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Randomized Controlled Trial of Early Zoledronic Acid in Men with Castration-Sensitive Prostate Cancer and Bone Metastases: Results of CALGB 90202 (Alliance)

Smith, et al

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Includes Update #9

CANCER AND LEUKEMIA GROUP B

**CALGB 90202/CTSU 90202**

**A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF EARLY VERSUS  
STANDARD ZOLEDRONIC ACID TO PREVENT SKELETAL RELATED EVENTS IN MEN WITH  
PROSTATE CANCER METASTATIC TO BONE**

*Investigational Agent: Zoledronic Acid (Zometa) NSC #721517, CALGB-sponsored IND #62,751, will be  
supplied by Novartis Pharmaceuticals, and distributed by CTEP, DCTD, NCI.*

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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 AMS account contact information current. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

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**A RANDOMIZED DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF EARLY VERSUS STANDARD ZOLEDRONIC ACID TO PREVENT SKELETAL RELATED EVENTS IN MEN WITH PROSTATE CANCER METASTATIC TO BONE**

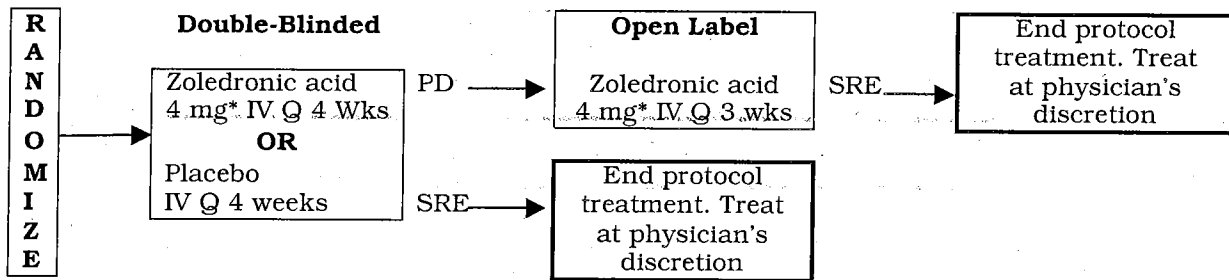
**Patient Eligibility**

- Histologic documentation of prostate adenocarcinoma (see Section 5.1)
- At least one bone metastasis by radiographic imaging (see Section 5.2)
- Patients must receive androgen deprivation therapy for treatment of prostate cancer (see Sec. 5.3)
- Hormone therapy at any point prior to 6 months before enrollment is prohibited (see Sec. 5.4)
- Prior neoadjuvant and/or adjuvant hormone therapy is allowed provided that the duration of hormone therapy was six months or less and the hormone therapy was discontinued more than 6 months prior to study entry.
- No prior treatment with a bisphosphonate
- No prior treatment with denosumab
- No prior treatment with radiopharmaceuticals
- ≥ 4 weeks since completion of prior radiation therapy (See Section 5.4)
- ECOG (CTC) performance status 0-2
- Age ≥ 18 years of age

**Required Initial Laboratory Values**

|                            |                               |
|----------------------------|-------------------------------|
| Calc. Creatinine Clearance | ≥ 30 mL/min*                  |
| Corrected Serum Calcium    | ≥ 8.0 mg/dL and < 11.6 mg/dL* |
| * see Section 5.7          |                               |

**SCHEMA**



**Progressive disease (PD)** is defined as new bone metastases or three consecutive rises in PSA with each PSA measurement at least two **weeks** apart and at least one PSA value > 4.0 ng/mL. **Skeletal-related events (SRE)** are defined as radiation to bone, clinical fracture, surgery to bone, or spinal cord compression (see Section 13.1).

During the double-blind part of the study, patients will receive **zoledronic acid 4 mg\* IV OR placebo IV** over 15 minutes every four weeks.

Patients who experience progressive disease will receive open label **zoledronic acid 4 mg\* IV** over 15 minutes every three weeks.

\* **Creatinine clearance is to be calculated for all patients at baseline using the Cockcroft-Gault formula using actual body weight. Starting dose should be adjusted per Section 8.1. There will be no dose modifications after the initiation of protocol treatment. Zoledronic acid (or placebo) will be held for elevation in serum creatinine as described in Section 10.1.**

**Protocol treatment will continue until patients experience an SRE.**

All patients will be instructed to take approximately 500 mg of elemental calcium by mouth daily and one multivitamin tablet (containing 400-500 IU vitamin D) by mouth daily, or a combination tablet containing approximately 500 mg calcium and vitamin D 400-500 IU.

**Randomization:** This study utilizes the CALGB on-line Patient Registration System. Randomization will be accepted only through CALGB Main Member/At Large institutions, selected affiliate institutions, and CCOPs using the on-line Patient Registration system. Randomization must occur prior to the initiation of protocol therapy.

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## 1.0 INTRODUCTION

### 1.1 Background

Skeletal complications are a major cause of morbidity in men with prostate cancer. More than 80% of men with metastatic prostate cancer have radiographic evidence of bone involvement. A similar majority of men who die from prostate cancer have bone metastases at autopsy. The clinical manifestations of bone metastases include pain, fractures, spinal cord compression, and myelophthisis.

In February 2002, the Food and Drug Administration approved zoledronic acid (Zometa®) to treat men with prostate cancer and bone metastases after failure of primary hormonal therapy. This approval was based on the results of Zometa 039, a placebo-controlled study of 643 men with prostate cancer, bone metastases, and disease progression after primary hormonal therapy (1). The primary study endpoint was skeletal related events (SRE), defined as pathological fracture, spinal cord compression, surgery or radiation therapy to bone, or change in antineoplastic treatment to treat bone pain. Zoledronic acid significantly decreased the proportion of men experiencing any skeletal related event at fifteen months (44% versus 33%,  $p = 0.02$ ). Mean time to first skeletal related event was significantly increased by zoledronic acid (329 days versus  $> 500$  days,  $p = 0.011$ ).

No study has evaluated the efficacy of zoledronic acid before failure of primary hormonal therapy. The issue of earlier treatment is clinically important because the response rate for primary hormonal therapy for men with bone metastases exceeds 80% and the median duration of response is approximately 18 months.

The proposed study will evaluate the efficacy of early versus delayed zoledronic acid in men with prostate cancer metastatic to bone. The study will include men with prostate cancer and radiographically documented bone metastases who have started androgen deprivation therapy within six months prior to study entry. Patients will be randomly assigned to either zoledronic acid (4 mg intravenously every 4 weeks) or placebo. The primary study endpoint will be time to first skeletal related event. Patients will receive open-label treatment with zoledronic acid if they fail primary hormonal treatment prior to experiencing a skeletal related event.

The results of the proposed study are likely to change clinical practice. If the study has a positive result, we will recommend starting zoledronic acid with primary hormonal therapy in men with prostate cancer metastatic to bone. In contrast, a negative result would indicate there is no advantage for early zoledronic acid treatment in men with bone metastases.

