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Includes Update #5

CANCER AND LEUKEMIA GROUP B

CALGB 70604

A RANDOMIZED, PHASE III STUDY OF STANDARD DOSING VERSUS LONGER DOSING INTERVAL OF ZOLEDRONIC ACID IN METASTATIC CANCER

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).
Institutions not aligned with CALGB 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 CTSU Members' side of the website located at https://www.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU logistical appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CALGB. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to CALGB 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 CALGB. (generally via email but may be sent via fax or postal mail). Please send query responses and delinquent data to CALGB and do not copy the CTSU Data Operations. Query responses should be sent to CALGB via postal mail or fax (no transmittal form needs to accompany response). Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP IAM account contact information current. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

Endorsing cooperative groups:

A RANDOMIZED, PHASE III STUDY OF STANDARD DOSING VERSUS LONGER DOSING INTERVAL OF ZOLEDRONIC ACID IN METASTATIC CANCER

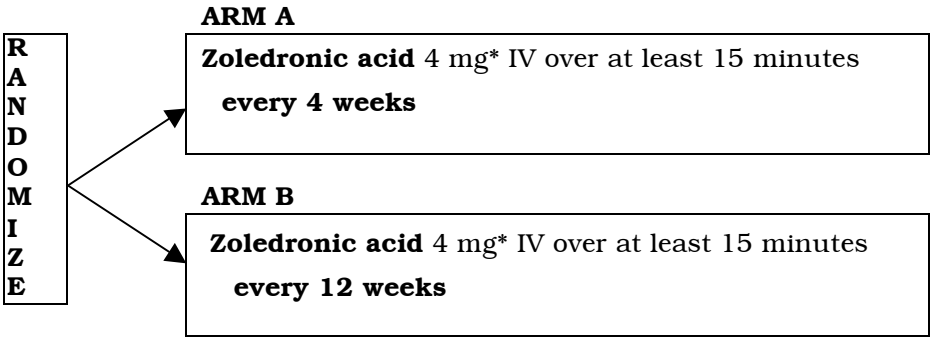
Patient Eligibility

Histologic documentation of one of the following: breast adenocarcinoma, prostate adenocarcinoma or multiple myeloma.
At least one bone metastasis by radiographic imaging (see Section 4.2).
No prior treatment with IV bisphosphonates. Prior treatment with oral bisphosphonates is allowed, but must be discontinued prior to the initiation of protocol therapy.
No prior treatment with denosumab.
No prior treatment with radiopharmaceuticals. Prior treatment with radioactive iodine is allowed. Prostate cancer patients treated with brachytherapy are eligible.
Prior radiation therapy to bone is allowed, provided that at least one site of bone metastasis has not been irradiated and radiation is completed prior to registration. There should be no plan for radiation therapy to non-irradiated sites of bone metastases.
Prior non-investigational adjuvant and metastatic chemotherapy, biologic therapy and endocrine therapy is allowed.
No current treatment with investigational agent(s).
Patients with brain metastases are not eligible.
Not pregnant and not nursing.
ECOG (CTC) performance status 0-2.
Age ≥ 18 years of age

Required Initial Laboratory Values	
Calc. Creatinine Clearance	≥ 30mL/min*
Corrected Serum Calcium	≥ 8.0 mg/dL and < 11.6mg/dL *

* see Section 4.8

SCHEMA



* Starting dose of zoledronic acid will be adjusted according the calculated creatinine clearance using the Cockcroft-Gault formula (see Section 8.0).

All patients will be also be instructed to take approximately 500 mg of **elemental calcium** by mouth daily and 400-800 IU **vitamin D** by mouth daily. This can be taken as one combination product, or as a multivitamin in addition to calcium or any other product or combination of products to achieve the desired doses.

Treatment with zoledronic acid will continue for 2 years or until patients experience unacceptable toxicity.

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1.0 INTRODUCTION

1.1 Background:

Skeletal complications are a major cause of morbidity in patients with metastatic prostate cancer, breast cancer and multiple myeloma. The incidence of skeletal related events defined as radiation therapy to bone, clinical fracture, spinal cord compression and surgery to bone ranges from 44-64% [1-3].

Zoledronic acid (Zometa®) is approved by the Food and Drug Administration for the treatment of patients with multiple myeloma and patients with documented bone metastases from solid tumors including prostate cancer and breast cancer. Zoledronic acid reduces the incidence of skeletal related events (SRE) by 25-40% in patients with metastatic breast, lung, renal, and prostate cancers, and multiple myeloma (1,2,4-8); and also reduces metastatic bone pain due to metastatic solid tumors and myeloma [8,9,10].

Unfortunately, zoledronic acid does not improve survival and is costly. A recent cost effectiveness analysis for zoledronic acid in prostate cancer showed a nominal within-trial cost per quality adjusted life year of over $159,000 (11). The standard dosing interval, every three to four weeks, for zoledronic acid was determined empirically rather than on the basis of compelling pharmacodynamic evidence or comparative clinical observations. Indeed, there is some pharmacodynamic and clinical trial evidence to suggest that the standard dosing interval is unnecessarily frequent. Although generally well tolerated, evolving clinical experience suggests that cumulative bisphosphonate exposure increases the risk of osteonecrosis of the jaw. Furthermore, cumulative exposure may be nephrotoxic. Thus, if less frequent dosing were found to be non-inferior to three- or four-weekly dosing in terms of skeletal events, there would be a strong rationale based on convenience, cost, and toxicity to change the standard dosing interval.

The proposed study will compare the efficacy and safety of standard dosing interval versus longer dosing interval of zoledronic acid in patients with multiple myeloma and breast and prostate cancer that has metastasized to bone. Patients with histologically confirmed diagnoses and radiographically documented bone metastases will be randomly assigned to zoledronic acid intravenously every 4 weeks or every 12 weeks for 2 years. The primary study endpoint will be the proportion of patients with at least one SRE at 2 years.

The results of the proposed study are likely to change clinical practice. If the study demonstrates that less frequent dosing is non-inferior to standard dosing in terms of preventing SREs, we will recommend every 12 week zoledronic acid for patients with prostate cancer or breast cancer that has metastasized to bone or multiple myeloma.

1.2 Adverse events from bisphosphonate use

Osteonecrosis of the jaw: Osteonecrosis of the jaw (ONJ) is an increasingly reported adverse event with bisphosphonate use. In a retrospective study of multiple myeloma patients, Badros and colleagues (12) found that variables predictive for the development of ONJ in multiple myeloma patients included dental extraction ($p = 0.009$) and treatment with pamidronate followed by zoledronic acid ($p = 0.009$). Bamias and colleagues (13) evaluated 252 patients, most of whom had myeloma, breast or prostate cancer, treated with bisphosphonates (pamidronate, zoledronic acid and/or ibandronate) between 1997 and 2005. The incidence of ONJ increased with time of exposure from 1.5% for patients treated for 4 to 12 months, to 7.7% for patients treated for 37 to 48 months. The cumulative hazard of developing ONJ was significantly higher in the zoledronic acid group compared to pamidronate alone or pamidronate followed by zoledronic acid ($p \leq 0.001$). For zoledronic acid, the hazard for development of ONJ was 1% within the first year of treatment and increased to 21% at 3 years, whereas the hazard among the pamidronate group was 0% for the first 2 years, and increased to 7% after 4 years of treatment. The risk of ONJ appears to be increased with cumulative exposure to zoledronic acid and is a significant

problem for myeloma, breast cancer or prostate cancer patients with relatively indolent disease who are expected to survive longer than 18-24 months.

Renal safety: Bisphosphonates, as a class, are potentially nephrotoxic. Strategies to minimize clinical nephrotoxicity have involved dose optimization and, in the case of IV bisphosphonates, administration over a longer time. Nevertheless, nephrotoxicity (primarily elevations in serum creatinine, but also abnormalities in cation homeostasis) have been observed in patients receiving zoledronic acid at recommended dosing regimens, especially for prolonged periods of time and especially in patients with baseline renal dysfunction. Information summarized in the Manufacturer's Prescribing Information indicates that in placebo controlled trials subjects receiving zoledronic acid typically develop somewhat higher creatinine levels than those receiving placebo, but that the difference has not reached statistical significance in any trial (14). We are aware of no meta-analysis. Perhaps reflecting evolving concern about cumulative nephrotoxicity, there was a post-approval modification of the prescribing information to recommend dose adjustments for patients with a measured or calculated creatinine clearance less than 60 mL/min (15).

1.3 Rationale for the selected trial design

Preliminary data: Limited published information indicates that in patients with metastatic cancer a single 4 mg dose of zoledronic acid suppresses serum markers of bone turnover for at least 8 weeks. Berenson and colleagues (16) demonstrated that 2 mg, 4 mg, 8 mg and 16 mg doses all appear to suppress bone turnover markers (urinary N-telopeptide) for at least 8 weeks, but longer time points were not reported. Indeed, in women with post-menopausal osteoporosis, a single dose of zoledronic acid at 4 mg suppresses serum markers for at least one year (17). In men with non-metastatic prostate cancer, a single 4 mg dose of zoledronic acid increases bone mineral density and suppresses serum N-telopeptide levels for 12 months (18). One recent study in patients with prostate cancer metastatic to bone (19) demonstrated that every 3-month dosing of zoledronic acid significantly reduces bone turnover markers compared to placebo.

Open-label, non-placebo: CCOP members of the CALGB were surveyed about the intent and design of this study. There was unanimous interest among the members, but two-thirds of the members surveyed stated that a double-blind, placebo-controlled study would be prohibitively difficult to conduct due to patients' concerns about receiving a placebo in the every 3 month arm and the inconvenience of monthly placebo infusions for the every 3 month arm. Furthermore, while patients may be willing to trade a possible decrease in efficacy in exchange for the convenience and reduced toxicity of every 3 month dosing, requiring a patient to undergo the inconvenience of monthly infusions in a placebo-controlled study may negate any of the perceived benefits of the every 3 month arm (e.g. less inconvenience).

Patients randomized to either arm of the study will be required to be seen monthly. This interval is close to the community standard for follow-up of a patient with metastatic cancer involving bone. Furthermore, the number of patients who drop out will be carefully tracked by their treatment assignment as these numbers may differ between the arms.

To minimize ascertainment bias, a number of objective parameters are being assessed: *Primary objective:* The proportion of patients who experience at least one SRE over 2 years will be evaluated. (SRE will be defined as radiation therapy to bone including bone-targeted radiopharmaceuticals, clinical fracture, spinal cord compression and surgery to bone). The potential bias in a opn-label non-placebo arm would be greater if we were evaluating the time to first SRE because patients and providers may be more aware of any change in pain or performance status; thus, prompting earlier than expected evaluation with imaging or referral for radiation therapy or surgery. Since we are evaluating the cumulative incidence of SREs and providing consistent monthly assessments in both arms, as well as objective pain

assessment evaluations (Brief Pain Inventory), the potential bias in the every 12 week treatment arm should be minimized.

Secondary objectives: Other open-label, non-placebo studies (10,20) of zoledronic acid in patients with metastatic cancer have reliably assessed pain and quality of life without concern for bias due to lack of a placebo-containing arm. Biases in pain assessment will be minimized because of the close monthly follow-up required in both treatment groups. The evaluation of osteonecrosis of the jaw, renal function and bone turnover markers involve discrete, objective events less prone to bias.

Every 3 month dosing: Bisphosphonates reduce the risk of skeletal events, but they have not been shown to improve survival in myeloma (21), prostate cancer (22), or breast cancer (23). There are no published data to suggest that every 3 to 4 weeks is the optimal dosing interval for zoledronic acid (compared to less frequent dosing) in metastatic cancer. Standard monthly dosing may be more toxic and is certainly less convenient and more costly than every 3 month dosing. We believe that toxicity is an important consideration in this area, but the long follow-up required would prohibit the conduct of preliminary trials of various schedules looking for differences in the toxicity. In light of the findings that a single dose of zoledronic acid suppresses bone turnover markers for at least 8 weeks and that every 3 month dosing reduces bone turnover markers in metastatic prostate cancer patients (19), extending the dosing interval to 12 weeks seems to be a conservative and rational choice. Lastly, this trial has been designed with early stopping rules (see Section 15.0) to ensure that the trial will be stopped if the experimental arm is inferior.

Study Duration: This trial has been designed to observe patients for 24 months because that is the commonly used interval in clinical practice, which has also been adopted into ongoing trials. [For example, Novartis Protocol CZOL446E2352 is a randomized phase trial III for breast cancer patients with skeletal metastasis who have received standard dosing (every 3 to 4 weeks for a total of 9-20 doses or 12-15 months) of IV zoledronic acid and randomizes them to either continue monthly or every 3 month zoledronic acid for an additional 12 months]. The cumulative incidence of ONJ is 7% (95% CI 1-13%) at 2 years using a monthly treatment schedule (13). Based on the observation that treatment durations beyond 2 years are associated with increases in ONJ, the 2-year interval has been empirically adopted with longer durations of treatment individualized based on clinical judgments as to ongoing benefits versus risks.

