

Has the patient had prior implants? ☐ Yes ☐ No

If Yes, indicate number of implants: ☐ 1-3 ☐ > 3

Has the patient had prior orthodontics? ☐ Yes ☐ No

---

continued on next page
For the baseline dental assessment, please complete all items below. For on-study dental assessments, please complete the items below if a dental examination has been performed during this reporting period. If multiple exams have been performed during this reporting period, complete the items only from the most recent exam.

## DENTAL EXAMINATION

**Dental examination date:**

**Number of dental cleanings since this form was last completed?**
- [ ] 0
- [ ] 1
- [ ] 2
- [ ] ≥ 3

**Were tori present?**
- [ ] Yes
- [ ] No

**If Yes, location:**
- [ ] Alveolar bone
- [ ] Palate

**Size:**
- [ ] < 5 mm
- [ ] ≥ 5 mm

If more than one, indicate size of largest torus.

**Were dental films done?**
- [ ] Yes
- [ ] No

**If Yes, indicate type of films (select all that apply):**
- Panorex
- Individual teeth
- Other, specify: __________________________

**Date:**

## PERIODONTAL EXAMINATION

**Dental plaque levels:**
- [ ] None
- [ ] Mild
- [ ] Moderate
- [ ] Severe

**Calculus:**
- [ ] None
- [ ] Mild
- [ ] Moderate
- [ ] Severe

**Gingivitis:**
- [ ] None
- [ ] Mild
- [ ] Moderate
- [ ] Severe

**Periodontitis:**
- [ ] All pockets 4 mm or less
- [ ] Pockets ≥ 4 mm and ≤ 6 mm, Teeth numbers: __________________________
- [ ] Pockets > 6 mm, Teeth numbers: __________________________

**Overall periodontal disease level:**
- [ ] None
- [ ] Mild
- [ ] Moderate
- [ ] Severe

## DENTITION EXAMINATION

**Number of maxillary teeth present:**

**Number of mandibular teeth present:**

**Number of caries:**

**Deep caries (within 3 mm or pulp):** (List teeth numbers) __________________________

**Fractured teeth/restorations:** (List teeth numbers) __________________________
Patient Initials (L, F, M)  

SWOG Study No. S0702  
Registration Step 1  
Reporting Period Start Date:__/__/__

ENDODONTIC EXAMINATION  
None

Endodontically treated teeth: (List teeth numbers)

Failing Root Canals: (List teeth numbers)

REMOVABLE DENTURES

None  Complete dentures  Removable partial dentures

Age of dentures:  Last reline/adjustment date:__/__/__

Upper:
Stability: Good  Fair  Poor  Retention: Good  Fair  Poor

Lower:
Stability: Good  Fair  Poor  Retention: Good  Fair  Poor

Evidence of denture sores/denture stomatitis: (select one) None  Mild  Moderate  Severe

Signature of examining dentist  Date

Print Name

Comments:
Instructions: For Dental Professionals: Please complete this form at the time of diagnosis of suspected or confirmed osteonecrosis of the jaw (ONJ) and then every 3 months after diagnosis until 36 months after registration. Please submit the form to the office of the treating medical oncologist within 10 business days of the dental exam. For follow-up assessments, please record all sites previously identified as suspected or confirmed ONJ, and record any new sites of suspected or confirmed ONJ.

For Registering Institutions: This form is to be completed by the patient’s dental professional if a dental examination has been performed. Please submit this form at the time of diagnosis of suspected or confirmed osteonecrosis of the jaw (ONJ) and then every 3 months after diagnosis until 36 months after registration, or until all suspected lesions have resolved and there are no confirmed lesions. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section. Place an X in appropriate boxes. Circle AMENDED in red and write AMENDED across top of form.

In order to participate in this study, the participant has already signed a HIPAA-related release allowing you to provide the information requested on this form. If you have any questions about this, please contact the participant’s study investigator.

FIRST DIAGNOSIS OF SUSPECTED OR CONFIRMED ONJ
Complete these items at the time of first diagnosis of suspected or confirmed ONJ only.

Date of first onset of ONJ lesions: __/__/____
Indicate presenting complaint for dental appointment:
☐ Referral for ONJ care ☐ Pain ☐ Drainage ☐ None

FIRST DIAGNOSIS AND FOLLOW-UP ASSESSMENT OF SUSPECTED OR CONFIRMED ONJ
Complete the remaining items at the time of first diagnosis of suspected or confirmed ONJ, and at each follow-up assessment of suspected or confirmed ONJ.

Has a dental examination been performed during this reporting period? ☐ Yes ☐ No
If Yes, date of exam: __/__/____
(Note: If multiple dental exams have been performed during this reporting period, enter the date only from the most recent exam.)

If No, please complete the remainder of the form with as much information as is available.