### 1.2 Supporting Preliminary Data

Only one study has evaluated bisphosphonates in men receiving initial androgen deprivation therapy for metastatic prostate cancer. Medical Research Council Pr05 Study randomly assigned 311 men who were starting or responding to primary androgen deprivation therapy for metastatic prostate cancer to either androgen deprivation therapy plus oral clodronate, a second generation bisphosphonate, or androgen deprivation therapy plus placebo (2). The primary study endpoints were skeletal disease progression or prostate cancer death. The clodronate-treated group had a lower risk of skeletal disease progression or prostate cancer death ( $P=NS$ ) and lower risk of all-cause death ( $P=NS$ ). Subset analyses indicated a greater treatment effect for men who entered the study shortly after initiating primary hormonal therapy. Although the primary efficacy analyses were negative, the non-significant improvements in outcomes for the clodronate-treated men provides an important background for the proposed study. Shortcomings of the Pr05 study include use of a relatively weak bisphosphonate, poor bioavailability after oral

administration, and inadequate sample size. The proposed study is designed to overcome these limitations.

### 1.3 Rationale for Selected Approach and Trial Design

Zoledronic acid decreases the risk of skeletal related events in men with prostate cancer metastatic to bone and disease progression after primary hormonal therapy. This study is designed to evaluate whether earlier treatment with zoledronic acid will further decrease the risk of skeletal related events.

The study has several important features:

- 1.3.1 Randomized design:** The efficacy of zoledronic acid in men with prostate cancer metastatic to bone and disease progression after primary hormonal therapy has been demonstrated in one multi-centered randomized study. The randomized design of the proposed study is required to evaluate whether earlier treatment with zoledronic acid further decreases the risk of skeletal related events.
- 1.3.2 Monthly schedule of zoledronic acid treatment:** Zoledronic acid (4 milligrams every 3 weeks) decreased the risk of skeletal related events in men with prostate cancer metastatic to bone and disease progression after primary hormonal therapy. The more convenient 4-week schedule in the proposed study is intended to increase patient and physician acceptance without compromising efficacy. In early dose-finding studies in patients with bone metastases from a variety of tumor types including prostate cancer, administration of a single 4 milligram dose of zoledronic acid decreased biochemical markers of osteoclast activity by > 50% and maximum osteoclast inhibition was maintained for at least 4 weeks. In the pivotal study of men with bone metastases and disease progression after primary hormonal therapy, zoledronic acid (4 milligrams every 3 weeks) decreased markers of osteoclast activity by approximately 70% and maximum inhibition was maintained throughout the 15 month study. Collectively, these observations suggest that efficacy will be maintained with an every 4 week schedule. In order to maintain consistency with the best arm of the Zometa 039 study, zoledronic acid will be administered every 3 weeks during the open-label treatment portion of the study.
- 1.3.3 Outcome based on skeletal related events:** Skeletal related events reflect the composite skeletal morbidity for patients with bone metastases. Skeletal related events were the primary efficacy variable for the three pivotal studies of pamidronate in patients with multiple myeloma and women with breast cancer metastatic to bone. Skeletal related events were also the primary efficacy variable for the three pivotal studies of zoledronic acid in patients with multiple myeloma and bone metastases from a variety of solid tumors including breast cancer and prostate cancer.
- 1.3.4 Treatment with zoledronic acid after disease progression or first skeletal related event:** Patients will begin the open-label treatment portion of the study at progressive disease. In addition, patients who experience a skeletal related event will end protocol treatment and may then receive zoledronic acid at the discretion of the treating investigator. The latter provision is designed to improve subject and physician acceptance of the randomized study design and will not affect the primary analysis. We anticipate that relatively few subjects will experience a skeletal related event prior to disease progression.
- 1.3.5 Substantial interval between early and delayed treatment:** Response rates to primary hormonal therapy for metastatic prostate cancer exceed 80 percent

and the median duration of response is approximately 18 months. We anticipate that most skeletal related events will occur after failure of primary hormonal therapy. Accordingly, the expected interval between early and delayed treatment is 12-18 months. The long interval between early and delayed treatment will increase the ability of this study to detect a treatment effect and minimize the effect of the crossover on secondary analyses including survival.

#### 1.4 Treatment-related osteoporosis

Androgen deprivation therapy by either bilateral orchiectomies or gonadotropin-releasing hormone agonist treatment decreases bone mineral density and increases fracture risk in men with prostate cancer (3). Treatment-related osteoporosis may be particularly important for men receiving long-term androgen deprivation therapy for nonmetastatic prostate cancer. In contrast, treatment-related osteoporosis may be a lesser concern for men initiating androgen deprivation therapy for bone metastases due to their relatively short life expectancy and competing disease-related skeletal morbidity.

Zoledronic acid increases bone mineral density in the hip and spine during androgen deprivation therapy for nonmetastatic prostate cancer. In a recent prospective randomized study, 106 men who were initiating androgen deprivation therapy for nonmetastatic prostate cancer were assigned to either zoledronic acid (4 mg intravenously every 12 weeks) or placebo (4). The primary study endpoint was change in bone mineral density of the lumbar spine after twelve months. Mean bone mineral density in the lumbar spine increased by 5.6% in men receiving zoledronic acid and decreased by 2.2% in men receiving placebo (mean difference 7.8%, 95% confidence interval 5.6%-10.0%,  $p < 0.001$ ). Mean bone mineral density of the femoral neck, trochanter, and total hip also increased in the zoledronic acid group and decreased in the placebo group. The study was not designed to evaluate the effect of zoledronic acid on fracture risk. No patient experienced a clinical (symptomatic) fracture. There were five radiographically diagnosed new or worsening vertebral fractures in zoledronic acid group and three in the placebo group ( $p = 0.29$ ). Three of the eight men with vertebral body fractures had low baseline bone mineral density of the spine and/or hip (T score  $< -1.0$ ).

In men with prostate cancer metastatic to bone and disease progression despite primary androgen deprivation therapy, zoledronic acid may decrease fracture risk. In the Zometa 039 study, zoledronic acid decreased the proportion of men experiencing any pathological fracture at fifteen months (22% versus 13%,  $p = 0.015$ ). Zoledronic acid decreased the proportion of men experiencing either vertebral (8.2% versus 3.7%,  $p = 0.053$ ) and nonvertebral fractures (15.9% versus 10.3%,  $p = 0.092$ ).

Men with bone metastases cannot be screened reliably for osteoporosis because osteoblastic metastases are characterized by increased bone mineral density (5). In men with bone metastases, changes in bone mineral density probably reflect the sum of response/progression of bone metastases, disease-related changes in uninvolved bone, and treatment-related changes in normal bone. Accordingly, disease-related changes in bone mineral density cannot be distinguished reliably from treatment-related changes in men with bone metastases. Because of these limitations, measurement of bone mineral density is neither required nor recommended in this study.