Oral bisphosphonates: In metastatic breast cancer, oral ibandronate 50 mg has been shown to reduce the skeletal morbidity rate (number of events per 12-week period) compared with placebo (0.95 vs. 1.18, $p = 0.004$). There was also a significant reduction in the mean number of events requiring radiotherapy (0.73 vs. 0.98, $p < 0.001$) and events requiring surgery (0.47 vs. 0.53, $p = 0.037$) (51). A study in the U.S. with metastatic breast cancer had similar results for oral ibandronate with a relative risk reduction of 39% for skeletal related events compared to placebo (52). These newly developed oral aminobisphosphonates have efficacy in metastatic cancer in terms of reducing skeletal related events. However, because these agents are often used for the treatment of osteopenia/osteoporosis, patients will be stratified based on the prior use of these agents rather than be excluded from this study.

Correlative sciences: We propose to evaluate serum bone turnover markers in a subset of patients. Previous studies have demonstrated that serum markers correlate with risk of fracture (14, 24). It is anticipated that every 12 week dosing will be as effective as monthly dosing in terms of skeletal related events and pain, and that every 12 week dosing will result in similar suppression of bone turnover markers. Comparison of marker data with clinical outcomes may provide further insights into the mechanism of this commonly used agent. Furthermore, suppression of bone turnover markers in the every 12 week treatment arm would support our clinical findings if equivalence is demonstrated in the every 4 week and every 12 week arms.

1.4 Inclusion of Women and Minorities

Women and minorities will be eligible for this study without alteration in eligibility criteria. Gender and race/ethnicity differences in the efficacy of alternative zoledronic acid schedules are not expected based on previously published clinical trial data.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	47	+	30	=	70
Not Hispanic or Latino	1128	+	560	=	1688
Ethnic Category: Total of all subjects	1175	+	583	=	1758
Racial Category					
American Indian or Alaskan Native	6	+	2	=	8
Asian	17	+	6	=	23
Black or African American	130	+	60	=	190
Native Hawaiian or other Pacific Islander	1	+	1	=	2
White	1021	+	514	=	1535
Racial Category: Total of all subjects	1175	+	583	=	1758

2.0 OBJECTIVES

Primary Objective

2.1 To determine whether every-12-week therapy with zoledronic acid is not inferior to every-4-week therapy for patients with metastatic breast cancer, metastatic prostate cancer, or multiple myeloma involving bone, as measured by the proportion who experience at least one skeletal related event within 24 months after randomization.

Secondary Objectives

2.2 To compare pain scores (Brief Pain Inventory) of patients with metastatic breast cancer, metastatic prostate cancer, or myeloma involving bone receiving every 12 week dosing of zoledronic acid to those receiving every 4 week dosing.

2.3 To compare functional status (ECOG performance status) of patients with metastatic breast cancer, metastatic prostate cancer, or myeloma involving bone receiving every 12 week dosing of zoledronic acid to those receiving every 4 week dosing.

2.4 To compare the incidence of osteonecrosis of the jaw in patients with metastatic breast cancer, metastatic prostate cancer, or myeloma involving bone receiving every 12 week dosing of zoledronic acid to those receiving every 4 week dosing.

2.5 To compare the incidence of renal dysfunction of patients with metastatic breast cancer, metastatic prostate cancer, or myeloma involving bone receiving every 12 week dosing of zoledronic acid to those receiving every 4 week dosing.

2.6 To compare the skeletal morbidity rate, defined as the number of skeletal-related events per year, of patients receiving every 12 week dosing to those receiving every 4 week dosing.

2.7 To compare the suppression of serum markers of bone resorption of patients with metastatic breast cancer, metastatic prostate cancer, or myeloma involving bone receiving every 12 week dosing of zoledronic acid to those receiving every 4 week dosing.

2.8 To determine whether every 12 week therapy with zoledronic acid is not inferior to every-4-week therapy for each subgroup of patients with either breast cancer, prostate cancer, or multiple myeloma, as measured by the proportion who experience at least one skeletal related event within 24 months after randomization.

Pharmacogenomic substudy objective

2.9 To explore the correlation between the genetic polymorphisms of interest, vitamin D receptor gene BSMI (RS ID 1544410), and the incidence of SRE in patients treated with zoledronic acid.

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate. Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.
- Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives (Norplant), or double barrier method (diaphragm plus condom).

4.0 ELIGIBILITY CRITERIA

4.1 Histologic documentation of disease: Histologic documentation of <u>one</u> of the following: breast adenocarcinoma, prostate adenocarcinoma <u>or</u> multiple myeloma.

4.2 Stage: At least one site of bone metastasis or bone involvement by radiologic imaging including plain radiograph, computed tomography, PET scan, PET/CT scan, magnetic resonance imaging, bone scan, or skeletal survey. Indeterminate lesions should be confirmed by a second imaging method.

4.3 Prior Treatment

- No prior treatment with IV bisphosphonates is allowed. Prior treatment with oral bisphosphonates is allowed, but they must be discontinued prior to the initiation of protocol therapy.
- No prior treatment with denosumab.
- No prior treatment with radiopharmaceuticals. Prior treatment with radioactive iodine is allowed. Prostate cancer patients treated with brachytherapy are eligible.
- Prior radiation therapy to bone is allowed, provided that at least one site of bone metastasis has not been irradiated and radiation is completed prior to registration. There should be no plan for radiation therapy to non-irradiated sites of bone metastases.
- Prior adjuvant and metastatic chemotherapy, biologic therapy and endocrine therapy is allowed.

4.4 No current treatment with investigational agent(s). See Section 12.0 regarding allowed therapies and concurrent enrollment to other clinical trials.

4.5 Brain metastases: Patients with known brain metastases are not eligible. Patients who develop brain metastases during the study will be allowed to continue treatment as assigned.

4.6 Pregnancy/Nursing Status: Not pregnant and not nursing

4.7 ECOG Performance Status: 0-2

4.8 Age: ≥ 18 years of age

4.9 Required Initial Laboratory Values:

Calculated creatinine clearance	≥ 30 mL/min. (Cockroft and Gault formula; see Section 8.0)
Corrected serum calcium*	≥ 8.0 mg/dL (2.00 mmol/L) and < 11.6 mg/dL (2.90 mmol/L)

* Corrected serum calcium should be calculated using standard institutional practices.

5.0 RANDOMIZATION AND STRATIFICATION

5.1 Registration Requirements

Informed Consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts. (Human protection committee approval of this protocol and a consent form are required.)

5.2 Patient Registration/Randomization

This study uses the CALGB Web-based Patient Registration system. Randomization will be accepted only through CALGB Main Member Institutions, selected affiliate institutions and CCOPs using the Web-based Patient Registration system. Registration must occur prior to the initiation of therapy.

Confirm eligibility criteria (Section 4.0). Complete the Registration Worksheet. Access the Web-based Patient Registration system via the Patient Registration tab on the CALGB Member Website at www.calgb.org. If the study does not appear on the list of studies in the Patient Registration system, the registration must be performed by the CALGB Registrar via phone or fax. If the registering CRA requires assistance, he/she may consult the on-line help file at the bottom of the screen or call the IS Help Desk at 1-888-44CALGB. If further assistance is required, the registering CRA may call the CALGB Registrar (919)-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time. Enter the following information:

CALGB patient ID #, if applicable
Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of person in contact with the patient record (responsible contact)
Protocol IRB approval date
Date of signed consent
Treatment Start Date
Date of HIPAA authorization signed by the patient
Patient's initials (L, F, M)
Patient's Social Security #, date of birth, hospital ID #, and survival status

Patient's gender
Patient's race
Patient's ethnicity
ECOG performance status
Patient's height (cm) and weight (kg)
Type of insurance (Method of Payment)
Patient's postal code
Disease, type and stage, if applicable
Eligibility criteria met (no, yes)
Companion studies to which the patient has consented

When the patient is registered, a CALGB patient identification number will be generated. Please write the number in your records. Registration to any mandatory or optional companion studies will be done at the same time as registration to the treatment study. Registration to both treatment and companion studies will not be completed if eligibility requirements are not met for all selected trials (treatment and companions).

After registration is complete, the patient may be randomized. The patient is randomized according to the stratification factors, which must be entered to obtain a treatment assignment. Once the randomization is complete, note the patient's treatment assignment in your records.

The Main Member Institution and registering institution will receive a Confirmation of Registration and a Confirmation of Randomization. Please check both confirmations for errors. Submit corrections in writing to the data coordinator at the CALGB Statistical Center, Data Operations, 2424 Erwin Rd, Ste 802 Hock Plaza, Durham, NC 27705, or fax to 919-668-9397.

5.3 Registration to Companion Studies

5.3.1 Substudies

There are two substudies within CALGB 70604. These correlative science studies must be offered to all patients enrolled on CALGB 70604 (although patients may opt not to participate). The substudies included within CALGB 70604 are:

- CALGB 150804: Correlation of bone turnover markers with the risk for developing skeletal related events for patients enrolled to CALGB 70604 (Section 10.1). [CLOSED WITH UPDATE 1]
- CALGB 60803 Pharmacogenomic studies: (Section 10.2)

If a patient answers "yes" to "I agree that my specimen may be used for the research studies described above," question #1 in the model consent, they have consented to participate in the substudy described in Section 10.1. The patient should be registered to CALGB 150804 at the same time they are registered to the treatment trial (70604). Samples should be submitted per Section 6.2.1.

The accrual goal for CALGB 150804 is 196 patients. At the time that this goal is met, this study will be updated to indicate that registration to the companion study has been completed. *[**Added with Update #1:** The accrual goal for this companion study was met at the time of the issuance of Update #1 to the protocol and new patient registrations to this companion will no longer be accepted.]*

If a patient answers "yes" to "I agree that my blood may be used for the genetic research studies described above" (question #2) in the Model Consent, they have consented to participate in the studies described in Section 10.2. Patients should be registered to CALGB 60803. Samples should be submitted per Section 6.2.2.

5.4 Stratification

5.4.1 Tumor type

a) Breast cancer

b) Prostate cancer

c) Multiple Myeloma

5.4.2 Baseline serum creatinine

a) ≤ 1.4 mg/dL

b) > 1.4 mg/dL

5.4.3 Prior skeletal related events (see Section 13.1)

a) No

b) Yes

5.4.4 Prior oral bisphosphonate use

a) No

b) Yes

6.0 DATA AND SAMPLE SUBMISSION

6.1 Data Submission: Forms should be submitted to the Alliance Statistics and Data Center (SDC) in compliance with the Data Submission schedule below.

Forms should be submitted electronically using the "Submit to CALGB" button located at the bottom of the last page of each form. Forms may also be mailed to the address below.

Reports and other supporting documentation should be mailed to:

Alliance Data Center
Attention: Quality Assurance Office
RO FF-3-24-CC/NW Clinic
200 First street SW
Rochester, MN 55905

For the most up-to-date data forms, please visit the CALGB website at www.calgb.org.

Data Submission: Submit forms to the CALGB Statistical Center, Data Operations at the following intervals:

Form		Submission Schedule
	Baseline	
C-1789 C-1790 C-358 Report*	70604 Registration Worksheet 70604 Eligibility Checklist 70604 On Study Form 70604 SRE Form Brief Pain Inventory (short form) Pathology and imaging	Submit within 2 weeks after registration.
	Treatment	
C-1791 C-1792 C-1793 C-358 C-1790 Report*	70604 Treatment Form 70604 Adverse Event Form 70604 Follow Up Form Brief Pain Inventory (short form) 70604 SRE Form Imaging	Submit every 4 weeks while patient is on treatment and at the end of treatment.
	Follow-up (after end of protocol treatment)	
C-1793 C-1790 C-358	70604 Follow Up Form 70604 SRE Form Brief Pain Inventory (short form)	Submit every 4 weeks until 2 years from date of registration, and/or death.
C-300	Off Treatment Form	Submit when patient completes treatment at any time.
	Other	
Report	Dental records	At the time of diagnosis of osteonecrosis of the jaw
C-1742	CALGB Confirmation of Lost to Follow-up Form	After determination that the patient is lost to follow-up, submit every 6 months for up to 2 years.

* Submit copies of all required reports to confirm eligibility and restaging results.

Common Terminology Criteria for Adverse Events: This study will utilize the NCI Common Terminology Criteria for Adverse Events version 3.0 for routine toxicity and adverse event reporting.