Were dental films done? ☐ Yes ☐ No
If Yes, indicate type of films (select all that apply):
☐ Panorex Date: __/__/____
☐ Individual teeth Date: __/__/____
☐ Other, specify: __/__/____

PERIODONTAL EXAMINATION
Overall periodontal disease level (select one): ☐ None ☐ Mild ☐ Moderate ☐ Severe

DENTITION EXAMINATION
Overall dental disease level (select one): ☐ None ☐ Mild ☐ Moderate ☐ Severe

ENDODONTIC EXAMINATION
Overall endodontic disease level (select one): ☐ None ☐ Mild ☐ Moderate ☐ Severe

continued on next page
**ONJ LESIONS**

**ONJ stage (see Dental Appendix, attached):**
- [ ] Stage 0 (No evidence of necrotic bone, but non-specific signs and symptoms)
- [ ] Stage 1 (Asymptomatic, exposed, necrotic bone, without evidence of infection)
- [ ] Stage 2 (Exposed, necrotic bone with infection - pain and erythema with or without purulence)
- [ ] Stage 3 (Exposed and necrotic bone associated with pain and infection and one or more of the following: necrotic bone extending beyond the alveolar ridge, pathologic fracture, extraoral fistula, oral antral/oral nasal communication or osteolysis extending to the inferior border of the mandible or the sinus floor)

**ONJ Grade (see Dental Appendix, attached):**
- [ ] Grade 1A (Single lesion < 0.5 cm)
- [ ] Grade 1B (Multiple lesions, largest < 0.5 cm)
- [ ] Grade 2A (Single lesion 0.5 - 0.99 cm)
- [ ] Grade 2B (Multiple lesions, largest 0.5 - 0.99 cm)
- [ ] Grade 3A (Single lesion 1 - 2 cm)
- [ ] Grade 3B (Multiple lesions, largest 1 - 2 cm)
- [ ] Grade 4A (Single lesion > 2 cm)
- [ ] Grade 4B (Multiple lesions, largest > 2 cm)

**Any signs/symptoms of infection (e.g. mucosal erythema, swelling, pus, bad taste)?**
- [ ] Yes
- [ ] No

**Number of ONJ lesions:**
- [ ]

*If more than 3 ONJ lesions, list details for the first 3 lesions detected.*

**Lesion 1:**
- [ ] Newly identified site of suspected or confirmed ONJ
- [ ] Follow-up for previously identified site of suspected or confirmed ONJ

**Site of lesion (select all that apply):**

**Maxilla:**
- [ ] Anterior
- [ ] Posterior
- [ ] Buccal
- [ ] Lingual
- [ ] Palate

**Mandible:**
- [ ] Anterior
- [ ] Posterior
- [ ] Buccal
- [ ] Lingual
- [ ] Mylohyoid Plate

**Nearest tooth number:**
- [ ]

**Size of lesion:**
- [ ] mm

**ONJ symptom severity:**
- [ ] Asymptomatic
- [ ] Mild
- [ ] Moderate
- [ ] Severe

**Associated factors (select all that apply):**

- [ ] Periodontal infection
- [ ] Dental extraction
- [ ] Denture trauma
- [ ] Other dental surgery
- [ ] Other trauma
- [ ] No identified factor
### Lesion 2:

- [ ] Newly identified site of suspected or confirmed ONJ
- [ ] Follow-up for previously identified site of suspected or confirmed ONJ

**Site of lesion (select all that apply):**

Maxilla: [ ] Anterior  [ ] Posterior  [ ] Buccal  [ ] Lingual  [ ] Palate

Mandible: [ ] Anterior  [ ] Posterior  [ ] Buccal  [ ] Lingual  [ ] Mylohyoid Plate

**Nearest tooth number:**

**Size of lesion:**

**ONJ symptom severity:**

[ ] Asymptomatic  [ ] Mild  [ ] Moderate  [ ] Severe

**Associated factors (select all that apply):**

- [ ] Periodontal infection
- [ ] Dental extraction
- [ ] Denture trauma
- [ ] Other dental surgery
- [ ] Other trauma
- [ ] No identified factor

### Lesion 3:

- [ ] Newly identified site of suspected or confirmed ONJ
- [ ] Follow-up for previously identified site of suspected or confirmed ONJ

**Site of lesion (select all that apply):**

Maxilla: [ ] Anterior  [ ] Posterior  [ ] Buccal  [ ] Lingual  [ ] Palate

Mandible: [ ] Anterior  [ ] Posterior  [ ] Buccal  [ ] Lingual  [ ] Mylohyoid Plate

**Nearest tooth number:**

**Size of lesion:**

**ONJ symptom severity:**

[ ] Asymptomatic  [ ] Mild  [ ] Moderate  [ ] Severe

**Associated factors (select all that apply):**

- [ ] Periodontal infection
- [ ] Dental extraction
- [ ] Denture trauma
- [ ] Other dental surgery
- [ ] Other trauma
- [ ] No identified factor

**Intervention**

Were any procedures performed in the management of ONJ at this dental visit?  [ ] Yes  [ ] No

If Yes, indicate type (select all that apply):

- [ ] Rinses
- [ ] Antibiotics
- [ ] Cultures taken, results:
- [ ] Dental imaging
- [ ] Debridment
- [ ] Biopsy
- [ ] Invasive procedure, describe:
- [ ] Other, specify:

**Response of ONJ (suspected or confirmed) to therapy since last assessment:**

- [ ] Progression
- [ ] Stable
- [ ] Improved
- [ ] Resolved

---

*continued on next page*
<table>
<thead>
<tr>
<th>SWOG Patient ID</th>
<th>SWOG Study No. S0702</th>
<th>Registration Step 1</th>
</tr>
</thead>
</table>

Patient Initials (L, F, M)  
Reporting Period Start Date: __________ / __________ / __________

__________________________  ____________________________
Signature of examining dentist  Date

__________________________
Print Name

Comments:
SOUTHWEST ONCOLOGY GROUP
S0702 IMAGE TRANSMITTAL FORM

SWOG Patient ID [Blank] SWOG Study No. S0702 Registration Step 1

Patient Initials [Blank] (L, F, M)

Institution / Affiliate [Blank] Physician [Blank]

Participating Group: Group Name/Study No./Patient ID [Blank] / [Blank] / [Blank]

Instructions: Complete this form and submit along with any required images that cannot be digitized and submitted electronically via AG Mednet. If the images are only available on film and you cannot locally digitize the film, the film images can be sent by mail. See protocol Section 15 for instructions and address. All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the Comments section. Place an X in appropriate boxes. Circle AMENDED items in red and write AMENDED across top of form.