**2.0 INCLUSION OF WOMEN AND MINORITIES**

Minorities will be eligible for this study without alteration in eligibility criteria. Based on previous data from advanced prostate cancer patients enrolled on CALGB 9594, the accrual targets in individual cells are not large enough to perform subgroup analysis by the two treatment groups. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets. However, we plan to perform subset analyses within racial and ethnic groups.

| <b>Accrual Targets</b>                        |                   |   |              |   |              |
|---|-------------------|---|--------------|---|--------------|
| <b>Ethnic Category</b>                        | <b>Sex/Gender</b> |   |              |   |              |
|   | <b>Females</b>    |   | <b>Males</b> |   | <b>Total</b> |
| Hispanic or Latino                            | 0                 | + | 28           | = | 28           |
| Not Hispanic or Latino                        | 0                 | + | 652          | = | 652          |
| <b>Ethnic Category: Total of all subjects</b> | 0                 | + | 680          | = | 680          |
| <b>Racial Category</b>                        |                   |   |              |   |              |
| American Indian or Alaskan Native             | 0                 | + | 0            | = | 0            |
| Asian   | 0                 | + | 0            | = | 0            |
| Black or African American                     | 0                 | + | 136          | = | 136          |
| Native Hawaiian or other Pacific Islander     | 0                 | + | 0            | = | 0            |
| White   | 0                 | + | 544          | = | 544          |
| <b>Racial Category: Total of all subjects</b> | 0                 | + | 680          | = | 680          |

**3.0 OBJECTIVES**

**Primary Objective**

**3.1** To determine whether treatment with zoledronic acid at the time of initiation of androgen deprivation therapy for metastatic prostate cancer will delay the time to first skeletal related event.

**Secondary Objective**

**3.2** To compare the effect of treatment with zoledronic acid to placebo on overall survival (OS), progression-free survival (PFS) and toxicity in men receiving androgen deprivation therapy for metastatic prostate cancer.

**4.0 ON-STUDY GUIDELINES**

The following guidelines are to assist physicians in selecting patients for whom protocol therapy is safe and appropriate. 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 any necessary therapy and are considered by their physician to be at less than 30% risk of relapse.

## 5.0 ELIGIBILITY CRITERIA

**5.1 Histologic Documentation:** Histologic documentation of prostate adenocarcinoma. Patients with small cell, neuroendocrine, or transitional cell carcinomas are not eligible.

**5.2 Staging:** At least one bone metastasis by radiographic imaging (bone scan, magnetic resonance imaging, computed tomography, or plain radiographs). Indeterminate lesions should be confirmed by a second imaging method.

Imaging to document bone metastases is to be completed either within 12 weeks before registration or within 12 weeks before initiating androgen deprivation therapy for bone metastases.

### 5.3 Hormone Therapy

- **While on this study, patients must receive androgen deprivation therapy (ADT) for treatment of prostate cancer.** Androgen deprivation therapy may have begun prior to enrollment on this study; however patients must have initiated ADT  $\leq$  6 months prior to enrollment.
- Androgen deprivation therapy is defined as bilateral orchiectomy or gonadotropin-releasing hormone (GnRH) agonist with or without an antiandrogen.
- Patients treated with intermittent androgen deprivation therapy are not eligible except for patients concurrently enrolled in SWOG-9346/INT-0162/CALGB 9594, "Phase III Study of Intermittent Androgen Deprivation in Patients with Stage D2 Prostate Cancer."

### 5.4 Prior Treatment:

- Hormone therapy at any point prior to 6 months before enrollment is prohibited. This includes any of the following treatments:
  - orchiectomy,
  - GnRH agonist (e. g., leuprolide, goserelin, triptorelin),
  - estrogen therapy,
  - antiandrogen (e. g., bicalutamide, flutamide, nilutamide), or
  - any other therapy known to lower testosterone level or inhibit testosterone effect.
- Prior neoadjuvant and/or adjuvant hormone therapy is allowed provided that the duration of hormone therapy was six months or less and the hormone therapy was discontinued more than 6 months prior to study entry.
- No prior treatment with a bisphosphonate
- No prior treatment with denosumab
- No prior treatment with radiopharmaceuticals
- $\geq$  4 weeks since completion of prior radiation therapy with at least one bone metastasis present that has NOT been radiated.

**5.5 ECOG (CTC) performance status 0-2**

**5.6 Age: ≥ 18 years**

**5.7 Required Initial Laboratory Data:**

Calculated Creatinine Clearance\* ≥ 30 mL/min  
 Corrected serum calcium ≥ 8.0 mg/dL (2.00 mmol/L) and  
 <11.6 mg/dL (2.90 mmol/L)

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

$$Cl_{Cr} \text{ (mL/min)} = \frac{(140 - \text{age}) (\text{actual weight in kg})}{72 \times \text{serum creatinine (mg/dL)}}$$

Note: in markedly obese patients, the Cockcroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

**6.0 REGISTRATION/RANDOMIZATION, STRATIFICATION, AND DATA AND SAMPLE SUBMISSION**

**6.1 Randomization Requirements**

**Informed Consent:** the patient must be aware of the neoplastic nature of his disease and willingly consent after being informed of the procedure 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.

**6.2 CALGB Randomization Procedures**

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

Confirm eligibility criteria (Section 5.0). Complete the Registration Worksheet. Access the on-line Patient Registration system via the patient registration icon on the CALGB Information Systems (IS) Application main menu. If the registering CRA requires assistance, he/she may consult the on-line help file located under the help menu of the CALGB IS Application. 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:

- Study
- Name of group (CALGB)
- Name of institution where patient is being treated
- Name of treating physician
- Name of responsible contact (treating physician or responsible CRA)
- CALGB patient ID #, if applicable
- Patient's initials
- Patient's Social Security #, date of birth, and hospital ID #
- Patient's gender
- Patient's race and ethnicity
- Patient's height in centimeters, weight in kilograms, and CTC performance status
- Type of insurance (method of payment)
- Patient's postal code (if applicable)
- Country of residence (if not USA)

Treatment start date  
 Date of signed consent  
 Companion study  
 Eligibility criteria met (no, yes)  
 Is the patient registered to SWOG 9346 (no, yes)

When the patient is registered, a 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 indicated below, which must be entered to obtain a treatment assignment. For example, if age is a stratification factor the actual age is collected. If the stratification question is a "no, yes" question, please enter the value "1" for no and "2" for yes. Treatment is to begin within 14 days of randomization.

The Main Member Institution and registering institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Data Operations, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705.

Blinded, patient-specific clinical supplies of zoledronic acid/placebo will be requested by the CALGB Statistical Center at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 11.2).