6.2 Specimen Submission for Correlative Studies

All participating institutions must ask patients for their consent to participate in the correlative substudies planned for CALGB 70604, although patient participation is optional. [At the time that Update #1 was issued, new patient enrollments to CALGB 150804 was closed.] Bone turnover marker and pharmacogenomic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 10.0. For patients who consent to participate, blood will be collected at the following time points for these studies:

	Prior to treatment	Every 12 weeks prior to zoledronic acid*
Blood[1] (10 mL/red-gray top)	X	X
Whole blood[2] (10 mL/purple top)	X	

1 Serum to be used for bone turnover marker analysis (150804)

2 To be used for pharmacogenomic assays (60803).

* Samples may be collected up to 48 hours prior to zoledronic acid.

USE OF THE ALLIANCE BIOSPECIMEN MANAGEMENT SYSTEM (BioMS) IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM.

BioMS is a web-based system for logging and tracking all biospecimens collected on Alliance trials. Authorized individuals may access BioMS at the following URL: http://bioms.allianceforclinicaltrialsinoncology.org using most standard web browsers (Safari, Firefox, Internet Explorer). For information on using the BioMS system, please refer to the 'Help' links on the BioMS web page to access the on-line user manual, FAQs, and training videos. To report technical problems, such as login issues or application errors, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org. For assistance in using the application or questions or problems related to specific specimen logging, please contact: 1-855-55-BIOMS or Bioms@alliancenctn.org.

After logging collected specimens in BioMS, the system will create a shipping manifest. This shipping manifest must be printed and placed in the shipment container with the specimens.

All submitted specimens must be labeled with the protocol number (70604), CALGB patient number, patient's initials and date and type of specimen collected (e.g., serum, whole blood). A copy of the Shipment Packing Slip produced by BioMS must be printed and placed in the shipment with the specimens.

Instructions for the collection of samples are included below. Please be sure to use a method of shipping that is secure and traceable. Extreme heat precautions should be taken when necessary.

Shipment on Monday through Friday by overnight service to assure receipt is encouraged. If shipping on Friday, FedEx or UPS must be used and the air bill must be marked "For Saturday delivery." Do not ship specimens on Saturdays.

All specimens should be sent to the following address:

Alliance Pathology Coordinating Office
The Ohio State University
Innovation Centre
2001 Polaris Parkway
Columbus, OH 43240
Tel: 614-293-7073 Fax: 614-293-7967

6.2.1 Blood submission (for serum)

Blood for bone turnover marker studies (see Section 10.1) should be collected at baseline and every 12 weeks until the end of protocol treatment. If possible, subsequent blood draws should be collected at approximately the same time of day as the baseline specimen was collected.

Ten mL of peripheral venous blood should be collected in a red/black tiger top tube(s) with a clot activator and gel for serum separation. Observe a dense clot. The tube(s) should be centrifuged for 10 to 15 minutes at 1300 x g (or in accordance with the manufacturer's instructions) and refrigerated immediately. Sample should be shipped on a cool pack within 24 hours. The CALGB PCO will aliquot the specimens upon receipt. If for any reason, the red/black tiger top tube(s) is not available and a red top serum tube is used, after the specimen is spun the serum must be transferred to a polypropylene tube before being refrigerated. Sample should be shipped over cool pack within 24 hours. The CALGB PCO will aliquot the specimens upon receipt.

6.2.2 Blood submission (for pharmacogenomic studies)

For patients who consent to participate, whole blood samples will be used for the pharmacogenomic studies described in Section 10.2. This sample should be collected prior to the initiation of protocol treatment.

Collect 10 mL of peripheral venous blood in an EDTA (purple-top) tube. The tube should be inverted several times to mix the EDTA, refrigerated until shipped on cool pack by overnight mail to the CALGB PCO. The sample should be shipped the same day that the blood is drawn.

7.0 REQUIRED DATA

Guidelines for Pre-Study Testing

To be completed within 16 DAYS before registration:

- History, physical and all bloodwork

To be completed within the 12 WEEKS prior to registration.

- Imaging to document bone metastases

	Prior to Registration	Every 4 weeks*	Every 12 weeks	Post treatment Follow up**
Tests & Observations				
Physical Examination	X			
Pulse, Blood Pressure	X			
Height	X			
Weight	X	B		
Brief Pain Index	X	X		X
ONJ screening ‡	X	X		X
Laboratory Studies				
CBC, Differential, Platelets	X			
Serum creatinine	X***	X***		
Serum calcium	X		X^	
Albumin	X		X^	
Pregnancy test	A			
Staging				
Imaging studies †	X			
Correlative studies				
Serum	*At baseline, then every 12 weeks for 2 years (see Section 6.2.1).*			
Whole blood	*At baseline (see Section 6.2.2).*			

* While a cycle is 4 weeks for arm A and 12 weeks for arm B, **patients in both arms will be assessed every 4 weeks.** These endpoint-related assessments need not be performed by a physician. For patients randomized to Arm B, the Brief Pain Index and ONJ screening assessment may be done by telephone and blood for serum creatinine levels may be drawn at a lab convenient to the patient's home.

** Every 4 weeks until 2 years after registration.

*** Serum creatinine may be obtained up to 7 days prior to treatment on each cycle and need not be repeated on day 1 of each cycle. In order to assess serum creatinine levels for patients on both arms at the same intervals, these levels must be measured every 4 weeks for patients enrolled on Arm B.

† At least one site of bone involvement which has not been irradiated is required for study entry. Imaging studies may include plain radiograph, CT scan, PET scan, PET/CT scan, MRI, bone scan, or skeletal survey. Indeterminate lesions should be confirmed by a second imaging method.

‡ These questions can be found on the C-1789, CALGB 70604 On-study form and the C-1793, CALGB 70604 Follow-up form.

^ Results of serum calcium and albumin tests need not be known prior to treatment.

A For women of child-bearing potential.

B Prior to every treatment with zoledronic acid.

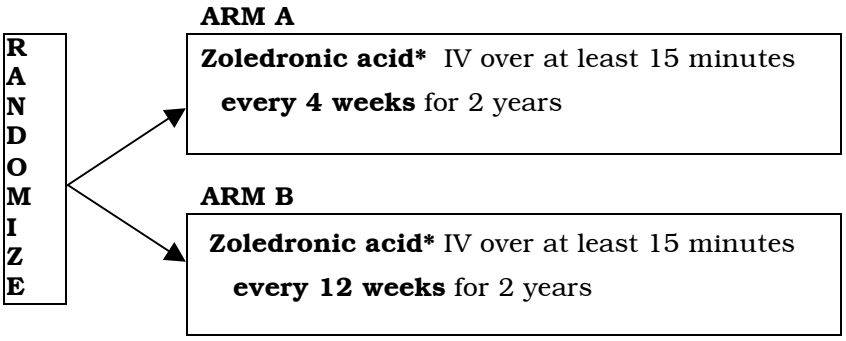
7.1 Screening questions for osteonecrosis of the jaw (ONJ): There are no validated screening assessments for ONJ; however, in the interest of collecting uniform data on the evaluation of ONJ, patients will be asked the following ONJ screening questions at baseline and at each monthly visit:

- Have you had any dental procedures in the last 12 months [at baseline] or in the last 4 weeks [at each monthly visit after baseline] (including general cleaning)? If yes, when?
- Do you have pain or tenderness in the mouth, jaw or gum line? If yes, is this pain new?
- Do you have any non-healing sores in the mouth or along the gum line?

Based on the responses to these questions, the treating physician should refer the patient to a specialist as appropriate.

8.0 TREATMENT PLAN

Protocol treatment is to begin within 7 days of randomization. Questions regarding treatment should be directed to the CALGB Study Chair.



Creatinine clearance is to be calculated for all patients within 7 days prior to each dose using the Cockcroft-Gault formula using actual body weight (see below). Each dose of zoledronic acid should be adjusted as follows:

Calc. Creatinine Clearance	Dose
> 60 mL/min	4.0 mg
50 – 60 mL/min	3.5 mg
40 – 49 mL/min	3.3 mg
30 – 39 mL/min	3.0 mg

Creatinine clearance (CrCl) will be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCI (ml/min)} = \frac{(140\text{-age}) \times \text{actual wt (in kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

For females, use 85% of calculated CrCl value

8.1 Zoledronic acid will be administered in an outpatient setting.

8.1.1 Arm A: Patients randomized to Arm A will receive zoledronic acid IV over at least 15 minutes **every 4 weeks.**

8.1.2 Arm B: Patients randomized to Arm B will receive zoledronic acid IV over at least 15 minutes **every 12 weeks.**

8.1.3 Duration of treatment: All patients are to be treated for 2 years.

8.1.4 Dental evaluations: The package insert for zoledronic acid recommends a dental evaluation prior to treatment. Treating physicians should follow their standard practice regarding dental assessments for patients receiving zoledronic acid. Patients will be asked screening questions for ONJ at each visit prior to receiving zoledronic acid (see Section 7.1).

8.2 Supplemental calcium and vitamin D: All patients will be also be instructed to take approximately 500 mg of **elemental calcium** by mouth daily and 400-800 IU **vitamin D** by mouth daily. This can be taken as one combination product, or as a multivitamin in addition to calcium or any other product or combination of products to achieve the desired doses.

9.0 Dose Modifications And Management of Toxicity

9.1 Renal: Serum creatinine will be measured within 7 days prior to each dose of zoledronic acid.

- **For creatinine clearance ≥ 30 mL/min.**, see Section 8.0 for dose of zoledronic acid based on creatinine clearance.
- **For creatinine clearance < 30 mL/min.**, zoledronic acid should be discontinued and the patient should be followed until 2 years following registration.

9.2 Acute Phase Reactions: Patients receiving initial intravenous treatment with zoledronic acid may experience an acute phase reaction characterized by fever and myalgias. Treatment-related acute phase reactions are typically transient (24-48 hours) and self-limited. Patients who experience an acute phase reaction will continue zoledronic acid treatment without dose or schedule modification. NSAIDs or other analgesics may be used at the treating physician's discretion.

9.3 Hypersensitivity reactions:

- **For grade 1 or 2 hypersensitivity reactions,** manage the reaction according to institutional procedures and consider pre-medication with antihistamines prior to the next dose.
- **For grade 3 or 4 hypersensitivity reactions,** discontinue protocol treatment.

9.4 Osteonecrosis of the jaw (ONJ) has been associated with the use of bisphosphonates. Patients who develop new onset jaw pain or tenderness or answer affirmatively to any of the three screening questions asked at each visit (see Section 7.1) should be evaluated by an appropriate specialist (e.g., dentist or oral surgeon).

Patients who develop ONJ will be taken off protocol treatment and treated at the discretion of their physician.

Patients who undergo invasive dental work (other than general cleaning) may have zoledronic acid delayed at the discretion of their treating physician. Treatment delays, date and type of dental procedure performed must be documented.

9.5 Dose Modification for Obese Patients

There is no clearly documented adverse impact of treatment of obese patients when dosing is performed according to actual body weight. Therefore, **all dosing is to be determined solely by (1) the patient's BSA as calculated from actual weight or (2) actual weight without any modification unless explicitly described in the protocol.** This will eliminate the risk of calculation error and the possible introduction of variability in dose administration. **Failure to use actual body weight in the calculation of drug dosages will be considered a major protocol deviation.** Physicians who are uncomfortable with administering chemotherapy dose based on actual body weight should not enroll obese patients on CALGB protocols.

10.0 CORRELATIVE SCIENCES AND PHARMACOGENOMIC COMPANION STUDIES

10.1 Correlation of bone turnover markers with the risk for developing skeletal related events for patients enrolled to CALGB 70604 (150804)

10.1.1 Background

Limited published information indicates that in patients with metastatic cancer a single dose of zoledronic acid at 4 mg suppresses serum markers for at least 8 weeks. Berenson and colleagues (16) demonstrated that 2 mg, 4 mg, 8 mg and 16 mg doses all appear to suppress bone turnover markers (urinary N-telopeptide) for at least 8 weeks, but longer time points were not reported. Indeed, in women with post-menopausal osteoporosis, a single dose of zoledronic acid at 4 mg suppresses serum markers for at least one year (17). In men with non-metastatic prostate cancer, a single dose of zoledronic acid at 4mg increases bone mineral density and suppresses serum N-telopeptide levels for 12 months (18). One recent study in patients with prostate cancer metastatic to bone (19) demonstrated that every 3-month dosing of zoledronic acid significantly reduces bone turnover markers compared to placebo.