IMAGE INFORMATION

Study Instance UID (Image ID #): [Blank]

Date of scan: [Blank] / [Blank] / [Blank]

Timepoint (select one):

☐ Baseline
☐ On study prior to ONJ diagnosis
☐ Time of ONJ diagnosis
☐ Follow-up assessment

Completed by name [Blank]

Completed by email [Blank]

Mailing address to return films [Blank]

Comments: [Blank]
**SOUTHWEST ONCOLOGY GROUP**

**S0702 OFF PROTOCOL NOTICE**

<table>
<thead>
<tr>
<th>SWOG Patient ID</th>
<th>SWOG Study No.</th>
<th>Registration Step</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S0702</td>
<td>1</td>
</tr>
</tbody>
</table>

Patient Initials ___________ (L, F, M)

Institution / Affiliate ___________________________ Physician ___________________________

**Participating Group:** Group Name/Study No./Patient ID ___________________________ / ___________________________ / ___________________________

**Instructions:** Submit this form within 2 weeks after completion (or discontinuation) of study follow-up.

All dates are MONTH, DAY, YEAR. Explain any blank fields or blank dates in the **Comments** section.

Place an **X** in appropriate boxes. Circle **AMENDED** items in red and write **AMENDED** at the top of the form.

---

**Off Protocol Reason** *(select one):*

- [ ] Completion of 3 years of follow-up per protocol.
- [ ] Patient refused, logistics (e.g., transportation) or scheduling conflicts, specify: ___________________________
- [ ] Patient refused, worsening disease, specify: ___________________________
- [ ] Patient refused, other reason, specify: ___________________________
- [ ] Death (submit Notice of Death form)
- [ ] Other, specify: ___________________________

**Off Protocol Date**

Date of completion, progression, death or decision to discontinue therapy: __________ / __________ / __________

**Date of Last Contact or Death:** __________ / __________ / __________

**Vital Status:**

- [ ] Alive
- [ ] Dead (submit Notice of Death form)

**Comments:**

---

12/15/2008
**SOUTHWEST ONCOLOGY GROUP**

**NOTICE OF DEATH**

- **SWOG Patient ID**: [Redacted]
- **Most Recent SWOG Study No.** [Redacted]
- **Patient Initials**: [Redacted] (L, F, M)
- **Institution / Affiliate**: [Redacted]
- **Physician**: [Redacted]

**Participating Group**: Group Name/Study No./Patient ID

**Instructions**: Answer all questions and explain any blank fields or blank dates in the Comments section. Place an [X] in appropriate boxes. Circle AMENDED items in red.

**Date of Death**: [Redacted] (month / day / year)

### CAUSES OF DEATH

- **Any cancer (select one):**
  - [ ] No
  - [ ] Primary Cause
  - [ ] Contributory
  - [ ] Possible
  - [ ] Unknown

  If cancer was the primary cause or if cancer possibly or definitely contributed to death, and the patient had had multiple tumor types, specify those which were causes of death:

  - [ ] Cancer of most recent SWOG study, specify cancer: [Redacted]
  - [ ] Cancer of other SWOG study, specify cancer: [Redacted]
  - [ ] Other cancer, specify: [Redacted]

- **Toxicity from disease related treatment (select one):**
  - [ ] No
  - [ ] Primary Cause
  - [ ] Contributory
  - [ ] Possible
  - [ ] Unknown

  If Primary Cause, Contributory or Possible, specify treatment and toxicity:

- **Non-cancer and non-treatment related causes (select one):**
  - [ ] No
  - [ ] Primary Cause
  - [ ] Contributory
  - [ ] Possible
  - [ ] Unknown

  If Primary Cause, Contributory or Possible, specify:

- **Autopsy?**
  - [ ] No
  - [ ] Yes
  - [ ] Unknown

- **Source(s) of death information:**
  - Autopsy report
  - Medical record / Death certificate
  - Physician
  - Relative or friend
  - Other, specify: [Redacted]

**Comments:**

[Redacted]
19.0 **APPENDIX**

19.1 Comparison of guidelines for ONJ and managing patients treated with osteoclast inhibitor therapy

19.2 Letter for Dental Health Professional including Suggested Staging and Management of ONJ and Grading ONJ and Severity Scores

19.3 Additional Information Regarding the Case Report Forms (Classes of bisphosphonates, radioisotope therapies)

19.4 Additional Information Regarding the Case Report Forms (Classes of Chemotherapies)

19.5 Novartis Pharmaceuticals Adverse Event Post-Marketing Program Fax Cover Sheet and Novartis Serious Adverse Event Reporting Form