### 6.3 Registration to the Companion Study

There is one sub-study within CALGB 90202. This correlative science study must be offered to all patients enrolled on CALGB 90202 (although patients may opt not to participate). The sub-study included within CALGB 90202 is:

- CALGB 150403; Serum N-telopeptide concentrations as a prognostic marker in men receiving primary hormonal therapy for metastatic prostate cancer, (Section 9.0)

If a patient answers "yes" to "I agree that my blood may be used for research studies to learn about the effects that the experimental treatment may be having." (Question #1) in the Model Consent, he has consented to participate in the study described in Section 9.0. The patient should be registered to CALGB 150403 at the same time that he is registered to the treatment trial (90202) and samples submitted per Section 6.7.

### 6.4 Stratification Factors

#### 6.4.1 Performance status

0-1  
 2

#### 6.4.2 Prior skeletal related event (see Section 13.1)

No  
 Yes

#### 6.4.3 Serum alkaline phosphatase

< Upper limit of institutional normal  
 ≥ Upper limit of institutional normal

### 6.5 Re-registration at Disease Progression

At the time of disease progression as defined in Section 13.5 patients will cross over to treatment with open-label zoledronic acid (see Section 8.1.2). Complete the Re-Registration Worksheet. Access the on-line Patient Registration system via the CALGB Web site (calgb.org). After clicking "patient registration" and re-entering the Username and Password, click "Randomize a Patient." Select 90202, enter the CALGB Patient ID number, and click "Continue" and then "Randomize." Institutions will receive an electronic Confirmation of Re-registration.

Open-label patient-specific clinical supplies of zoledronic acid will be requested by the CALGB Statistical Center at the time of re-registration and should arrive at the clinical site within 7 to 10 days of re-registration (see Section 11.2). The use of commercial zoledronic acid in the place of study-supplied open-label drug is a protocol violation.

### 6.6 Data Submission: Forms should be submitted to the CALGB Statistical Center, Data Operations in compliance with the Data Submission schedule below. There are three options for submitting forms that use the Teleform barcode and cornerstones:

- The preferred method is to submit the forms electronically using the "Submit to CALGB" button located at the bottom of the last page of each form. Forms submitted electronically should not be submitted by fax or mail.
- The forms may be faxed to 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- The forms may be mailed to the CALGB Statistical Center, Data Operations, Hock Plaza, 2424 Erwin Rd, Suite 802, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Amended data and supporting documentation (e.g., reports or flow sheets) should be submitted by fax (919-416-4990) or mail (CALGB Statistical Center, Data Operation, Hock Plaza, Suite 802, 2424 Erwin Road, Durham, NC 27705.)

For the most up-to-date data forms, please visit the CALGB website at [www.calgb.org](http://www.calgb.org).

| Form  | Submission Schedule   |
|---|---|
| C-1105   CALGB 90202 Registration Worksheet<br>CALGB 90202 Eligibility Checklist<br>CALGB 90202 On-Study Form<br><i>Copy of radiographic report documenting bone metastasis present at baseline</i><br>Pathology Report | Within one week of registration   |
|   | At disease progression (see Section 6.5)  |
| C-1104   CALGB 90202 Follow-Up Form†  | After every 2 cycles of protocol treatment, at progression (end of double-blinded phase), at first SRE, and at death. If protocol treatment ends before SRE, every 6 months until 3 years after registration. |
| C-1106   CALGB 90202 Adverse Event Form†  | After every 2 cycles during protocol treatment and at 1 month after protocol treatment ends.  |
| C-714   Prostate Specific Antigen Form  | After every cycle until first SRE. If protocol treatment ends before 1 <sup>st</sup> SRE, submit q 6 months until PSA progression is confirmed twice for up to 3 years after randomization.                   |
| C-1177   CALGB 90202 Treatment Form   | At the end of double-blinded, and the end of open-label treatment.  |
|   | <i>Documentation of progressive bone disease</i>   At the time of bone progression.   |
|   | <i>Documentation of skeletal related event</i>   At the time of first skeletal related event (see Sections 13.1 and 14.1).  |
| C-900   CALGB Survival Data Form  | After both progression <u>and</u> first SRE have occurred, every 6 months until 2 years after randomization, then annually until 10 years after randomization.  |
| C-260   CALGB Remarks Addenda   | As needed.  |

\* Send original with serum sample to the Pathology Coordinating Office and send a copy to the Statistical Center, Data Operations.

† During protocol treatment these forms cover a reporting period of 8 weeks during the double-blinded phase and 6 weeks during the open label phase.

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

## 6.7 Sample Submission

Collect blood for correlative sciences studies (see Section 9.0) for all patients who have consented to blood sample submission. Samples should be collected at baseline, at 6 and 12 months following randomization until progression, and at progression.

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 transferred to a polypropylene tube. Specimens should be refrigerated immediately after collection and shipped over cool pack within 24 hours. The CALGB PCO will aliquot the specimens upon receipt.

### **CALGB Specimen Tracking System (STS) Specimen Submission Instructions:**

USE OF THE SPECIMEN TRACKING SYSTEM IS MANDATORY AND ALL SPECIMENS MUST BE LOGGED AND SHIPPED VIA THIS SYSTEM. Specimens for patients registered on this study must be logged and shipped using the online CALGB Specimen Tracking System. All institutions may access this system via the CALGB Web site, <http://www.calgb.org>.

All submitted specimens must be labeled with the protocol number (90202), CALGB patient number, patient's initials and date and type of specimen collected (e.g., serum, plasma).

A copy of the Shipment Packing Slip produced by the CALGB Specimen Tracking System must be printed and placed in the shipment with the specimens.

For procedural help in logging and shipping specimens, please refer to the Specimen Tracking System User Guide, which can be accessed via the Help link within the Specimen Tracking System. To report technical problems with the CALGB Specimen Tracking System, such as login issues or application errors, and/or for further assistance using the application, please contact the CALGB Help Desk at 877-44CALGB or [calgb-support@calgb.duhs.duke.edu](mailto:calgb-support@calgb.duhs.duke.edu).