We propose to evaluate serum bone turnover markers in a subset of patients. Previous studies have demonstrated that serum markers correlate with risk of fracture (14, 24). We anticipate that quarterly dosing will be as effective as monthly dosing in terms of skeletal related events and pain, and that quarterly dosing will result in similar suppression of bone turnover markers. Comparison of marker data with clinical outcomes may provide further insights into the mechanism of this commonly used agent. Furthermore, suppression of bone turnover markers in the every 12 week treatment arm would support our findings if equivalence is demonstrated in the every 4-week and every 12-week arms.

10.1.2 Objectives

To compare bone turnover markers (e.g., serum NTX levels) in patients receiving zoledroinic acid every 4 weeks to those in patients receiving zoledronic acid every 12 weeks.

10.1.3 Methods

Serum will be collected from patients at baseline then before administration of zoledronic acid every 12 weeks for 24 months. Bone turnover markers (i.e., serum N-telopeptide levels) will be monitored in the first 196 patients who consent to enrollment onto the correlative sciences study. Serum N-telopeptide concentrations will be determined using a competitive inhibition enzyme-linked immunosorbent assay.

10.2 Pharmacogenomic Studies for CALGB 70604 (60803)

10.2.1 Background

To our knowledge, genetic polymorphisms which may impact response to zolendronic acid in cancer patients have not been explored. Zoledronic acid does not undergo biotransformation in vivo. Therefore assessment of known polymorphisms in common drug metabolizing enzyme genes is unlikely to be helpful in predicting response to zoledronic acid. However, polymorphisms in Vitamin D receptor, interleukin 1, and LDL-related protein genes have been implicated in osteoporosis and perhaps response to bisphosphonate therapy. Polymorphisms in VEGF, Nitric Oxide, and Factor V Leiden genes have been recently implicated in osteonecrosis.

Polymorphisms in the Vitamin D receptor gene, specifically BSMI, have been implicated in predisposition to osteoporosis. However, the literature is conflicting. For example, Fleet and colleagues (25) reported that BMD was lower in BB than Bb or bb even after controlling for known risk factors for osteoporosis. By contrast, Hansen and colleagues (26) evaluated 200 Danish perimenopausal women and found that VDR genotype was not associated with baseline BMD, subsequent bone loss, or biochemical markers of bone metabolism. Similarly Garnero (27) assessed VDR gene polymorphisms BSMI, ApaI and TaqI in 268 untreated patients and again found no association between baseline BMD or change in BMD. One large meta-analysis of studies conducted from 1994-2001 did show the VDR BsmI BB genotype to be associated with lower BMD (28). By contrast, a subsequent population based study of 3100 postmenopausal British women found no association with genotype after controlling for confounding factors (29). Intriguingly, Marc and colleagues (30) evaluated response to etidronate treatment as a function of VDR gene BSMI polymorphism and found lumbar spine bone density increased more in BB and Bb patients (7%) than in bb patients (2.5%) after a year of therapy.

Cytokines may play a role in osteoclast activity and bone remodeling in some bone diseases. Recently Corral-Gudino and colleagues (31) found that the -511 C/T genotype of the interleukin 1β(IL1B) gene is associated with higher resistance to bisphosphonate use in patients with Paget's disease of the bone.

Recently van Meurs and colleagues (32) have reported a large study from the GENOMOS project—a large scale study of candidate gene polymorphisms for osteoporosis outcomes—showing that variants in the low-density lipoprotein receptor-related protein 5 gene, specifically Val1330 and Met667 alleles were associated with lower BMD and higher fracture rates. This study included over 37,000 white individuals in whom bisphosphonate use was rare.

The pathogenesis of ONJ is not well understood. One theory is that bisphosphonates inhibit angiogenesis by inhibiting VEGF and other angiogenic factors, and that this may be a mechanism for ONJ. However, the available literature is conflicting (reviewed in 33). Polymorphisms in the VEGF promoter have been associated with osteonecrosis of the femur (34). Glueck (35) and colleagues have found that endothelial nitric oxide gene T786 TT or TC are associated with idiopathic osteonecrosis of the femur. Glueck and colleagues (36) also have reported an association with Factor V Leiden mutation and ONJ associated with bisphosphonates. In a case control study of 89 patients with ONJ and 209 controls they found the Factor V Leiden mutation in 24% of the patients with ONJ and 3% controls. Finally Yang XY (37) reported an association between MDR1 (ABCB1) gene polymorphism MDR 3435TT and lower rates of osteonecrosis of the femoral head in 127 Chinese patients with SLE. To our knowledge an association between MDR1 polymorphism and bisphosphonate-related ONJ has never been explored.

10.2.2 Objective

To explore the correlation between the genetic polymorphisms of interest, vitamin D receptor gene BSMI (RS ID 1544410), and incidence of SRE in patients treated with zoledronic acid. More broadly, to explore correlations between any genetic polymorphisms of interest (such as vitamin D receptor gene, VEGF, IL1, LDL-related protein, Factor V Leiden) and phenotypes relevant to the pharmacokinetics or pharmacodynamics (efficacy or toxicity) of the zoledronic acid.

10.2.3 Study plan and methods

Little is known about genetic predictors of response and toxicity following treatment with zoledronic acid in cancer patients. We hypothesize that patients with VDR BSM1 b allele will have lower response to zoledronic acid and therefore higher SRE rates. Further we hypothesize that relevant polymorphisms in Factor V Leiden and MDR1 will be associated with higher incidence of ONJ in this population. We propose to genotype patients enrolling in CALGB 70604 for VDR BsmI, IL1β, LRP5, VEGF, Factor V Leiden and MDR1 and to look for associations between these genotypes and drug response and/or toxicity. Additional candidate genes may be included once evidence is found for their importance in determining the drug level or response to bisphosphonates. It is anticipated that the results of this study will lead to further hypothesis-driven research into the importance of genetic variation in determining drug response. A long-term goal of these studies is to use pharmacogenetic information to appropriately dose patients with zoledronic acid thereby optimizing response and minimizing toxicity.

Additionally we will use a genome-wide association study approach to explore correlations between relevant polymorphisms and all available response and toxicity phenotypes. Most pharmacogenetic analyses have taken a candidate gene approach that utilizes biological data to guide the selection of drug response genes in a pathway. This approach is limited by our knowledge of the mechanisms underlying the phenotypes. In contrast, a genome-wide approach collects SNP data across the entire human genome and has significant power to detect common variants that confer a modest risk for a complex phenotype. Genome-wide studies capitalize on the large number of SNPs (more than 10 million available in dbSNP) that have been localized and validated across the genome, a majority of which have resulted from the HapMap project. This valuable collection of publicly available, validated SNPs has provided the framework for performing genome-wide association studies. Recent technological advancements in genotyping platforms have also enabled the development of genome-wide associations. For example, the Illumina HumanHap 550 chip has the capacity to genotype over 555,000 SNPs simultaneously. This new capability represents a paradigm shift in the number of genotypes that can be evaluated in any given individual with one genotyping assay and provides a platform for the identification of novel genes involved in the response to and toxicity associated with zoledronic acid.

Patients will be recruited to this companion protocol by the physician enrolling them on CALGB 70604. A single 10 mL blood sample will be collected prior to the initiation of protocol treatment and shipped to the CALGB Pathology Coordinating Office (PCO). Genomic DNA will be extracted using a commercially available kit from Qiagen. The concentration and quality of DNA will be quantified by ultraviolet spectroscopy. All DNA samples will be stored in the DNA bank at the CALGB PCO.

11.0 Drug Formulation, Availability, And Preparation

11.1 Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

11.2 Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

11.3 The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

11.4 Zoledronic Acid (Zometa®) (NSC #721517)

Zoledronic acid is a potent inhibitor of bone resorption. Although its antiresorptive mechanism is not completely understood, several factors are thought to contribute to this action. In vitro, zoledronic acid inhibits osteoclast activity and induces osteoclast apoptosis. Zoledronic acid also blocks the osteoclastic resorption of mineralized bone and cartilage through its binding to bone. Zoledronic acid inhibits the increased osteoclast activity and skeletal calcium release induced by various stimulatory factors released by tumors.

Availability

Patients will receive commercially available zoledronic acid. The use of zoledronic acid in this study is consistent with its FDA approved indication. Zoledronic acid is available as a concentrate solution for infusion containing 4 mg zoledronic acid in 5 mL.

In accordance with the FDA guidance regarding IND exemptions for marketed agents, the CALGB has determined that this study is IND exempt, primarily because the use of the drug in this study is not significantly different from the label, the study is not intended to result in a labeling change, and the risk/benefit ratio is not significantly changed.

Storage and Stability

Intact vials should be stored at room temperature (25˚ C, 77˚ F). Solutions diluted for IV infusion may be stored under refrigeration (2˚- 8˚ C, 36˚- 45˚ F) and should be administered within 24 hours.

Preparation

The concentrate solution (4 mg acid in 5 mL) must be further diluted prior to IV administration. The desired dose should be diluted in 100 mL of sterile 0.9% Sodium Chloride, USP or 5% dextrose in water. Calcium containing solutions (e.g., Lactated Ringers) should not be used for dilution.

Administration

The diluted solution of zoledronic acid will be administered as a short IV infusion over at least 15 minutes.

The duration of infusion should be no less than 15 minutes because of the risk of clinically significant deterioration in renal function, which may progress to renal failure.

Toxicities

Patients may develop clinically significant deterioration in renal function. Acute phase reactions characterized by fever and myalgias are common after the first treatment. Acute phase reactions are typically transient and self-limited. Treatment-related laboratory abnormalities including hypocalcemia, hypophosphatemia, and hypomagnesemia are rarely associated with symptoms.

Osteonecrosis of the jaw has been described in patients bisphosphonates including zoledronic acid. The incidence appears to increase with longer durations of treatment, and seems to be greater with zoledronic acid as compared to pamidronate. Bisphosphonates might inhibit bone formation as a result of their inhibition of osteoclasts, the activity of which is required for bone turnover and viability. Alternatively, bisphosphonates might inhibit bone blood flow through inhibition of angiogenesis.

Musculoskeltal pain, including severe and incapacitating pain, has been described with several oral nad parenteral bisphosphonates. The mechanism and the incidence of pain are not known. In some cases, pain was initially focal and became progressively more diffuse. The median time to onset of musculoskeletal pain, reported in patients receiving alendronate, was 14 days (range: 1 day to 52 months). A variety of analgesics was used to treat musculoskeletal pain. Pain was reportedly relieved with discontinuation of the bisphosphonate, either immediately or over time. Musculoskeletal pain should be distinguished from pain associated with acute phase reactions, described above.

Please refer to the FDA-approved package insert for a comprehensive list of adverse events for zoledronic acid.

Drug Interactions

Caution is advised when bisphosphonates are administered with aminoglycosides, since these agents may have an additive effect to lower serum calcium level for prolonged periods. Caution should also be exercised when zoledronic acid is used in combination with loop diuretics due to an increased risk of hypocalcemia. Caution is indicated when zoledronic acid is used with other potentially nephrotoxic drugs.

11.5 Vitamin D

Availability

Vitamin D analogs are fat-soluble vitamins, which are commercially available. Patients may receive 400-800 IU of vitamin D by taking a multiple vitamin that contains 400-800 IU of vitamin D, taking one of the calcium preparations that also contain vitamin D, or by taking a vitamin D supplement.

Administration

For the purposes of this study, 400 IU (10 μg) vitamin D will be administered orally every day.

Toxicities

Vitamin D is usually nontoxic; however, headaches, nausea, vomiting, diarrhea, and hypercalcemia have been reported.

Vitamin D should be administered with extreme caution in patients with impaired renal function, heart disease, renal stones, or arteriosclerosis.

11.6 Calcium

Availability

Calcium salts are commercially available in a wide range of preparations.

Elemental Calcium Content of Selected Calcium Salts	
$Ca^{++}CO_3$ 1250 mg	500 mg
Ca^{++} gluconate 500 mg	45 mg
Ca^{++} citrate 950 mg	200 mg

Administration

Calcium will be administered orally at a dose of 500 mg elemental calcium daily. Calcium will be given in 1-3 divided doses, depending on the amount of elemental calcium in the preparation.

Toxicities

Calcium is usually nontoxic; however, the following toxicities may occur in patients: irritation to the GI tract, hypercalcemia in patients with chronic renal failure, renal calculi, and constipation.

Contraindications

Cardiac glycosides and calcium are synergistic and arrhythmia may occur if these drugs are given together.

Drug Interactions

Tetracycline and calcium should not be given at the same time, as calcium complexes tetracycline antibiotics, rendering them inactive.

12.0 Ancillary Therapy

12.1 Patients may not receive treatment with other agents expected to alter osteoclast activity (e.g. calcitonin, mithramycin, gallium nitrate, denosumab, or any other bisphosphonate). If the treating physician determines that the patient's medical condition requires treatment with an inhibitor of osteoclast activity, then the patient will be withdrawn from protocol treatment and followed for skeletal-related events.