19.6 Cancer Trials Support Unit (CTSU) Participation Procedures

19.7 Quantifying Use of Steroids
19.1 Table 1: Comparison of guidelines for ONJ and managing patients treated with osteoclast inhibitor therapy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pre-osteoclast inhibitor evaluation</th>
<th>Follow up during osteoclast inhibitor therapy in patients without signs or symptoms of ONJ</th>
<th>Follow up of patients with ONJ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral Complications of Cancer Therapies: Diagnosis, Prevention, and Treatment. NIH Consensus Statement 1989 (27)</td>
<td>Not directly discussing bisphosphonate therapy; however, recommends: all patients with cancer should have an oral examination before initiating cancer therapy. Identify risk factors for the development of oral complications. Treatment of pre-existing or concomitant oral disease is essential. Studies of oral complications are recommended.</td>
<td>Not directly discussing bisphosphonate therapy; however, continued follow up is recommended but the interval is not specifically addressed. The document notes: to satisfy the objectives of the examination, the following data must be obtained in patients at risk for oral complications: cancer diagnosis, medical history, dental history, dental charting, periodontal charting, appropriate radiographs, and nutritional status. Some clinicians may wish to include volumetric assessment of resting and stimulated whole saliva. Additionally, study models could be obtained where deemed appropriate.</td>
<td>Not applicable</td>
</tr>
<tr>
<td>American Dental Association JADA 2002;133:1014 (31)</td>
<td>Not directly discussing bisphosphonate therapy; however, When possible, schedule a thorough dental check up at least 2 weeks before cancer treatment</td>
<td>Not directly discussing bisphosphonate therapy; however, During cancer treatment continue to gently brush and floss; use mouth rinses as directed, avoid tobacco and alcohol. Schedule regular dental check ups</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Zoledronic Packet Insert</td>
<td>A dental exam with appropriate preventive dentistry should be considered prior to treatment with bisphosphonates with concomitant risk factors (eg, cancer, chemotherapy, corticosteroids, poor oral hygiene)</td>
<td>While on treatment, these patients should avoid invasive dental procedures, dental surgery may exacerbate the condition. For patients requiring dental procedures, there are no data available to suggest discontinuation of bisphosphonate treatment reduces the risk of ONJ.</td>
<td>Clinical judgment of the treating physician should guide the management of each patient</td>
</tr>
<tr>
<td>Reference</td>
<td>Pre-osteoclast inhibitor evaluation</td>
<td>Follow up during osteoclast inhibitor therapy in patients without signs or symptoms of ONJ</td>
<td>Follow up of patients with ONJ</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------------------------</td>
<td>-----------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Ruggiero J Oncol Pract 2006</td>
<td>Dental exam prior to initiating intravenous bisphosphonate, include panoramic radiograph.</td>
<td>discretion of the treating physician or dentist, maybe as frequent as 3-4 months</td>
<td>3 month intervals with more frequent if needed</td>
</tr>
<tr>
<td>Migliorati JADA 2005</td>
<td>Dental exam prior to initiating intravenous bisphosphonate. A full-mouth radiographic series and a panoramic radiograph will help in the diagnosis of caries and periodontal disease, the evaluation of third molars and the identification of metastatic cancer and other bony pathology.</td>
<td>3-6 months</td>
<td>Every 2-3 weeks</td>
</tr>
<tr>
<td>Marx J Oral Maxillofac Surg 2005</td>
<td>Prior to initiating intravenous bisphosphonate therapy: dental examination and panoramic radiographic examinations. If surgical intervention is required, bisphosphonate therapy should be delayed 1 month to allow for recovery.</td>
<td>4 months while on bisphosphonate therapy</td>
<td>Not specified</td>
</tr>
<tr>
<td>ADA: oral bisphosphonate JADA 2006</td>
<td>Oral exam prior to initiating oral bisphosphonate. There are no diagnostic techniques to identify those at increased risk of developing ONJ</td>
<td>Routine dental treatment generally should not be modified</td>
<td></td>
</tr>
<tr>
<td>Woo Ann Int Med 2006</td>
<td>Evaluation prior to include treating active oral infections, encourage routine dental care (biannual examinations, cleaning). Panoramic and intraoral radiographs.</td>
<td>If less then 3 months of bisphosphonate therapy follow up biannual with exam and cleaning. If more then 3 months of bisphosphonate therapy no specific interval is stated and invasive procedures are to be minimized, antibiotics to be considered and follow up is recommended to ensure healing.</td>
<td>No specific interval of follow up is recommended.</td>
</tr>
<tr>
<td>AAOMS Ruggiero J Oral Maxillofac Surg 2009 (33)</td>
<td>Dental evaluation and treatment as needed prior to initiating IV bisphosphonate therapy</td>
<td>Maintain good oral hygiene and dental care. No specific interval of follow-up is recommended</td>
<td>Follow-up 3 months for Stage 1 ONJ</td>
</tr>
</tbody>
</table>
Dear Dental Health Professional,

Thank you for seeing our shared patient ________________________, who has enrolled in the clinical trial known as Southwest Oncology Group (SWOG) **S0702**: "A prospective observational multicenter cohort study to assess the incidence of osteonecrosis of the jaw (ONJ) in cancer patients with bone metastases starting zoledronic acid." This clinical study has been reviewed by the National Institute of Health’s National Cancer Institute, and the patient’s local treating facility’s Institutional Review Board. This study is being performed nationally and will enroll 3,500 patients. The primary objective of this study is to assess the incidence rates of ONJ in patients with metastatic cancer involving the bone after starting treatment with zoledronic acid.