Instructions for the collection of samples are included above. 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:

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

**7.0 REQUIRED DATA**

**Guidelines for Pre-Study Testing**

To be completed within 16 DAYS before registration:

- History, physical, and all bloodwork

Imaging to document bone metastases is to be completed either within 12 WEEKS before registration or within 12 WEEKS before initiating androgen deprivation therapy for bone metastases.

|   | Prior to Registration | Day 1 of each cycle until SRE* |
|---|-----------------------|--------------------------------|
| <b>Tests &amp; Observations</b>                                     |                       |                                |
| History and Progress Notes  | X                     | X                              |
| Physical Examination  | X                     |                                |
| Pulse, Blood Pressure   | X                     |                                |
| Height and Weight   | X                     |                                |
| CALGB Performance Status  | X                     |                                |
| Drug Toxicity Assessment  |                       | X                              |
| <b>Laboratory Studies</b>   |                       |                                |
| CBC, Differential, Platelets  | X                     |                                |
| Serum albumin, calcium, magnesium, phosphorus, alkaline phosphatase | X                     | A                              |
| LDH   | X                     |                                |
| Serum creatinine  | X                     | X**                            |
| Serum PSA   | X                     | X†                             |
| Urinalysis  | X                     |                                |
| Serum for correlative science studies                               | B                     | B                              |
| <b>Staging</b>  |                       |                                |
| Bone scan†  | X                     |                                |
| Gleason Score   | C                     |                                |

\* A cycle is 4 weeks long in during the double-blind portion of the study and is 3 weeks long during the open label portion of the study. After SRE, patients are to be followed for survival for up to 10 years following randomization.

\*\* 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. The serum creatinine level obtained within 7 days prior to Day 1 of the first cycle should be considered the baseline creatinine level for the purpose of calculating the zoledronic acid dose (see Section 8.1).

† At least one bone metastasis, which has not been irradiated, by radiographic imaging (bone scan, magnetic resonance imaging, computed tomography, or plain radiographs) is required for study entry. Indeterminate lesions should be confirmed by a second imaging method.

‡ Serum PSA may be obtained up to 7 days prior to each treatment cycle. Serum PSA prior to Day 1 of Cycle 1 is not required (provided pre-study PSA within 16 days of registration was obtained). For patients who discontinue protocol treatment prior to first SRE, PSA should be obtained at least every 3 months until 3 years after randomization.

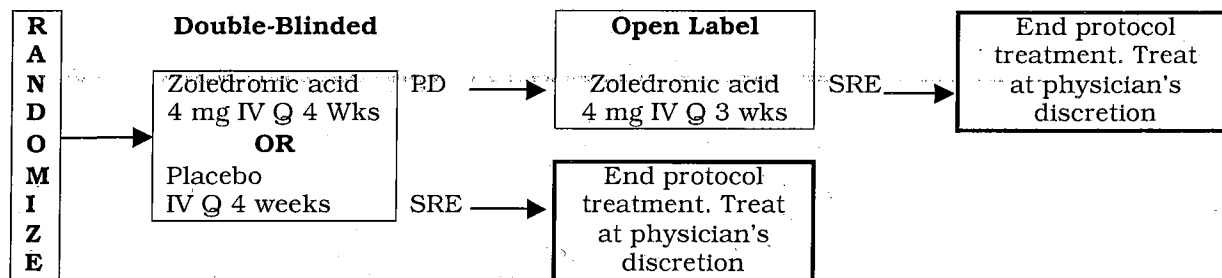
A Every 3 cycles. These labs may be obtained within 24 hours prior to treatment.

B See Section 6.7.

C If available. If Gleason Score is unavailable, it should be recorded as "unknown."



**8.0 TREATMENT PLAN**



**8.1 Zoledronic acid or placebo will be administered in an outpatient setting.**

Blinded, patient-specific clinical supplies of zoledronic acid/placebo will be requested by the CALGB at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 11.2).

Creatinine clearance is to be calculated for all patients at baseline (within 7 days prior to the initiation of treatment) using the Cockcroft-Gault formula using actual body weight (see Section 5.7). Starting dose 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 |

**8.1.1 Double-blinded treatment:** During the double-blinded portion of the study, patients will receive zoledronic acid or placebo IV over 15 minutes every **four** weeks until progression or first skeletal related event (SRE) (see Section 13.0).

**8.1.2 Open-label treatment for patients who progress to AIPC:** Patients who progress to androgen independent prostate cancer will begin open-label treatment with zoledronic acid IV over 15 minutes every **three** weeks. Patients must be re-registered per Section 6.5. Open-label patient-specific clinical supplies of zoledronic acid will be requested by the CALGB Statistical Center at the time of re-registration and should arrive at the clinical site within 7 to 10 days of re-registration (see Section 11.2).

Open-label treatment should begin 4 weeks after the last dose of blinded treatment. If open-label drug has not been received by the scheduled day, blinded drug should be used for one more cycle. The use of commercial zoledronic acid in the place of study-supplied open-label drug is a protocol violation.

See Section 12.3 for a list of the concurrent therapies allowed during open-label treatment.

**8.1.3 Patients will be treated until experiencing a skeletal-related event.** Upon experiencing an SRE, whether during the double-blinded or open label portion of the study, patients will be removed from protocol treatment and treated at the physician's discretion.

## **8.2 GnRH Agonist**

**8.2.1** Patients concurrently enrolled in SWOG-9346/INT-0162/CALGB 9594 (Phase III Study of Intermittent Androgen Deprivation in Patients with Stage D2 Prostate Cancer) will receive androgen deprivation therapy per SWOG-9346.

**8.2.2** All other patients receiving androgen deprivation therapy with a GnRH agonist will receive continuous androgen deprivation treatment at a standard dose and schedule throughout the entirety of the study.

## **8.3 Supplemental calcium and vitamin D**

**8.3.1** All patients will be instructed to take a calcium supplement (containing approximately 500 mg elemental calcium) by mouth daily and a multivitamin tablet (containing 400-500 IU vitamin D) by mouth daily, or a combination tablet (containing approximately 500 mg elemental calcium and 400-500 IU vitamin D) by mouth daily.

**8.3.2** Supplemental calcium and multivitamin will be administered with food.

## **9.0 CORRELATIVE SCIENCES COMPANION STUDY**

### **9.1 Background**

Biochemical markers of osteoclast and osteoblast activity are elevated in the serum and urine of patients with bone metastases from prostate cancer and other malignancies (6). Excessive osteoclast activation appears to contribute to skeletal morbidity from prostate cancer. In a recent prospective study, 34 of 112 (30%) men with androgen-independent prostate cancer and bone metastases experienced an adverse skeletal event during the course of their disease (7). At baseline, men with subsequent skeletal events had greater bone pain, more extensive bone metastases, lower performance status, higher serum alkaline phosphatase levels, and higher urinary deoxypyridoline levels than their counterparts without skeletal events. Multivariate analyses revealed that only baseline urinary deoxypyridinoline, a marker of osteoclast activity, was independently associated with the subsequent skeletal events. Additional studies are needed to confirm this preliminary observation and to evaluate the predictive value of novel markers.

The specific hypothesis of the companion correlative study is that baseline serum concentrations of N-telopeptide, a specific marker of osteoclast activity, predicts independently the risk of subsequent skeletal related events in men receiving primary hormonal therapy for metastatic prostate cancer. N-telopeptide will be used for this correlative study rather than deoxydyridinoline because N-telopeptide is a better predictor of the presence and extent of bone metastases than other biochemical markers including deoxypyridinoline (8). The relationship between other baseline markers of bone metabolism (e.g. OPG, RANKL) and skeletal related events will be evaluated in exploratory analyses. The relationship between changes in serum concentrations of N-telopeptide (and other markers) and skeletal related events also will be evaluated in exploratory analyses. We anticipate that the specimens collected for these correlative studies will facilitate the future evaluation of novel markers of bone metabolism.