12.2 During protocol treatment, the following treatments are allowed:

- Non-investigational antineoplastic therapies including antiandrogens, other hormonal agents, cytotoxic chemotherapy agents, and biologic response modifiers.
- In general, per CALGB policies, concurrent registration to other clinical trials utilizing investigational treatments is not allowed. However, concurrent registration to CALGB studies 40502 and 40503 and SWOG study S0702 is specifically permitted for this protocol. Other approved studies where concurrent enrollment has been approved are listed on the CALGB Memo entitled "CALGB 70604 Approved Trials for Concurrent Registration." This memo can be found at the study specific CALGB 70604 page on the CALGB and CTSU Web sites. Other exceptions will be considered on a case-by-case basis. Only phase III studies will be considered for concurrent enrollment. Contact either the CALGB 70604 Study Chair or Protocol Coordinator to request an exception.
- Standard radiation therapy to extra-skeletal and/or skeletal tumor sites. (Radiation therapy to skeletal tumor sites is considered a skeletal related event, see Section 13.1.)
- Patients should receive *full supportive care*, including transfusions of blood and blood products, antibiotics, antiemetics (including corticosteroids), etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the CALGB C-260 Remarks Addenda.

13.0 Criteria For Study Endpoints

Note that while patients may experience study endpoints as defined below, all patients should receive study treatment for two years as described in Section 14.0.

13.1 Skeletal Related Events (SREs): Skeletal related events are defined as any one of the following:

- radiation therapy to bone, including the use of bone-targeted radiopharmaceuticals,
- clinical fracture,
- spinal cord compression, or
- surgery to bone.

13.1.1 Radiation therapy to bone events include radiation of bone to palliate painful lesions, to treat or prevent fractures, or to treat or prevent spinal cord compression. Each port of radiation therapy is considered a separate skeletal related event. Treatment with bone-targeted radiopharmaceuticals (e.g. strontium-89 or samarium-153) is considered a skeletal-related event and will be categorized as radiation to bone.

13.1.2 Clinical fractures are defined as bone fractures diagnosed during evaluation of symptomatic patients and confirmed by written reports of radiographic tests. The following fractures are excluded from this definition:

- Fractures diagnosed by radiographic testing performed for other reasons (e.g. vertebral compression fracture diagnosed during a routine chest radiograph).
- Fractures of the skull, face, hand, or foot are also excluded because they are not associated with either osteoporosis or disease-related processes.

Clinical fractures will be classified as pathological or traumatic.

- Pathological clinical fractures are defined as clinical fractures caused by no trauma or trauma insufficient to fracture healthy bones in most young adults in the opinion of the local investigator.
- Traumatic clinical fractures are defined as clinical fractures caused by trauma sufficient to fracture healthy bones in most young adults, in the opinion of the treating physician.

Subgroups of clinical fractures will also be classified into the following categories:

- all clinical fractures,
- clinical vertebral fractures,
- nonvertebral fractures,
- hip fractures, and
- wrist fractures.

13.1.3 Spinal cord compression results from impingement of tumor on the cord and its associated neurologic impairment and/or back pain. Spinal cord compression events will be documented by an appropriate radiographic study, preferably magnetic resonance imaging (MRI).

13.1.4 Surgery to bone events are defined as surgical procedures to treat pathological fractures or spinal cord compression or surgical procedures to prevent imminent pathological fractures or spinal cord compression.

13.1.5 Vertebral fractures diagnosed during evaluation of symptomatic patients will be classified as a skeletal related event as described in Section 13.1.2.

13.2 Skeletal Morbidity Rate (SMR) is defined as number of events/time on study in years. Skeletal-related events that occur within 21 days of each other are counted as a single event.

14.0 Removal Of Patients From Protocol Therapy

14.1 Duration of Treatment: Patients will be treated on their assigned treatment arm for 24 months.

While zoledronic acid reduces the risk of SRE when compared to placebo, it is expected that a majority of patients randomized to either every 4-week or every 12-week aoledronic acid will experience an SRE during the 2-year course of palliative zoledronic acid. Thus, if a patient on the every 12-week treatment arm develops a SRE, physicians will be encouraged to not remove patients from the study, because the development of a single SRE during the course of zoledronic acid treatment is not considered a treatment failure. Patients on the every 4-weeks treatment arm are receiving the standard of care, and as such, should also continue protocol treatment should they experience an SRE.

14.2 Extraordinary Medical Circumstances: If, at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on the C-1793, CALGB 70604 Follow Up Form.
- Follow the patient for subsequent zoledronic acid therapy and skeletal related events for 2 years after randomization.

15.0 Statistical Considerations

15.1 Endpoints and Study Design

The primary objective of this randomized, open-label phase III study is to determine whether less frequent zoledronic (4 mg every 12 weeks, arm T) is non-inferior to standard schedule zoledronic (4 mg every four weeks. arm S) in preventing skeletal related events (SRE) for patients with metastatic breast cancer, metastatic prostate cancer and multiple myeloma involving bone. A skeletal-related event (SRE) is defined as a pathologic fracture, spinal cord compression, surgery to bone and radiation therapy to bone; it will be assessed at each monthly visit for 2 years.

Although a double-blind study design would be preferred from a scientific standpoint, upon evaluation of this approach we consider it not to be feasible. Such a design would require blinding treating physicians to the study drug assignment. This requires that study drug (zoledronic acid or placebo) be provided by a central pharmacy. However, no funding source for drug has been secured and would represent a formidable cost. CALGB CCOP investigators were surveyed about the study concept; although there was nearly unanimous interest in the study, approximately half of the potential investigators considered a double-blind format to be a significant barrier to study participation.

The **primary endpoint** is the proportion of patients having at least one SRE within 2 years after randomization. **Secondary endpoints** include: 1) pain as assessed by the BPI; 2) ECOG performance status; 3) osteonecrosis of the jaw; 4) renal dysfunction; 5) skeletal morbidity rate (SMR); 6) suppression of bone turnover (serum N-telopeptide or NTX) levels; and 7) the proportion of patients having at least one SRE within 24 months after randomization for the subgroups of patients with breast cancer, prostate cancer, and multiple myeloma.

Eligible patients will be randomized to two treatment arms with equal probability. Randomization will be stratified by disease type (breast cancer, hormone refractory prostate cancer, or multiple myeloma), baseline serum creatinine (normal: ≤ 1.4 mg/dL; abnormal: > 1.4 mg/dL), history of previous SRE (yes, no), and previous oral bisphosphonate use (yes, no). A stratified permuted block randomization scheme will be used to accomplish treatment assignment (38).

A total of 1538 patients will be accrued and randomized. At an accrual rate of 32 patients per month, accrual should be completed within 4 years; a minimum 24-month follow-up is needed to assess the primary endpoint. The actual sample size may be smaller due to possible early stopping of the trial for futility (arm T is substantially worse than arm S) and non-inferiority (arm T is non-inferior to arm S).

15.2 Sample Size Determination

The rate of SRE in breast cancer patients treated with zoledronic acid was 31/114 (27%) compared to 52/113 (46%) in the placebo arm. In breast cancer and myeloma patients, 47% of patients treated with zoledronic acid developed a SRE compared to 51% treated with pamidronate. In prostate cancer, 33% of patients treated with zoledronic acid developed SREs compared to 44% in the placebo arm.

Let π_T and π_S be the proportions of patients with at least one SRE at 2 years for arm T (less frequent dose) and arm S (standard dose), respectively, and let θ be their difference $\pi_T - \pi_S$. In this study, the sample size is determined to have a very low probability to conclude that arm T is non-inferior to arm S if θ is greater than Δ, where Δ is called non-inferiority bound or margin and is often chosen to be a proportion of the effect of active control arm over placebo. Statistically, the null hypothesis H0: $\theta > \Delta$ versus the alternative Ha: $\theta \leq \Delta$ is going to be tested. Rejection of the null hypothesis will be evidenced if the possibility that θ is Δ or less is high. Operationally, to demonstrate non-inferiority, we will compute a two-sided confidence interval at the significance level of 2α, where α is the Type I error of the test, for the case of non-inferiority when θ is small is better, the upper inferential bound needs to be lower than Δ; the lower bound is descriptive. Non-inferiority will be concluded if the upper limit of the $(1-2\alpha)$ confidence interval of θ is below Δ.

Based on the published data on the effect of a standard of dosing schedule of zoledronic acid compared to placebo, we choose Δ = 7%, π_T = 42%, and π_S = 35%. With a total of 1230 eligible patients (615 per arm), the probability of rejecting the null hypothesis using a one-sided test is at most 0.05 (Type I error α) when $\theta \geq 7\%$ and the probability of rejecting the null hypothesis (the power) is at least 82% when $\theta \leq 0$. With an allowance of 30% for ineligible/cancellation or drop-out due to early death or adverse events before the start of follow-up, 1758 patients will be randomized with 1:1 allocation to two treatment arms. All patients will be followed for at least 24 months to assess the primary endpoint. The above sample size is calculated for a fixed sample design.

The following table gives a sensitivity analysis of the sample size with an equivalence margin varying from 0.03 to 0.11 and a fixed 35% 1+SRE rate over 2 years for the high dose arm for 82% power.

Rate of 1+SRE in 2 years for low dose	Rate of 1+SRE in 2 years for high dose	Equivalence margin	Total eligible patients	Total enrolled patients
0.46	0.35	0.11	492	703
0.45	0.35	0.1	596	852
0.44	0.35	0.09	736	1052
0.42	**0.35**	**0.07**	**1218**	**1740**
0.4	0.35	0.05	2368	2960
0.38	0.35	0.03	6628	8285

15.3 Interim Analysis

A total of 1758 patients will be registered and randomized if the study is not terminated early. With allowance for a 30% ineligible/cancellation/drop out rate, we expect 1230 valid assessments of the primary endpoint to be available for the final analysis if the study is not stopped early. The trial will be monitored by interim analyses for early stopping for futility (arm T is substantially worse than arm S on SRE) or the conclusion of non-inferiority (arm T is non-inferior to arm S on SRS). The dual stopping boundaries will be built using the group sequential method implemented in S+ SeqTrial (29, 30).

The first interim analysis will occur after 154 patients (~13% evaluable patients) have been followed at least 2 years. After that, interim analyses will occur every six months until the final analysis at 6 years. A total of seven interim analyses and one final analysis are anticipated to occur at years 2.5, 3, 3.5, 4, 4.5, 5, 5.5 and 6 after the first randomization. Early stopping at any of these times can occur for futility or the finding of non-inferiority. Early stopping for futility will occur if the one-sided p-value from such a Fisher's exact test is less than 0.15, 0.15, 0.20, 0.20, and 0.25 at the five interim analyses, respectively. Less aggressive futility boundaries are used here to echo the spirit demonstrated by Freidlin and Korn (2002) (41) for superiority trials. On the other hand, the non-inferiority test for two-sample proportions will be used to test the non-inferiority hypothesis at a one-sided significance level of 0.001 (42). The pre-specified non-inferiority margin of $\Delta = 0.07$ will be used. We will conclude non-inferiority at any of these time points if the p-value is less than 0.001 from the interim analysis. If the study is not stopped early for futility or non-inferiority, the final analysis at 6 years will conclude non-inferiority if the p-value of the non-inferiority test is less 0.05. The following table displays the operating characteristics including power, average study size, and stopping probabilities under true proportion differences of -0.14, -0.07, 0.00, 0.07, and 0.14.

Proportion Difference ($\theta = \pi_T - \pi_S$)	**Expected Number of Valid Assessments**	**Probability to Reject H0 (Power)**	**Early Stop Probability for Non-inferiority**	**Early Stop Probability for Futility**
-0.14	293	0.9999	0.9999	0.0001
-0.07	541	0.9975	0.9643	0.0023
0.00	1038	0.8088	0.3046	0.0369
0.07	889	0.0500	0.0500	0.4293
0.14	357	0.0001	0.0000	0.9760

The CALGB Data and Safety Monitoring Board (DSMB) will review the results of each interim analysis at each of its semiannual meetings. This will include the primary endpoints and secondary endpoints. In determining whether the trial should be continued, the DSMB will consider the results at each interim analysis, as described above. The DSMB will use its discretion in weighing the combined impact of treatment-related adverse events and the rate of at least one SRE rate at 24 months.

15.4 Accrual and Follow-up

A maximum of 1758 patients will be accrued to the study. At an accrual rate of 45 patients per month, accrual should be completed within 3 years and four months. An additional follow-up of 2 years after the last enrollment is needed to assess the primary endpoint on all patients. The actual sample size may be smaller due to the possible early stopping of the study for futility and non-inferiority.