As you may be aware, there have been reports of osteonecrosis of the jaw (ONJ) reported in patients treated with bisphosphonates including alendronate (Fosamax™), ibandronate (Boniva™), risedronate (Actonel™) and zoledronic acid (Zometa™ or Reclast™), as well as other bisphosphonates. Denosumab, the monoclonal antibody to RANKL, has received FDA approval (Prolia™ for osteoporosis and Xgeva™ for metastatic bone disease). In the Phase III study comparing denosumab to zoledronic acid in patients with metastatic bone disease the incidence of ONJ was 1-2% and was not statistically different between the two agents. Patients with cancer appear to be at the greatest risk of developing ONJ. The cause of ONJ is unknown.

The patient whom you are caring for has a history of cancer involving the bone(s) and will either have, or has had, treatment with the bisphosphonate zoledronic acid. This study, **S0702**, evaluates patient risks associated with developing ONJ during their treatment of their cancer involving the bone and will assess the incidence of ONJ.

This patient may be at risk for ONJ due to having cancer, exposure to potent osteoclast inhibitor therapy and/or planned treatment with a bisphosphonate to reduce the risk of the cancer damaging their bones and causing fractures, spinal cord compression, hypercalcemia of malignancy, pain or other skeletal related events. Patients enrolled on **S0702** will be followed over 3 years with monitoring of their medical and dental events as they relate to ONJ.

We ask that you care for the patient as clinically indicated according to the American Dental Associations Guidelines, or other established guidelines, and your clinical judgment. *(1,2,3)* This study, **S0702**, does not dictate what dental care is given.

The attached form is to be completed. It documents your dental evaluation in a manner that will allow comparison among the 3,500 patients to be studied. The study recommends that the patient will follow up with their dental health care provider with this dental evaluation form every 6 months for 3 years. However, if ONJ is diagnosed, the interval between dental evaluations is every 3 months. Dental appointments and care may occur more frequently, as clinically indicated; however, the study forms are filed on a standing timetable. Below briefly summarizes a routine evaluation:

**Dental Exam Procedures:**
- Overall Dental History and Exam
- Periodontal Exam
- Dental Imaging
- Panoramic X-Ray is the preferred imaging technique, although, other imaging modalities such as intraoral films, (small films), bite wings; x-ray films and/or digital files may be appropriate for some individuals. Dental imaging is obtained at baseline and every 6-24 months or as clinically indicated.
- The dental imaging and report obtained as part of clinical care may be requested to be forwarded to the Southwest Oncology Group at a future date. If this patient’s dental images are requested as a component of this clinical research then instructions on the submission process will be made available with the request for the films.
- In addition to the dental medical record that you generate for clinical care, the patients on this clinical trial are to have the attached forms completed by their dental health care professional team for submission to the Southwest Oncology Group. The study forms are to be completed and returned to the patient’s treating medical oncologist’s office identified below in this letter.
For the purpose of this clinical study, the following definitions are applied:

**A suspected case of ONJ:** is defined as an area of exposed bone in the maxillofacial region that had been identified by a health care provider and had been present for less then 8 weeks in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation therapy to the craniofacial region. Suspected cases of ONJ should receive follow up evaluation to determine whether they ultimately meet the definition of a confirmed case of ONJ.

**A confirmed case of ONJ:** is defined as an area of exposed bone in the maxillofacial region that has been identified by a health care provider and has been present for 8 weeks or more in a patient who was receiving or had been exposed to a bisphosphonate, and had not had radiation to the craniofacial region. Confirmed cases of ONJ should receive follow up and there is a change in the study follow up interval from every 6 months to every 3 months until 3 years after study registration.

**General Time Line For Study Dental Forms**

<table>
<thead>
<tr>
<th>Dental Assessment</th>
<th>Baseline</th>
<th>6 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
<th>30 months</th>
<th>36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental history &amp; oral exam with completion of study form*</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Imaging (approximate time intervals)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

* The completed forms should be submitted back to the treating institution/medical oncologist office within 10 business days.

If a patient with suspected ONJ has a complete resolution of the suspected ONJ lesion without developing confirmed ONJ as evaluated by serial monitoring, and if clinically indicated, dental follow-up form submission may be changed from every 3 months (ONJ Assessment Form) back to every 6 months (Dental Assessment Form).

If ONJ is diagnosed in this patient, the frequency of dental assessment and form completion will change from every 6 months to every 3 months. The form associated with ONJ is slightly different than the routine dental evaluation form. The ONJ form captures data that grades the ONJ and the below table outlines a general approach to the management of a patient with ONJ. (4)