## 9.2 Correlative Science Objectives

The primary objectives of this correlative science study are to determine the prognostic importance of serum N-telopeptide concentrations on overall survival and time to first SRE.

## 9.3 Correlative Science Methods

Sera will be collected from patients at baseline, 6 months, 12 months, and at disease progression and will be stored in five one-milliliter aliquots in 1.8 cc cryovials. (See Section 6.5 for sample collection and submission instructions.)

Serum N-telopeptide concentrations will be determined at a Massachusetts General Hospital core laboratory using a competitive inhibition enzyme-linked immunosorbent assay (ELISA/EIA) (Osteomark®, Ostex International, Inc., Seattle, Washington). The intra-assay and interassay variability are 4.6% and 4.9%, respectively.

## 10.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

**There will be no dose modifications.** Zoledronic acid (or placebo) will be held for elevation in serum creatinine as described in Section 10.1.

**10.1 Renal:** Serum creatinine will be measured within 7 days prior to each dose of zoledronic acid (or placebo).

- If baseline serum creatinine was < 1.4 mg/dL, then an increase of  $\geq 0.5$  mg/dL requires delay in treatment until the patient's serum creatinine returns to no higher than 10% above the baseline value.
- If baseline serum creatinine was  $\geq 1.4$ , then an increase of 1.0 mg/dL requires delay in treatment until the patient's serum creatinine returns to no higher than 10% above the baseline value.
- Serum creatinine should be monitored weekly in patients for whom treatment has been delayed. Delay of  $\geq 4$  weeks will mandate withdrawal from protocol treatment.

**10.2 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 (or placebo) without dose or schedule modification. NSAIDs or other analgesics may be used at the treating physician's discretion.

**10.3 Hypersensitivity reactions:** Hypersensitivity reactions are a rare adverse effect of bisphosphonate treatment. Patients who experience a moderate (generalized pruritis, flushing, rash, dyspnea, or hypotension with SBP > 80 mg Hg) or severe (bronchospasms, generalized urticaria, hypotension with SBP  $\leq 80$  mg Hg, or angioedema) hypersensitivity reaction during treatment will be withdrawn from protocol treatment.

**10.4 Osteonecrosis of the Jaw** has been associated with the use of bisphosphonates. Patients who develop new onset jaw pain or tenderness should be evaluated by an appropriate specialist (e.g., dentist or oral surgeon).

## 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 Zoledronic Acid (Zometa®) (NSC #721517, IND #62751) or Placebo

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*

**Blinded Phase:** Zoledronic acid for the blinded phase of this study is considered an investigational agent under a CALGB-sponsored IND 62751. Zoledronic acid and matching placebo will be provided free of charge by Novartis Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Zoledronic acid and matching placebo will be supplied as a "concentrate solution for infusion" in plastic vials each containing 4 mg (Zoledronic acid) or 0 mg (Placebo for Zoledronic acid) of zoledronic acid. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal. Each box will be labeled with:

- the protocol number (i.e., "CALGB-90202")
- the box number (i.e., "Box 1 of 1")
- the number of vials (i.e., "6 vials")
- the patient ID number (e.g., "99999", where "99999" represents a unique patient identifier assigned at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])
- the agent identification (i.e., "Zoledronic acid 4 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store at controlled room temperature. Do not store above 30°C/86°F.")
- emergency contact instructions
- a Julian date

The Julian date indicates the day the box was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2004 = 04, 2005 = 05) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a box labeled and shipped on January 1, 2004 would have a Julian date of '04001' and a box labeled and shipped on December 31, 2005 would have a Julian date of '05365'. The Julian date will be used by PMB for recalls. When a lot expires, PMB will determine the last date the expired lot was shipped and will recall all vials (i.e., both Zoledronic acid and Placebo) shipped on or before that date thus eliminating any chance of breaking the blind.

**Open Label Phase:** Zoledronic acid will be provided free of charge by Novartis Pharmaceuticals and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Zoledronic acid will be supplied as a "concentrate solution for infusion" in plastic vials each containing 4 mg of zoledronic acid. The patient-specific vials will be sealed in a cardboard box with a tamper-evident seal. Each box will be labeled with:

- the protocol number (i.e., "CALGB-90202")
- the box number (i.e., "Box 1 of 1")
- the number of vials (i.e., "9 vials")
- the patient ID number (e.g., "99999", where "99999" represents a unique patient identifier assigned at registration)
- the patient initials (i.e., last initial, first initial, middle initial [e.g., "L, FM"])
- the agent identification (i.e., "Zoledronic acid 4 mg or Placebo")
- a blank line for the pharmacist to enter the patient's name
- storage instructions (i.e., "Store at controlled room temperature. Do not store above 30°C/86°F.")
- emergency contact instructions
- a Julian date

#### *Drug Orders, Transfers, Returns, and Accountability*

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725 Monday through Friday between 8:30 am and 4:30 pm Eastern Time.

#### Drug Orders:

**Blinded Phase** (zoledronic acid or placebo 4 mg IV every four weeks):

**No blinded starter supplies will be available for this study.** Blinded, patient-specific supplies will be sent to the registering investigator at the time of randomization and **should arrive at the institution within 7 to 10 days.**

Randomization will be performed by the CALGB Statistical Center. The assigned patient ID number must be recorded by the registering institution at the time of randomization for proper vial dispersion. Once a patient has been registered, the Statistical Center will electronically transmit a clinical drug request for that patient to the PMB. This request will be transmitted on the day the patient is registered and will be processed by the PMB the next business day and shipped the following business day.

- For example, if a patient is randomized on Monday, the CALGB Statistical Center would submit a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). U.S. sites could expect to receive their order on approximately Friday or Monday and Canadian sites could expect to receive their order on either Thursday or Friday.

The initial request will be for **6 – 4 mg vials** (a 6 cycle/24 week [6 month] supply) of zoledronic acid or matching placebo. Five (5) months after the initial electronic request (i.e., one month before needed), sites may reorder an additional **6 – 4 mg vials** by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. The assigned patient ID number (e.g., "99999") and the patient initials (e.g., "L,FM") should be entered in the "Patient or Special Code" field. All drug orders will be shipped directly to the physician responsible for treating the patient.