15.5 Analysis Methods

The primary analysis will include all randomized patients by following the intent-to-treat principle. The Cochran-Mantel-Haenszel (CMH) test (43), stratified by randomization factors, will be used to compare the proportion of patients with at least one SRE at 24 months between treatment groups. Logistic regression models (44) will be used to assess the relationship of the primary endpoint with treatment arms, while adjusting for any imbalances of patient-specific covariates at baseline. A stratified permutation test (45) will be conducted with the combined ratio for patients with and without a prior pathologic fracture. The Kaplan-Meier method (46) and a stratified Cox regression analysis (47) will be used to compare time to first SRE between treatment arms. Multiple-event analysis will be performed using the stratified intensity method (48), the WLW method (49), and the robust estimate of variance. The robust estimate of variance is used to minimize the impact of correlations between events that occurred closely in time or in clusters. The same analyses used for the primary endpoint will be conducted for the three subgroups of patients (i.e., those with breast cancer, prostate cancer, and multiple myeloma).

In the analyses of the secondary endpoints, including those for pain scores, functional assessment, osteonecrosis of the jaw (ONJ), and renal dysfunction, a rigorous adjustment for multiple testings will be adopted because of the exploratory nature of these analyses. However, given the relatively large number of endpoints of interest, we will choose a strict significance level of 0.001 to reduce the chance of spurious significant findings.

The incidence rate of osteonecrosis of the jaw and renal dysfunction (at least one occurrence over 2 years) will be compared between treatment arms using Fisher's exact test as well as the Cochran-Mantel-Haenszel (CMH) test (43) stratified by randomization factors. Logistic regression (43) will be used to evaluate the treatment effect on the incidence rate with patient-specific characteristics being adjusted. The cumulative frequency of these events will be evaluated using Poisson regression (50) with at risk time defined as from randomization to the last follow-up date for the treatment effect while controlling for other baseline risk factors. The skeletal morbidity rate (SMR) will be estimated for each treatment arm as well as the 95% confidence intervals. SMR is defined as the number of skeletal-related events per year.

The changes in the pain intensity score for each Brief Pain Inventory (BPI) item and the BPI composite score at each time point against baseline values will be compared between the treatment arms using Wilcoxon rank sum test with stratification on randomization factors. The change scores will be evaluated in a general linear model with repeated measures for treatment effect and the time trend with patient-specific characteristics being adjusted. The covariates to be included in the model will be selected using a stepwise procedure.

The functional assessment score at each time point will be compared using Cochran-Mantel-Haenszel (CMH) test (43) stratified by randomization factors and baseline performance status. Logistic regression for ordinal outcomes (44) with generalized estimation equation estimators will be used to evaluate the treatment effect and the time trend with patient-specific characteristics being adjusted. Again, the covariates to be included in the model will be selected using a stepwise procedure.

Toxicity as graded by NCI's Common Terminology Criteria for Adverse Events will be tabulated by maximum grade by treatment arm.

Sensitivity analyses will also be carried out by excluding ineligible patients and/or patients who drop out before 24 months. If the drop out rate is larger than 10% and if there is evidence that the missing mechanism is not MCAR (missing completely at random) but MAR (missing at random), multiple imputation will be conducted.

15.6 Statistical considerations for the bone turnover marker substudy

The objective of the correlative sciences study is to determine if bone turnover markers correlate with higher probability of experiencing at least one SRE at 2 years for patients in both arms.

Specifically, NTX assessments of 196 patients enrolled to the treatment study will be taken at baseline and at 12 week intervals for 2 years. Assuming: 1) patients with baseline NTX greater than the median will be classified as high NTX group and those with NTX less than the median as low NTX group; 2) the rate of at least one SRE over 2 years is 39% for all patients, 50% for high NTX group and 27% for low NTX group; 3) 90% of participating patients will have valid NTX assessments. It corresponds to an odds ratio of 2.704 and a relative risk of 1.85 against the high NTX group. With 176 valid NTX assessments (88 in each NTX group), the study has 85% power to detect the 23% difference in the rate of at least one SRE over 2 years between high NTX group and low NTX group using a continuity corrected Chi-Square test at a 2-sided significance level of 0.05.

The correlation of the primary endpoint (proportion of at least one SRE over 2 years) and NTX will be examined using nonparametric tests, including Chi-square test for dichotomized NTX level and Wilcoxon rank sum test for NTX raw score. The relationship of the primary endpoint and baseline NTX will be explored in multivariate analysis using a logistic regression model after adjusting for other significant prognostic factors. Cox regression models will be used to assess the association between NTX level and the time to the first SRE and death. The effect of NTX on the time to the first SRE will also be examined in Cox model as a time-varying covariate.

15.7 Statistical considerations for the pharmacogenomic substudy

The primary statistical objective for the pharmacogenetic companion of this study is to investigate the potential association between VDR BSMI (RS ID 1544410) and Skeletal Related Events (SRE) at two-years as defined in Section 13.1. In the Caucasian population it is hypothesized that the presence of the b allele is associated with increased risk of experiencing an SRE within two years. A dominant (in b) genetic model will be assumed (i.e., $P[D=1 \mid G=bb] >= P[D=1 \mid G=Bb] = P[D=1 \mid G=BB]$, where $D=1$ indicates experiencing an SRE and G denotes the genotype outcome).

A total of 1230 eligible patients are to be randomized to the study. It is assumed that 85% of these patients will provide consent and usable samples for this companion study. The primary analysis will be based on those patients who consent and are self-reported as Caucasian on the CRF form. The expected proportion for this population is 0.75. As such, the companion study will be powered based on a sample size of 784 (=1230*0.75*0.85).

The putative genotypic relative frequencies of p=0.28 for {bb} versus 0.72 for {Bb or BB group}[2] It is assumed that the targeted SRE probabilities at two years are 0.35 and 0.42 for the two arms of the study. For the power calculations, we will assume that each event is binary with the mixture probability of 0.385=(0.5)(0.42+0.35). The power, at the one-sided level of 0.05, is 0.71 for a gene-relative risk GRR of 1.248 and 0.93 for a GRR of 1.357. In this case, the GRR is defined as $P[D=1 \mid G=bb] / P[D=1 \mid Bb]$.

The genotypic prevalence of this SNP is expected to be race-dependent. To avoid the potential confounding due to this source of heterogeneity, we have proposed to limit the primary analysis to those patients who consent and self-report as Caucasian which is expected to be the majority of patients to register to this study.

As a secondary analysis, we will consider the scientific questions of interest in all patients consenting to the pharmacogenetic companion by repeating the analysis in the entire population and then stratified by race. We will contrast these three sets of results (Caucasian population, unstratified based on combined population, and stratified based on combined population). Although, given the relatively small numbers, definitive results extending to the entire patient population may not be reached, these secondary analyses should generate important hypotheses which can be further investigated.

It is noted that this is a hypothesis of association (gene by outcome) and not a hypothesis of interaction (gene by dosing regimen with respect to outcome) as no such interaction is expected. Nevertheless, we will investigate this interaction using a log-linear multiplicative logistic model.

In addition, DNA collected from patients could be used for a genome-wide study to identify novel gene candidates of response and side effects. This will also allow us to refine the analyses by using genome-wide ancestry stratification approaches.

As a secondary analysis we will stratify by history of osteoporisis; using prior history of oral bisphosponates and patient self-report (i.e., whether the patient has reported having been afflicted by osteoporosis or not) and compare the result to that from the unstratified version.

Other SNPs related to skeletal detriments including osteonecrosis of the jaw will be considered. The addition of other important clinical and demographic co-variables will be considered. Multivariable models, with molecular, clinical and demographic variables, will be constructed using conditional inference trees and random forests. The primary objective will be tested at the one-sided level of 0.05. All secondary and exploratory objectives will be tested at an unadjusted two-sided level of 0.05. In addition, DNA collected from patients will be used for a genome-wide study to identify novel gene candidates of SRE and other skeletal events.

15.8 Justification for amending sample size and accrual rate (added with Update #4)

A preliminary review of 70604 data revealed that the rate of ineligible/cancellation/drop-out due to early death or adverse event is higher than the 20% originally expected. Based on data through Oct. 25, 2011, it is projected that approximately 55% of patients will be alive at 24 months, and 45% of those patients who have died before 24 months will have had at least one SRE, and 5% of enrolled patients will be ineligible or lost to follow-up. It is therefore expected that 70% of enrolled patients will have valid assessments (55%+45%*(1-55%)-5%). In order to preserve the scientific goal of this trial, with Update #4 to this study the sample size been increased from 1538 (1230/0.8) to 1758 (1230/0.7). The increase in target accrual is feasible since the actual accrual rate has been 45 patients per month, higher than the originally expected rate of 32 patients per month.

16.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Investigators are required to notify the CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep .cancer.gov). All reactions determined to be "reportable" in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS).

In the rare occurrence when Internet connectivity is lost, an AE report may be submitted using CTEP's Adverse Event Expedited Report – Single Agent or Multiple Agent paper template (available at http://ctep.cancer.gov) and faxed to 301-230-0159. A 24-hour notification is to be made to CTEP by telephone at 301-897-7497, **only** when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted on a paper template or a 24-hour notification phoned in must be entered electronically into AdEERS by the original submitter at the site.

CALGB requires investigators to route all adverse event reports (AERs) through the Central Office for CALGB-coordinated studies.

Any medical event equivalent to CTC Grade 4 or 5 which precipitated hospitalization (or prolongation of existing hospitalization) must be reported, UNLESS the medical event is excluded from reporting in the footnotes of the table below. In that case, the adverse event will be reported on the standard data forms for this study.

CALGB 70604 Reporting Requirements

Phase 2 and 3 Trials: AdEERS Expedited Reporting Requirements for Adverse Events that Occur Within 30 Days[1] of the Last Dose of Treatment

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[1]	Grades 4 & 5[1]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:**

AdEERS 10 calendar day report:

- Grade 4 unexpected events
- Grade 5 expected or unexpected events

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS.

- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exclusions to AdEERS Expedited Reporting Requirements for CALGB 70604:

- All grade 5 events must be reported via AdEERS within 10 calendar days.
- Grade 5 events occurring more than 30 days after the last dose of treatment that are due to progressive disease do not require reporting via AdEERS.
- Grade 4 myelosuppression (from concurrent anti-cancer therapy) and hospitalization from such do not require reporting via AdEERS.
- All grade 4 events that are unexpected and that are at least possibly related to treatment must be reported via AdEERS within 10 calendar days.
- Any unexpected medical event equivalent to CTCAE grade 4 that precipitates hospitalization (or prolongs an existing hospitalization) and is at least possibly related to treatment must be reported via AdEERS within 10 calendar days.
- Grade 4 expected events do not require expedited reporting.
- Cases of osteonecrosis of the jaw of any grade should be submitted via AdEERS within 10 calendar days.
- A list of specific expected adverse events can be found in Section 11.0 (Drug Formulation, Availability and Preparation). Please also refer to the zoledronic package literature for a complete listing of adverse events.
- AdEERS reports are to be submitted electronically (http://ctep.info.nih.gov/reporting/adeers.html) to the CALGB Central Office (calgb@uchicago.edu).
- The reporting of adverse events described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 6.6 for required CALGB forms).
- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- Cases of secondary AML/MDS are to be reported using AdEERS. The event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy; 2) Myelodysplastic syndrome; or 3) Treatment related secondary malignancy.
- New primary malignancies should be reported using study form C-1001.

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18.0 MODEL CONSENT FORM:

A Randomized, Phase III Study of Standard Dosing versus Longer Dosing Interval of Zoledronic Acid in Metastatic Cancer

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 breast cancer, prostate cancer or multiple myeloma and are at risk for problems with your bones. These problems include pain, fractures (broken bones), or the need for radiation therapy or surgery to bone.

Why Is This Study Being Done?

The purpose of this study is to compare the effects (good, bad or no difference) of less frequent treatment (every 12 weeks) with zoledronic acid (Zometa) compared to standard treatment (every 4 weeks) with zoledronic acid.

We know that treatment with zoledronic acid decreases the risk of certain bone related complications in people with breast cancer, prostate cancer or multiple myeloma AFTER the cancer has spread to the bones and continues to grow even with standard anti-cancer therapy. This research is being done because we do not know whether giving zoledronic acid less frequently will be as good as the standard dosing at preventing bone complications due to cancer. The research also hopes to find out whether less frequent dosing (every 12 weeks) of zoledronic acid is safer than more frequent dosing (every 4 weeks).

How Many People Will Take Part in the Study?

About 1760 people will take part in this study.

What Is Involved in the Study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures 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.