**Suggested Staging and Management of ONJ (5)**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>At Risk</td>
<td>Exposure to oral or IV bisphosphonate</td>
<td>No treatment indicated. Patient education</td>
</tr>
<tr>
<td>0</td>
<td>No evidence of necrotic bone, but non-specific signs and symptoms</td>
<td>Systemic management consider: pain control, antibiotics</td>
</tr>
<tr>
<td>1</td>
<td>Asymptomatic, exposed, necrotic bone, without evidence of infection.</td>
<td>Antibacterial mouth rinse. Review indications for bisphosphonate therapy</td>
</tr>
<tr>
<td>2</td>
<td>Exposed, necrotic bone with infection (pain and erythema with or without purulence)</td>
<td>Symptomatic management, oral antibiotics and pain control. Superficial debridement to relieve soft tissue irritation</td>
</tr>
<tr>
<td>3</td>
<td>Exposed and necrotic bone associated with pain and infection and one or more of the following: necrotic bone extending beyond the alveolar ridge, pathologic fracture, extraoral fistula, oral antral/oral nasal communication or osteolysis extending to the inferior border of the maxible or the sinus floor</td>
<td>Antibacterial mouth rinse. Antibiotic therapy and pain control. Surgical debridement/resection for longer term palliation of infection and pain</td>
</tr>
</tbody>
</table>
Grading ONJ and Severity Scores (4)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A</td>
<td>Single lesion &lt; 0.5 cm</td>
</tr>
<tr>
<td>1B</td>
<td>Multiple lesions, largest &lt; 0.5 cm</td>
</tr>
<tr>
<td>2A</td>
<td>Single lesion 0.5–0.99 cm</td>
</tr>
<tr>
<td>2B</td>
<td>Multiple lesions, largest 0.5–0.99 cm</td>
</tr>
<tr>
<td>3A</td>
<td>Single lesion 1–2 cm</td>
</tr>
<tr>
<td>3B</td>
<td>Multiple lesions, largest 1–2 cm</td>
</tr>
<tr>
<td>4A</td>
<td>Single lesion &gt; 2 cm</td>
</tr>
<tr>
<td>4B</td>
<td>Multiple lesions, largest &gt; 2 cm</td>
</tr>
</tbody>
</table>

ONJ symptom severity (4)

1. Asymptomatic  
2. Mild  
3. Moderate  
4. Severe

Instructions for the Dental Health Professional

1. Note the documentation that the patient has provided release of their health information as it pertains to this clinical trial.  
2. Complete these forms to the best of your ability  
3. Return this form to the patient's medical oncology team within 10 business days. The address and fax of the medical oncology team is included in this memo. Methods of returning this form may include hand delivery, fax or mail.

Should you wish to discuss your clinical findings, or this study, with the involved researchers, please contact any combination of the below individuals:

The patient's treating medical oncologist:

Name: ____________________________________________________________

Address: __________________________________________________________

Phone/Fax: ________________________________________________________
The **S0702** Lead Dental Researchers:

University of Michigan  1011 N. University Ave, Room 3309
School of Dentistry, Box 356370  School of Dentistry
University of Washington  University of Michigan
Seattle, WA 98195-6370  Ann Arbor, MI 48109-1078
Phone: 206/288-1331  Phone: 734/647-4239
FAX: 206/288-1332  FAX: 734/763-5503
E-mail: mschuber@Seattlecca.org  E-mail: robtbagr@umich.edu

The **S0702** Study Chairs:

Catherine Van Poznak, M.D.  Julie Gralow, M.D.
University of Michigan  Seattle Cancer Care Alliance
1500 E. Medical Center Drive  825 Eastlake Ave E.
C346 Med Inn Bldg  MS G3-2000
Ann Arbor, Michigan 48109  Seattle, Washington 98109-1023
Phone: 734-936-9209  Phone: 206-228-7722
Fax: 734-615-2109  Fax: 206-288-2054
Email: cvanpoz@med.umich.edu  Email: pink@u.washington.edu

Additional information on this clinical trial may be found at the following websites:
The National Cancer Institute’s clinical trial page: [http://www.nci.nih.gov/clinicaltrials/search](http://www.nci.nih.gov/clinicaltrials/search)
The Southwest Oncology home page: [http://www.swog.org](http://www.swog.org)

References:

**THANK YOU FOR YOUR CARE OF THIS INDIVIDUAL AND FOR YOUR CONTRIBUTION IN INVESTIGATING ONJ.**
19.3 Additional Information Regarding the Case Report Forms (Classes of bisphosphonates, radioisotope therapies)

<table>
<thead>
<tr>
<th>Classes of bisphosphonates: Drug name (Brand name)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Nitrogen containing</td>
</tr>
<tr>
<td>• Clodronate (Bonefos)</td>
</tr>
<tr>
<td>• Etidronate (Didronel)</td>
</tr>
<tr>
<td>Nitrogen Containing (oral)</td>
</tr>
<tr>
<td>• Alendronate (Fosamax)</td>
</tr>
<tr>
<td>• Ibandronate (Boniva)</td>
</tr>
<tr>
<td>• Risedronate (Actonel)</td>
</tr>
<tr>
<td>Nitrogen Containing (intravenous)</td>
</tr>
<tr>
<td>• Ibandronate (Boniva)</td>
</tr>
<tr>
<td>• Pamidronate (Aredia)</td>
</tr>
<tr>
<td>• Zoledronic Acid (Zometa, Reclast, Aclasta)</td>
</tr>
</tbody>
</table>

Denosumab (Xgeva, Prolia) (osteoclast inhibitor, monoclonal antibody to RANKL)

Radioisotope therapies that have been FDA approved include:
- strontium-89 (Metastron)
- samarium-153 (Quadramet)

Other radiopharmaceuticals such as may be considered investigational include:
- rhenium,
- phosphorus-32
- radioactive tin (tin-117m)

Monoclonal with radiopharmaceutical:
- Ibritumomab
- Tositumomab tiuxetan
### 19.4 Additional Information Regarding the Case Report Forms (Classes of Systemic Therapies)