**Open Label Phase** (zoledronic acid 4 mg IV every three weeks):

At the time of disease progression (see Section 13.5), all patients will cross over to open label zoledronic acid. This crossover will require a second registration (see Section 6.5 for re-registration instructions). **No open label starter supplies will be available for this study.** Open label, patient-specific supplies will be sent to the registering investigator at the time of the second registration and **should arrive at the institution within 7 to 10 days.**

Re-registration will be performed by the CALGB Statistical Center. **The patient ID number will remain the same.** Once a patient has been re-registered, the Statistical Center will electronically transmit an open label clinical drug request for that patient to the PMB. This request will be transmitted on the day the patient is re-registered and will be processed by the PMB the next business day and shipped the following business day.

- For example, if a patient is re-registered on Monday, the CALGB Statistical Center would submit a clinical drug request for that patient on Monday and PMB would process that request on Tuesday and ship the drug on Wednesday. Shipments within the United States will be sent by US Priority Mail (generally two to three day delivery) and shipments to Canada will be sent by FedEx (generally one to two day delivery). U.S. sites could expect to receive their order on approximately Friday or Monday and Canadian sites could expect to receive their order on either Thursday or Friday.

The initial request will be for **9 – 4 mg vials** (a 9 cycle/27 week [6 month] supply) of zoledronic acid. Five (5) months after the initial electronic request (i.e., one month before needed), sites may reorder an additional **9 – 4 mg vials** by completing an NCI Clinical Drug Request form and faxing it to the PMB at 301-480-4612. The NCI Clinical Drug Request form is available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. The assigned patient ID number (e.g., "99999") and the patient initials (e.g., "L,FM") should be entered in the "Patient or Special Code" field. All drug orders will be shipped directly to the physician responsible for treating the patient.

**Drug Transfers:** Vials MAY NOT be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) must be approved in advance by the PMB. To obtain an approval for transfer, investigators should complete and submit to the PMB (fax number 301-402-0429) a Transfer Investigational Agent Form available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "99999") and the patient initials (e.g., "L, FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "CALGB-90202").

**Drug Returns:** Only undiluted vials should be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators should return the study drug to the PMB using the NCI Return Drug List available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "99999") and the patient initials (e.g., "L, FM") should be entered in the "Lot Number" field.

**Drug Accountability:** The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the CTEP home page (<http://ctep.cancer.gov>) or by calling the PMB at 301-496-5725. A separate NCI Investigational Agent Accountability Record must be maintained for each patient ID number (e.g., "99999") on this protocol.

#### *Preparation*

Zoledronic acid and placebo (NSC 721517/IND #62751) will be supplied in plastic vials each containing 4 mg (zoledronic acid) or 0 mg (placebo for zoledronic acid) of zoledronic acid concentrate solution for infusion. The blinded, patient-specific vials will be sealed in a cardboard box with a tamper-evident seal. The concentrate solution (4 mg or 0 mg zoledronic acid in 5 mL) must be further diluted prior to IV administration. The entire contents of the vial 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.

#### *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.

#### *Administration*

The diluted solution of zoledronic acid (or placebo) will be administered as a short IV infusion over 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.**

#### *Unblinding Procedures*

**Unblinding can be done only in the case of an emergency or at the time of a documented skeletal related event. Follow the directions below to unblind patient treatment.**

Examples of emergencies include: 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Follow the directions below to unblind patient treatment. Please note that if a treatment assignment is revealed (unblinded), the patient must discontinue protocol therapy.

1. Emergency Unblinding Procedures:

Examples of emergencies include 1) a life-threatening unexpected adverse event that is at least possibly related to the investigational agent and for which unblinding would influence treatment decisions; or 2) medication error, such as accidental overdose. Expected adverse events are listed in the "Toxicities" section below.

Contact a CALGB Approving Physician (i.e., Executive Officer) by calling 312-208-2325. If an Executive Officer cannot be reached, contact the CALGB Statistical Center Help Desk at 1-877-442-2542 and the Statistical Center will contact an Approving Physician. Note that the Statistical Center cannot give permission for unblinding. Only a CALGB Approving Physician can authorize emergency unblinding.

The following information will be required when contacting the CALGB Approving Physician:

- CALGB study number (i.e., CALGB-90202)
- CALGB patient ID number (e.g., 99999)
- Patient initials (e.g., "L.FM")
- Institution name
- Name and telephone number of treating physician
- Name and telephone number of person requesting the unblinding procedure
- Name and telephone number of contact person to inform of treatment assignment
- Reason for emergency unblinding

After authorization by a designated CALGB Approving Physician, the treatment assignment will then be provided to the contact person by the CALGB Statistical Center.

2. Non-Emergency Unblinding Procedures

Unblinding may also be done at the time of a documented skeletal related event. The treating physician should contact the CALGB 90202 Staff Statistician (see cover page) during normal business hours to obtain the treatment assignment. **Unblinding at the time of disease progression (and prior to SRE) will not be allowed, except in the case of an emergency.**

*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.

Several recent reports describe the occurrence of osteonecrosis of the jaw in patients receiving chemotherapy and a bisphosphonate (pamidronate or zoledronic acid). Although osteonecrosis in these patients cannot be definitely attributed to a bisphosphonate, the use of such was noted in all of the cases. It is not known if this effect is dose and/or duration-dependent. 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.



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.

**11.3 Vitamin D**

*Availability*

Vitamin D analogs are fat-soluble vitamins, which are commercially available. Patients may receive the recommended 400 IU of vitamin D by either taking a multiple vitamin that contains 400 IU of vitamin, or taking one of the calcium preparations that contain vitamin D as described in Section 10.3.

*Administration*

For the purposes of this study, 400 IU (10  $\mu$ g) 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.

**11.4 Calcium**

*Availability*

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

*Administration*

Calcium is administered orally, in 1-3 divided doses.

*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 should receive *full supportive care*, including transfusions of blood and blood products, erythropoetin, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the CALGB C-260 Remarks Addenda.

**12.2** Patients may not receive treatment with other agents expected to alter osteoclast activity (e.g. denosumab, calcitonin, mithramycin, gallium nitrate, 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.

**12.3 During open label treatment, the following treatments are allowed:**

- Standard marketed antineoplastic therapies including antiandrogens, other hormonal agents, cytotoxic chemotherapy agents, and biologic response modifiers.
- Standard radiation therapy to extra-skeletal tumor sites.
- Corticosteroids to prevent/treat chemotherapy-induced nausea/vomiting.

**12.4 CALGB Policy Concerning the Use of Growth Factors**

The following guidelines are applicable unless otherwise specified in the protocol:

**12.4.1 Erythropoetin (EPO)**

Use of erythropoetin (EPO) is **permitted** at the discretion of the treating physician.