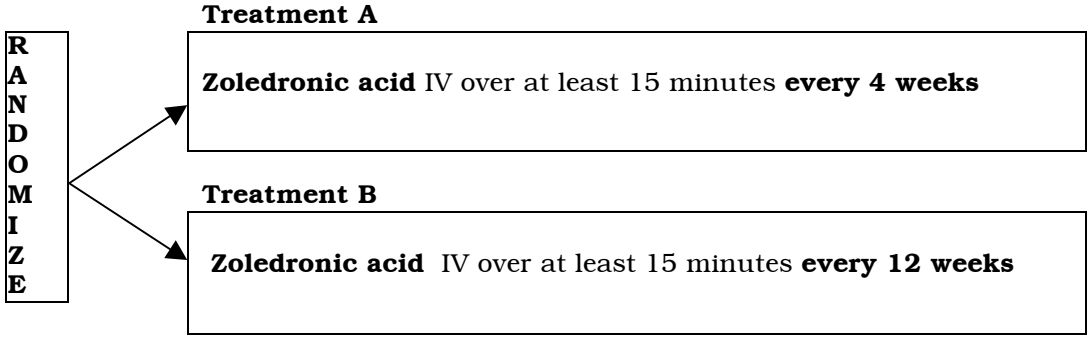
- A complete history and physical exam
- Blood tests
- Bone scan or other bone imaging
- Pregnancy test

In addition, you will be asked to answer a few questions about your dental history and complete a short questionnaire about any pain you may be feeling.

On rare occasions, patients treated with zoledronic acid have developed a serious dental problem (see below). It is recommended, but not required, that you see a dentist before starting treatment with zoledronic acid.

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 "randomized" into one of the two study groups described below. Randomization means that you are put into a group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose which group you will be in. You will have an equal chance of being put into either of the two groups.



Treatment A

Patients randomized to Treatment A will receive zoledronic acid by intravenous infusion (IV) over 15 minutes or more once every 4 weeks for 2 years. This is done though a needle placed in a vein in your arm.

Treatment B
Patients randomized to Group B will receive zoledronic acid by intravenous infusion (IV) over 15 minutes or more once every 12 weeks for 2 years. This is done though a needle placed in a vein in your arm.

Daily calcium and vitamin D are recommended to maintain strong bones. You will be asked to take supplemental calcium (500 mg daily) and a multivitamin containing 400 to 800 IU vitamin D daily. You will be asked to take the calcium and vitamin D supplements with food. There are many preparations of calcium and vitamin D available without a prescription. You may choose one or discuss with your doctor which preparation would be best for you.

Tests and Procedures
If you take part in this study, you will have the following tests and procedures, which are part of regular cancer care and may be done even if you do not join the study.

- Blood tests every 4 weeks to measure kidney and liver functioning

If you participate in this study, some of these procedures may be done more frequently than if you were not taking part in this research study.

In addition, every 4 weeks we will ask you to answer the few questions about your dental history and to continue to complete the short questionnaire about any pain you may be feeling.

How Long Will I be in the Study?

You will be asked to take zoledronic acid for 2 years. The study doctor will ask you to visit the office every 4 weeks for the tests and questionnaires listed above for 2 years after you began participation in the study. We will ask you to continue to answer the questions about your dental history and complete the pain questionnaire every 4 weeks for 2 years whether or not you continue to take zoledronic acid.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the zoledronic acid can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow up care and testing could be most helpful for you.

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

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

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking zoledronic acid. In some cases, side effects can be serious, long lasting, or may never go away. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to zoledronic acid include those which are:

LIKELY:

- Fever
- Fatigue (tiredness)
- Anorexia or loss of appetite
- Nausea, vomiting, constipation, and /or abdominal pain
- Low levels of calcium in the blood, which may cause muscle cramps
- Flu-like symptoms including fever, chills, and joint and muscle aches, which are generally seen after the first infusion of zoledronic acid

LESS LIKELY:

- Headaches
- Insomnia
- Anxiety
- Abnormal heart rate or heart rhythm
- Abnormal kidney function tests
- Diarrhea
- Tingling in the fingers and toes
- Bone, back, muscle, and joint pain. In some cases, this pain could be severe and could interfere with your going about your normal activities. You should tell your doctor if you have any new bone or joint or muscle pain.
- Allergic reactions, which include itching, flushing, rash, and shortness of breath
- Low levels of potassium, magnesium, and/or phosphate in the blood. In almost all cases, you would not experience symptoms from these effects. If these levels fall to extremely low levels, possible side effects could include muscle twitching, muscle weakness, and abnormal heart rhythm.
- A reaction at the injection site, which might include pain, redness, tenderness, swelling, and/or bruising.

RARE BUT SERIOUS
- Kidney failure
- Severe allergic reactions, which could include the inability to breathe and dangerously low blood pressure, which could be fatal
- Permanent damage to the jawbone (osteonecrosis of the jaw) that may be painful and might require surgery to remove the damaged area. This might be more likely to happen in patients who have certain dental procedures. If you see a dentist, you should inform him or her that you are receiving zoledronic acid.

Risks of Calcium and Vitamin D (Both Treatment Groups)
LIKELY:
- Constipation

LESS LIKELY:
- Headaches
- Kidney stones
- Stomach irritation
- High levels of calcium in the blood
- Nausea, vomiting
- Diarrhea

Other medications You should discuss all of your medications with your healthcare provider caring for you because certain drugs may increase the risk of developing side effects from zoledronic acid.

Unanticipated side effects may occur which have not been reported. If you have any unusual symptoms, report them immediately to your physician.

Reproductive risks: Because the drugs in this study may affect an unborn baby, you should not become pregnant or father a baby while on this study. Women should not breastfeed a baby while on this study. It is important you understand that you need to use birth control while on this study. Check with your study doctor about what kind of birth control methods to use and how long to use them. For more information about risks and side effects, ask the study doctor or contact _____.

Are There Benefits to Taking Part in the Study?

Taking part in this study may or may not make your health better. While doctors hope zoledronic acid taken every 3 months will be as effective as when it is taken every month, there is no proof of this yet. We do know that the information from this study will help doctors learn more about zoledronic to prevent skeletal related events. This information could help future cancer patients.

What Other Options Are There?

Instead of being in this study, you have these options:

- You may choose to have treatment with zoledronic acid on a monthly schedule, which is considered standard treatment.
- You may choose not to receive treatment with zoledronic acid.
- You may choose another research study.

Please talk to your health care providers caring for you about these and other options.

What about Confidentiality?

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 Cancer and Leukemia Group B (CALGB)
- 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 NCI to provide greater access to cancer trials
- Novartis Pharmaceuticals

It may be necessary to contact you at a future date regarding new information about the treatment you have received. For this reason, we ask that you notify the institution where you received treatment on this study of any changes in address. If you move, please provide your new address to the following person:

(name) _____ (title)_____
(address) _____
_____
(phone number)_____

What Are the Costs?

You or your insurance company will be billed for the cost of zoledronic acid and its administration and for the vitamin D and calcium, as well as for the blood tests that are part of the standard of care for receiving zoledronic acid.

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

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

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

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

It is important that you tell your study doctor, _____ [investigator's name(s)], if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ [telephone number].

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

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

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

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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

A Data Safety and Monitoring Board, an independent group of experts, will be reviewing the data from this research throughout the study. We will tell you about the new information from this or other studies that may affect your health, welfare, or willingness to stay in this study.

Related Studies (optional participation):

In addition to the treatment study, the study doctor would also like to collect additional samples of your blood. We ask that you give approval for these tests to be performed using these samples.

The following two paragraphs describe the sub-study CALGB 150804. Accrual to this sub-study has been completed and this information should no longer be provided to new patients enrolling CALGB 70604:

Approximately 2 additional teaspoons of blood would be collected at the beginning of the study and every 12 weeks after that for up to 2 years when your other tests are done. The blood will be sent to a central laboratory for analysis.

These tests may provide additional information that will be helpful in understanding zoledronic acid's effect on skeletal related events. But, it is unlikely that what we learn from these studies will have a direct benefit to you. The information learned from these studies may benefit other patients in the future.

The results of these research studies will not be provided to you or your doctor. They will not be put in your health record, nor will the results have any effect on your treatment. In addition, some of the blood may be used to establish products to be patented or licensed. There are no plans to provide financial compensation to you if this occurs.

The greatest risk to you is the release of information from your health records. Blood samples will be stored at a CALGB laboratory. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special CALGB identification number. The only location where your name and special identification number will be stored together is at the CALGB Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy. The results from these studies may be published, but individual patients will not be identified in these publications.

There will be no charge to you for participating in these related research studies.

The choice to participate in this study is entirely up to you. No matter what you decide to do, it will not affect your care. If you decide now that your blood can be used for research, you can change your mind at any time. Just let your doctor know that you do not want us to use your blood. Then any blood that remains will no longer be used for research.

Consent Question #1 applies to the sub-study CALGB 150804. Accrual to this sub-study has been completed and this question should no longer be asked of new patients enrolling CALGB 70604:

1. I agree that my specimen may be used for the research studies described above.

_____ Yes_____ No

Participant _____ Date _____

Genetic studies on blood cells:

The researchers would like to investigate whether substances in your blood are related to the way that your body responds (or doesn't respond) to the zoledronic acid. These markers are inherited through your family, and could be passed to your children. These are also called genetic studies.

Your blood will be used to learn how certain genes influence the effectiveness and side effects of zoledronic acid. In order to study the genes the DNA must be removed from your blood sample. DNA is the substance that makes up your genes. Genes are the units of inheritance that are passed down from generation to generation. They are responsible for eye color, hair color, blood type, and hundreds of other traits.

There are specific risks associated with genetic studies. Genetic research may find medical conditions that affect you and your blood relatives since it looks at inherited traits. While your genes are unique to you, you share some of them with your blood relatives. It is possible that genetic research may find potential health concerns for you or your family. While this situation is rare, information could be misused by employers, insurance companies, and others. Your privacy and confidentiality will be protected to the fullest extent possible.

To help you make your decision, additional information about participation in genetic studies is included at the end of this consent form. This information identifies how your personal information will be protected by the Cancer and Leukemia Group B and its researchers.

Blood taken for these studies will be done only once at the time you enter the study. About 1 tablespoon of blood would be taken.

2) I agree that my blood may be used for the genetic research studies described above.

_____ Yes _____ No Initials _____

Future Studies (Optional participation):

The study doctors would also like to store any portion of the blood that is not used up by the related study described above. These samples may be stored indefinitely. You can still take part in the treatment study, and the research study described above without giving your consent for your samples to be stored.

It is not possible for you or the CALGB to know what studies using your stored samples may be appropriate in the future. We ask that you give permission in advance for other studies to be performed using the blood without being re-contacted to give permission for each test.

3. My specimen may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.
_____ Yes _____ No Participant _____ Date _____
4. My blood may be kept for research about other health problems (for example: causes of diabetes, Alzheimers disease and heart disease.
_____ Yes _____ No Participant _____ Date _____
5. My doctor or someone from CALGB may contact me in the future to ask me to take part in more research.
_____ Yes _____ No Participant _____ Date _____

Whom Do I Call if I Have Questions or Problems?

For questions about the study or a research-related injury, contact the study doctor Dr. _____ at _____.

For questions about your rights as a research participant, contact the _____ Medical Center's Institutional Review Board (which is a group of people who review the research to protect your rights) at _____.

You may also call the Project Office of the NCI Central Institutional Review Board (CIRB) at 888-657-3711 (from the continental US only)
[And, if available, list patient representative (or other individual who is not on the research team or IRB).]

Where can I get more information?

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

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

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

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

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

Safeguards of Confidentiality in Studies Involving Genes (genetic studies):

It is possible to use blood samples to study many different kinds of genes. The Cancer and Leukemia Group B recognizes this possibility and will take the following steps to protect your privacy and to protect you from having your sample tested for any genetic changes not directly related to cancer:

- Blood samples will be stored at a Cancer and Leukemia Group B laboratory. The Cancer and Leukemia Group B Statistical Center will perform all analyses of data and store all study results. Your blood sample will not be stored with your name on it. Instead, it will be labeled with a special Cancer and Leukemia Group B identification number. The only location where your name and special identification number will be stored together is at the Cancer and Leukemia Group B Statistical Center. The greatest effort will be made to see that all personal information that can identify you is kept under conditions that protect your privacy.
- Information about your participation in this study and results of any tests performed on your sample will be kept only at the Cancer and Leukemia Group B Statistical Center at Duke University. This information will not be made available to your doctors or to individual researchers at Cancer and Leukemia Group B. Test results from this study will not be put in your medical records. All study information, including test results, is stored under conditions that limit access in order to protect the privacy of the people participating in this study.
- Your blood will be used only for the study of genes involved in cancer.
- There are no absolute legal protections against discrimination on the basis of genetic information. Instances are known in which a patient has been required to provide genetic information before applying for health insurance and/or a job. Since neither you nor your physician will be notified of the results of this test, it is unlikely that any discrimination could take place.