#### Classes of systemic therapies

<table>
<thead>
<tr>
<th>Classes of systemic therapies</th>
<th>Chlorambucil</th>
<th>Cyclophosphamide</th>
<th>Estramustine</th>
<th>Ifosfamide</th>
<th>Mechlorethamine</th>
<th>Melphalan</th>
<th>Thiopeta</th>
<th>Busulfan</th>
<th>Carmustine</th>
<th>Lomustine</th>
<th>Streptozocin</th>
<th>(Platinum complexes)</th>
<th>Carboplatin</th>
<th>Cisplatin</th>
<th>Oxaliplatin</th>
<th>(Non-classic Alkylators)</th>
<th>Altretramine</th>
<th>Dacarbazine</th>
<th>Procarbazine</th>
<th>Temozolomide*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alkylating Agents</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nitrogen mustard</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Nitrosoureas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Platinum complexes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-angiogenic</strong></td>
<td>Bevacizumab*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotics</strong></td>
<td>Bleomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Camptothecin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anthracyclines</strong></td>
<td>Dactinomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Irinotecan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-HER2</strong></td>
<td>Trastuzumab*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Topotecan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antimetabolite</strong></td>
<td>Methotrexate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Folate analogs</td>
<td>Pemetrexed</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Purine analogs</td>
<td>Fludarabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Adenosine analogs</td>
<td>Mercaptopurine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pyrimidine analogs</td>
<td>Thioguanine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Substituted ureas</td>
<td>Cladribine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pentostatin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Capecitabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cytarabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Floxuridine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluorouracil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydroxyurea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asparaginase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Classes of systemic therapies

<table>
<thead>
<tr>
<th>Biologics</th>
<th>Interleukins</th>
<th>Interferons</th>
<th>Retinoids</th>
<th>Bexarotene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Microtubule agents/Taxanes)</td>
<td>Etoposide</td>
<td>Teniposide</td>
<td>Docetaxel</td>
<td>Ixabepilone</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>Paclitaxel</td>
<td>(include</td>
<td>Vinblastine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>nanoparticle)</td>
<td>Vincristine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Vinorelbine</td>
</tr>
<tr>
<td>Monoclonal antibodies</td>
<td>Rituximab</td>
<td>Trastuzumab</td>
<td>Cetuximab</td>
<td>Bevacizumab</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trastuzumab</td>
<td>Bevacizum</td>
<td>Panitumumab</td>
</tr>
<tr>
<td>Myeloablative with rescue</td>
<td>Allogeneic</td>
<td>Autogenic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Bortezomib*</td>
<td>Arsenic trioxide</td>
<td></td>
<td>histone deacetylase inhibitor</td>
</tr>
<tr>
<td>Targeted agents, Signal transduction inhibitors: and Tyrosine Kinase</td>
<td>Imatinib</td>
<td></td>
<td></td>
<td>Vorinostat</td>
</tr>
<tr>
<td></td>
<td>Trastuzumab*</td>
<td></td>
<td></td>
<td>CRA-024781</td>
</tr>
<tr>
<td></td>
<td>Lapatinib</td>
<td></td>
<td></td>
<td>SNDX-275</td>
</tr>
<tr>
<td></td>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Erlotinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bortezomib*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sorafinib*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sunitinib*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dasatinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nilotinib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocrine (hormonal)</td>
<td>Aminogluthemide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anastrozole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bicalutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Exemestane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Flutamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Goserelin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Letrozole</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leuprolide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tamoxifen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toremifene</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Not all antineoplastic agents may be listed here and some drugs may be classified in multiple categories. Please categorize your patient’s therapy as best possible, using multiple categories if indicated.

* signifies the agent may be classified into multiple categories
## Other Therapies

<table>
<thead>
<tr>
<th>WBC Growth Factor</th>
<th>Filgrastim (Neupogen)</th>
<th>Pegfilgrastim (Neulasta)</th>
<th>Sargramostim (Leukine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC Growth Factor</td>
<td>Epoetin alfa</td>
<td>Darbepoieten</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>Dexamethasone</td>
<td>Hydrocortisone</td>
<td>(other than topical)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Methylprednisolone</td>
<td>Prednisolone</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>Prednisone</td>
</tr>
</tbody>
</table>
SAE REPORT – SWOG 0702
Please fax to Integrated Medical Safety (IMS) within 24 hours
FAX: 1-888-299-4565
(If you encounter problems with the fax transmission please call 1 (800) 882-6577)

CONTACT INFORMATION

<table>
<thead>
<tr>
<th>From</th>
<th>Number of pages* (including fax cover sheet)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>*Please remember to include a copy of the MedWatch form</td>
</tr>
<tr>
<td></td>
<td>Phone Number</td>
</tr>
</tbody>
</table>

STUDY INFORMATION (please print)

<table>
<thead>
<tr>
<th>Investigator Name</th>
<th>Trial Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Study/ Protocol Number</td>
<td>Patient ID/ Number</td>
</tr>
<tr>
<td>Novartis #</td>
<td>IRB #</td>
</tr>
</tbody>
</table>

CAUSALITY

<table>
<thead>
<tr>
<th>Serious Adverse Event</th>
<th>Relationship to Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>□ Possibly suspected</td>
<td>□ Not Suspected</td>
</tr>
<tr>
<td>□ Possibly suspected</td>
<td>□ Not Suspected</td>
</tr>
<tr>
<td>□ Possibly suspected</td>
<td>□ Not Suspected</td>
</tr>
<tr>
<td>□ Possibly suspected</td>
<td>□ Not Suspected</td>
</tr>
<tr>
<td>□ Possibly suspected</td>
<td>□ Not Suspected</td>
</tr>
</tbody>
</table>

WAS THIS REPORT SENT TO THE FDA? □ NO

□ YES Date __/______/______ (day) (month) (year)

INVESTIGATOR SIGNATURE: ____________________________ Date ____________

SWOG 0702 SAE FAX COVER SHEET

Oct 2008
19.6 Cancer Trials Support Unit (CTSU) Participation Procedures

**Registration/Randomization**

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an ‘active’ investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member website or by calling the PMB at 301/496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. EST.