The same precautions to protect your privacy will be in place for such future studies. Future investigators will receive blood samples with the special Cancer and Leukemia Group B identification number only, and your blood sample will not be identified with your name. These future investigators must apply to the Cancer and Leukemia Group B and have their research project reviewed and approved by the Cancer and Leukemia Group B.

If you decide now to give a sample of blood and then change your mind at any time about participating in the study, just contact your institution and let them know that you do not want the researchers to use your sample. The results from these studies may be published, but individual patients will not be identified in the publications.

APPENDIX I

CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

To submit site registration documents:

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-CTSU
Fax: 215-569-0206

For patient enrollments:

CTSU Patient Registration
Voice Mail: 1-888-462-3009
Fax: 1-888-691-8039
Hours: 9:00 AM – 5:30 PM Eastern Time, 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.]

Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:

CALGB Statistical Center
Hock Plaza
2424 Erwin Road, Suite 802
Durham, NC 27705
Tel: 919-668-9350
Data Operations Fax: 919-668-9348
Teleform Fax: 919-416-4990

Sites should submit Teleforms via Fax or Mail. See Section 6.0 Data Submission Section for details on forms submission.

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment related questions: Contact the CALGB Study Chair.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Web site is located at https://www.ctsu.org

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 Web site (enter credentials at https://www.ctsu.org; then click on the Register tab) or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

Each 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 CTSU members' area at https://www.ctsu.org.

All forms and documents associated with this study can be downloaded from the CALGB 70604 Web page on the CTSU members' area of the web site at https://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 CALGB 70604 site registration:

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

Note: CCOPs may consider co-enrolling patients on the SWOG trial 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 Treatment

Pre-study requirements for patient enrollment on CALGB 70604

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms
- All baseline laboratory tests and prestudy evaluations performed, including blood samples and imaging to document bone metastases, within the time period specified in the protocol.

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-Fri.. 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 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - CALGB 70604 Eligibility Checklist
   - CALGB 70604 Registration Worksheet (Indicate participation on companion study CALGB 60803. Note: the patient should be registered to CALGB 60803 at the same time as the treatment trial provided consent is obtained.)
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. Registration is limited to operating hours of the CALGB Registration office (9AM- 5PM ET). 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 will follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the CALGB within the confines of CALGB's registration hours to obtain assignment of a treatment arm and assignment of a unique patient ID (to be used on all future forms and correspondence). The CTSU registrar will confirm registration by fax.

Protocol treatment should begin within 7 days of randomization.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the CALGB 70604 Web page located on the CTSU members' area of the web site (https://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 CALGB (see contacts table or Section 6.1) unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-CALGB coversheet should accompany all data submissions.

3. The CALGB Statistical Center will send (generally via email but may be sent via postal mail or fax) query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the CALGB Statistical Center and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must maintain current CTEP IAM account contact information**. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

SPECIAL MATERIALS OR SUBSTUDIES

There are two sub-studies in CALGB 70604. Following Update #1 to this study, new patient registrations to substudy 150804 will not be allowed. Sub-study 60803 must be offered to all patients, although patients may opt not to participate. The patient should be registered to CALGB 150804 and 60803 at the same time they are registered to the treatment trial.

1. Specimen collection for correlation of bone turnover markers – CALGB 150804 (Protocol Section 10.1)
   - Collect, prepare, and submit specimens as outlined in the protocol
   - Do not send specimens, supporting clinical reports, or transmittals to the CTSU

2. Specimen collection for pharmacogenetic correlative – CALGB 60803 (Protocol Section 10.2)
   - Collect, prepare, and submit specimens as outlined in the protocol
   - Do not send specimens, supporting clinical reports, or transmittals to the CTSU

SERIOUS ADVERSE EVENT (AE) REPORTING (SECTION 16.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU members' area of the web site (https://www.ctsu.org) or by drilling down to the Adverse Event Reporting Forms link under the documents folder of the CALGB 70604 Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (SECTION 11.0)

Commercial agents:	Zoledronic Acid (Zometa®) (NSC #721517); *and* Vitamin D; *and* Calcium.

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 11.0 of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy within the tree under the Documents folder on the CALGB 70604 Web page.

REGULATORY AND MONITORING

Study Audit

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

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

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be funded by the CTSU but issued by the credited Group.

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-US 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.

APPENDIX II
Clinical Economic Analysis for CALGB 70604

1.0 BACKGROUND AND RATIONALE

This economic companion study is designed to estimate the cost-effectiveness of 12-week vs. 4-week dosing intervals for zoledronic acid in patients with metastatic breast or prostate cancer or multiple myeloma. Prior studies have shown a relatively high cost-effectiveness ratio of zoledronic acid in standard dosing (every 3 weeks) compared with placebo (11). The aim of the proposed clinical economic analysis is to assess whether a less frequent dosing schedule is also less costly, and whether it offers equivalent or better value, in terms of preventing SREs.

Cost-effectiveness analysis is a method of economic assessment in which the costs and health outcomes of two or more interventions are compared. The endpoint of a cost-effectiveness analysis is the incremental cost-effectiveness ratio (ICER) which is estimated as the difference in cost between a more costly and less costly intervention, divided by the difference in health benefits, expressed in non-monetary terms. The denominator of this ratio includes direct costs, primarily direct medical costs, associated with the treatment and disease being studied. The preferred metric of effectiveness in a cost-effectiveness analysis is the quality-adjusted life-year (QALY), because it accounts for differences between interventions in both mortality and morbidity, and because it is comparable across diseases and interventions. However, estimation of QALYs requires assessment of health-state utilities that reflect the quality of life (QOL) associated with the various health states that result from the interventions being studied. If preference-based QOL assessment has not been conducted prospectively or if QOL information has not been collected in a manner consistent with the estimation of QALYs, there may be value to the assessment of an endpoint more proximal to the intervention decision than long-term quality-adjusted survival.

The comparison of standard dosing versus less frequent dosing for zoledronic acid in metastatic cancer warrants economic assessment. If this study finds that 12-week dosing is not inferior to 4-week dosing, then it is important to understand the economic impact of these two strategies. When two interventions offer equivalent health outcomes, then the one that is less costly can be considered a dominant strategy. If health outcomes are truly equivalent, then the decision maker would have little rational justification for advocating the use of the more costly strategy. If one strategy is more costly but also more effective—that is, neither strategy is dominant—then the decision maker must consider the value attained, in terms of health outcomes, but implementing the more costly strategy. This economic companion will provide this information.

2.0 SPECIFIC OBJECTIVE

The aim of this companion study is to estimate the costs associated with each dosing schedule. If the main study finds that 12-week dosing is not inferior to 4-week dosing, in terms of skeletal-related events (SREs) and zoledronic acid toxicity, then we will estimate the direct medical costs of each strategy. If however, one strategy is more effective (i.e., associated with fewer SREs), then we will also estimate the cost-effectiveness of the more effective strategy, expressed as the incremental cost per SRE prevented. Although cost per SRE prevented is not a standard metric in cost-effectiveness analysis, it is reasonable within this context and it can be compared with results of other studies that have estimated these endpoints among cancer patients treated with bisphosphonates.

3.0 DATA COLLECTION

The following information will be collected from specified protocol forms:

3.1 Zoledronic Acid Administration and Dosage

The actual zoledronic acid dose given in each cycle will be obtained from the C-1791, CALGB 70604 Treatment Form. This form will also be used to identify interruption, discontinuation and restarting of zoledronic acid treatment.

3.2 SREs

SREs will be identified from the C-1790 CALGB 70604 SRE Form. SREs will be classified as radiation to bone including bone-targeted radiopharmaceuticals, clinical fracture, spinal cord compression and surgery to the bone, as defined in Section 13.1 of the protocol:

- Radiation therapy to bone events include radiation of bone to palliate painful lesions, to treat or prevent fractures, or to treat or prevent spinal cord compression. Each port of radiation therapy is considered a separate skeletal related event. Treatment with bone-targeted radiopharmaceuticals (e.g. strontium-89 or samarium-153) is considered a skeletal-related event and will be categorized as radiation to bone.
- Clinical fractures are defined as bone fractures diagnosed during evaluation of symptomatic patients and confirmed by written reports of radiographic tests. The following fractures are excluded from this definition:
  - Fractures diagnosed by radiographic testing performed for other reasons (e.g., vertebral compression fracture diagnosed during a routine chest radiograph).
  - Fractures of the skull, face, hand, or foot are also excluded because they are not associated with either osteoporosis or disease-related processes.
- Spinal cord compression results from impingement of tumor on the cord and its associated neurologic impairment and/or back pain. Spinal cord compression events will be documented by an appropriate radiographic study, preferably magnetic resonance imaging (MRI).
- Surgery to bone events are defined as surgical procedures to treat pathological fractures or spinal cord compression or surgical procedures to prevent imminent pathological fractures or spinal cord compression.

For each type of SRE, we will use estimates from the published literature and expert opinion to define expected health service utilization related to the event, including hospital days, surgical procedures, physician visits, imaging, medications, rehabilitation services and durable medical equipment.

3.3 Adverse Events (AEs)

Adverse events will be identified from the C-1792 CALGB 70604 Adverse Events Form. Adverse events, classified by grade; include fever, renal toxicity, hypocalcemia, hypophosphatemia, hypomagnesemia, nausea, vomiting, diarrhea, hypercalcemia, constipation and pain. For each type and grade of AE, we will use estimates from the published literature and expert opinion to define expected health service utilization related to the event, including hospital days, surgical procedures, physician visits, imaging, medications, rehabilitation services and durable medical equipment.

3.4 Costs

Zoledronic acid costs, SRE costs, and AE costs for every patient will be estimated by multiplying unit cost values by units of health care service utilization. Unit cost information will be obtained from Medicare, assuming national average reimbursement rates for the relevant services, procedures, pharmaceutical agents and durable medical equipment.

The table below summarizes the required data elements and their sources for the proposed economic analysis.

Data Element	**Data Source**
Health service utilization	
Zoledronic acid (dosage, frequency)	CALGB 70604 Treatment Form
For management of SREs*	CALGB 70604 SRE Form, published literature
For management of AEs*	CALGB 70604 AE Form, published literature
Costs	
Zoledronic acid	95% of average wholesale price (AWP) [53]; microcosting analysis of bisphosphonate therapy in metastatic cancer [54]
Physician visits, diagnostic tests, imaging	Medicare Physician Fee Schedule
Hospital stays	Medicare Acute Inpatient Prospective Payment System
Medications	95% of AWP[53]

* Rates of SREs and AEs with 12-week and 4-week zoledronic acid dosing schedules will be based on the experience of patients in CALGB 70604, using information reported in study forms. Health service utilization associated with SREs and AEs will be based on the published literature, including studies of the costs and cost-effectiveness of bisphosphonate therapy in the setting of metastatic cancer.

4.0 Analysis

We will estimate total cumulative costs for each patient by summing costs over the study period for zoledronic acid, SREs and AEs. We will report total costs in each arm, as well as average total cost per patient in each arm and average total cost by month of study enrollment. We will assess differences between arms in average survival duration, and weight total cost estimates to adjust for survival differences as warranted.

If the clinical primary endpoint analysis shows a statistically significant difference in SREs between study arms, then we will calculate an incremental cost-effectiveness ratio (ICER) as the difference in average costs between the two arms, divided by the difference in SREs. The ICER will be expressed as the cost per SRE prevented of the more costly strategy compared with the less costly strategy. If the less costly strategy is also more effective, this strategy will be considered dominant, and no ICER will be calculated.

Sensitivity analysis will be used to assess the robustness of results to important assumptions. In particular, we will explore the impact of alternative reimbursement rates for zoledronic acid, as well as the impact of alternative assumptions about health care utilization associated with SREs and AEs.

Limitations:

1) Detailed resource utilization profiles associated with SREs and AEs will not be derived directly from participants in the randomized clinical trial. This economic companion study was not planned at the time of trial inception, and therefore detailed reports of health service utilization were not collected prospectively. Retrospective collection of this information is not advisable, since the majority of enrolled patients have completed study follow-up, and because the lengthy recall period might compromise the validity of patient reports.
2) This analysis will not be able to report cost-effectiveness in terms of dollars per QALY gained with the more effective strategy. Although this is a preferred metric for cost-effectiveness analysis, it requires standardized collection of health-state

utility information to characterize the quality of life associated with the treatments being compared and with their clinical outcomes. Information from the Brief Pain Inventory will provide important information about one aspect of QOL among study participants, but this information cannot be used to derive quality-adjusted life expectancy estimates. Moreover, survival is not included as a study endpoint.