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

All forms and documents associated with this study can be downloaded from the S0702 web page on the CTSU registered member Web site (www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as ‘approved’ in the CTSU RSS.

**Requirements for S0702 site registration:**
- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Order blood collection kits from the SWOG Solid Tumor Tissue Bank (Section 15.1)

**Prestudy requirements for patient enrollment on S0702:**

*In order to participate in S0702, all participants must be planning to receive zoledronic acid for metastatic bone disease within 30 days after registration.*

- Patient must meet all inclusion criteria, and no exclusion criteria should apply.
- Patient has signed and dated all applicable consents and authorization forms.
- All baseline laboratory tests and prestudy evaluations/exams performed within the time period specified in the protocol.
- Enrolling institution must provide the Dental Health Professional with the forms specified in Section 7.5b.2.

**CTSU Procedures for Patient Enrollment**

1. Contact the CTSU Patient Registration Office by calling 1-888/462-3009 between 9:00 a.m. and 5:30 p.m. Eastern Time, Mon.-Friday. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 301/704-2376.

2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - Eligibility Criteria Checklist (Section 5.0 of the protocol)
   - SWOG S0702 Registration Worksheet (Complete all sections of form except for SWOG-specific data fields)
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 9:00 a.m. and 5:30 p.m., Mon-Fri, Eastern Time (excluding holidays); however, please be aware that registrations received after 5:00 p.m. will be processed the next day. The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.

4. Once investigator eligibility is confirmed and enrollment documents deemed complete, the CTSU registrar will contact the Southwest Oncology Group to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

*Treatment initiation should commence within 30 days of registration.*

**Data Submission and Reconciliation**

1. All case report forms (CRFs) associated with this study must be downloaded from the [S0702](http://www.ctsu.org) web page located on the CTSU registered member website (www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.

2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the SWOG Data Operations Center. Do not send study data to CTSU.

3. The SWOG Data Operations Center will send query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the SWOG Data Operations Center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and *must keep their CTEP AMS account contact information current*. This will ensure timely communication between the clinical site and the SWOG data center.

**Special Materials or Substudies**

1. Specimen collection for correlatives (Protocol section 15.0)
   - Institutions must seek additional patient consent to submit and bank the following specimens: serum for banking; whole blood for DNA analysis and banking. Patient participation is optional.
   - Order S0702 blood collection kits as specified in section 15.1
   - Collect, prepare, and submit specimens as outlined in the protocol
   - Do not send specimens, supporting clinical reports, or transmittals to the CTSU

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

   You can also access the Tracking System from the members’ section of the CTSU Web Site. Go to the [S0702](http://www.ctsu.org) protocol page and click on the link provided under the Case Report Forms header.

2. Dental Imaging Submission (protocol section 15.2)
   - Set-up electronic submission through AG Mednet
   - Submit completed scans and images as outlined in the protocol
Serious Adverse (AE) Reporting (Section 16.0)

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

2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. Links to the FDA MedWatch Form and the Novartis AE Cover Form are located on the Adverse Events tab of the CTSU homepage (www.ctsu.org).

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

Regulatory and Monitoring

Study Audit

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

Responsibility for assignment of the audit will be determined by the site’s primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up can be found in the CTMB Monitoring Guidelines and are available for download from the CTEP web page http://ctep.cancer.gov/monitoring/guidelines.html.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

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

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

Clinical Data System-Web (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-Web). The sponsoring Group fulfills this reporting obligation by transmitting the CDS data collected from the study-specific case report forms, via the Web to the NCI center for Biometrics (NCICB). Cumulative CDS data are submitted quarterly.
19.7 Quantifying Use of Steroids

The case report forms asks: “Has the patient ever received steroids (> the equivalent of 5 mg prednisone daily)?” For the purpose of this registry, steroid use may be averaged over time. The details of the calculations and how best to answer this question will be at the discretion of the clinical team; however, below outlines a general approach to be considered when addressing steroid exposure.

A rule of thumb for converting dexamethasone to the prednisone equivalent is that dexamethasone is roughly 8-10 times more potent than prednisone. Conversions for other steroids to prednisone exist and should be used as needed.

In oncology, the steroids are often used in a pulsatile fashion. For the purpose of this registry, it is appropriate to average the steroid dose across a period of time.

The below serves as a working example of how calculations may be made:

A patient is receiving 8-10 mg dexamethasone as part of their supportive medications with a chemotherapy regimen. This amount of dexamethasone converts to approximately 64-100 mg of prednisone.

If that dexamethasone is being used weekly, then that individual is receiving more than 5 mg of prednisone equivalent daily.

- 64 mg /7 days = 9 mg daily or 100 mg /7 days = 14 mg prednisone equivalent

If that dexamethasone is being used over the course of 1 month, then that individual is not receiving more than 5 mg of prednisone equivalent daily.

- then 64 mg /30 days = 2 mg or 100 mg /30 days = 3 mg prednisone equivalent

The same exercise can be done for regimens that are administered every 2 or 3 weeks.

In the situation where the calculation includes the possibility of an equivalent to 5 mg of prednisone daily, then select the response indicating YES on the case report form.