**12.4.2 Filgrastim (G-CSF) and sargramostim (GM-CSF)**

1. Filgrastim (G-CSF) and sargramostim (GM-CSF) treatment for patients on protocols that do not specify their use is discouraged.
2. Filgrastim and sargramostim may not be used:
  - a. to avoid dose reductions, delays or to allow for dose escalations specified in the protocol,
  - b. prophylactically because of concern about myelosuppression from prior chemotherapies
3. For the treatment of febrile neutropenia, the use of CSF's should not be routinely instituted as an adjunct to appropriate antibiotic therapy. However, the use of CSF's may be indicated in patients who have prognostic factors that are predictive of clinical deterioration such as pneumonia, hypotension, multi-organ dysfunction (sepsis syndrome) or fungal infection, as per the ASCO guidelines. Investigators should therefore use their own discretion in using the CSF's in this setting. The use of CSF (filgrastim or sargramostim) must be documented and reported on the CALGB form C-260 Remarks Addenda.
4. If filgrastim or sargramostim are used, they must be obtained from commercial sources.

### 13.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE

**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,
- surgery to bone, or
- death due to prostate cancer.

**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 part 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.

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

**13.3 Time to First Skeletal Related Event** is defined as the interval between the date of registration and the date of the first skeletal related event.

**13.4 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.

**13.5 Progressive Disease (PD)**

**13.5.1 PD is defined as disease progression despite androgen deprivation therapy; either:**

1) New bone metastases,

or

2) Biochemical (PSA) Progression: Three consecutive rises in PSA with each PSA measurement at least two weeks apart and at least one PSA value > 4.0 ng/mL. The date of PSA progression is defined as the first of the three consecutive rises in PSA,

or

3) Treatment with radiation therapy to bone while on treatment.

**13.5.2** Patients concurrently treated on the intermittent arm of SWOG 9346/CALGB 9594 should not be considered PD while off androgen deprivation therapy.

**13.6 Progression Free Survival** is defined as the interval between study registration and date of progression or death from any cause, whichever occurs first.

**13.7 Overall Survival** is defined as the interval between study registration and the date of death from any cause.

## 14.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

**14.1 Duration of Treatment:** Patients will begin open-label treatment at the time of progressive disease (as defined in Section 13.5). Patients will be treated until experiencing a skeletal-related event (SRE). (See Section 12.3 for a list of concurrent therapies allowed during open-label treatment.)

Upon experiencing an SRE, whether during the double-blinded or open label portion of the study, patients will be removed from protocol treatment and treated at the physician's discretion. (These patients may receive commercially supplied zoledronic acid, 4 mg intravenously every three weeks, at the discretion of the treating investigator.)

**Documentation of the first skeletal related event** must be submitted to the CALGB Statistical Center; including:

- **radiation therapy treatment summaries** for patients treated with radiation therapy to bone;
- **operative reports** for patients undergoing surgery to bone; or
- **radiographic reports** for other skeletal related events listed in Section 13.1. Plain radiograph, CT scan, or MRI are all acceptable forms of documentation of SRE.

If further radiologic workups are performed after the initial diagnosis of SRE, these reports should also be submitted to the CALGB Statistical Center.

**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 forms.
- Follow the patient for progression and first skeletal related event for at least 3 years after randomization and follow the patient for survival for 10 years following randomization.

## 15.0 STATISTICAL CONSIDERATIONS

**15.1 Study Design:** This is a randomized, double-blinded, placebo-controlled, phase III study. Patients will be stratified according to performance status (0-1 or 2), elevation of serum alkaline phosphatase defined as below the upper limit of the laboratory institution (yes or no), and prior skeletal related event (yes or no).

### 15.2 Statistical Considerations for the Clinical Study

**15.2.1 Endpoints:** The primary endpoint is time to first skeletal related event. Skeletal related events are defined as radiation to bone, clinical fracture, surgery to bone, and spinal cord compression and death due to prostate cancer. Because most or all subjects in this study who die from prostate cancer will experience symptomatic skeletal progression prior to death, we propose to include prostate cancer death in the definition to avoid potential under-reporting of skeletal related events (e.g., difficulty in documenting clinical fracture or spinal cord compression for men in home hospice). Time to first skeletal related event (SRE) is defined as the interval between study entry and date of the first skeletal related event. Secondary endpoints for the bisphosphonate portion of the study will be overall survival (OS), progression-free survival (PFS), and toxicity. OS is defined as the interval between randomization and death due to any cause. PFS is defined as the interval between randomization and date of progression or death due to any cause, whichever occurs first.

**15.2.3 Sample Size Determination:** The following calculations assume a total of 680 patients accrued over a 48-month period, and followed for 36 months after study closure and a one-sided alpha level of 0.05. Time to SRE is assumed to follow an exponential distribution and an accrual rate of about 14 patients per month is assumed. Four hundred and seventy skeletal related events are expected at the end of the follow-up period. The power to detect a 30% decrease in hazard rate (equivalent to an increase in median time to SRE from 30 months to 39 months) is 88%. Based on an independent study of men with bone metastases who failed primary hormonal therapy, 44% of men in the placebo group had SRE at 15 months compared to 33% of men in the zoledronic acid group. In the Zometa 039 study of men with prostate cancer metastatic to bone and disease progression after primary hormonal therapy, zoledronic acid significantly decreased the proportion of men experiencing any skeletal related event at fifteen months (44% versus 38%,  $P = 0.02$ ) and significantly increased mean time to first skeletal related event (329 days versus > 500 days,  $P = 0.011$ ). (1, 2)

#### 15.2.4 Interim Analysis:

Efficacy (time to SRE) analyses will be conducted on semiannual basis to coincide with the meetings of the CALGB Data and Safety Monitoring Board (DSMB). Under the alternative hypothesis, 470 events (skeletal related events) are expected at the end of the follow-up period. There will be eight interim analyses plus the final analysis. The first interim analysis for the SRE endpoint will be performed when 23% of the full information has occurred (approximately 30 months after study activation). Other interim analyses will be performed when 32% of the full information (about 36 months), 41% (about 42 months), 52% (about 48 months), 63% (about 54 months), 72% (about 60 months), 81% (about 66 months), 88% (about 72 months), and at 100% of the full information (about 84 months after study activation). To help ensure complete data on which to base the interim analyses, skeletal related events and deaths should be faxed to the CALGB Statistical Center no less than one week after being reported to the institution.

A group sequential test design by Emerson and Fleming (9) will be used to stop the trial early to reject the null hypothesis. Alpha levels less than 0.005 will be truncated to 0.005. Assuming the above percent information available at each look, the boundaries for stopping for superiority (time to first SRE) are: 2.58, 2.58, 2.58, 2.58, 2.269, 2.123, 2.001, 1.920 and 1.801. The z-score boundaries for stopping for futility at a fixed alpha level = 0.005 for time to first SRE are: -1.212, -0.967, -0.755, -0.525, -0.319, -0.163, -0.016, 0.092, and 1.801. Should any boundary be crossed, accrual to the study will be stopped. These rules have a negligible impact on the type I and II error rates of this trial (10). The power for the time to SRE is at least 85% and the type I error rate is 5% with this design.

**15.2.5 Data Analysis:** An intent-to-treat approach will be used in this phase III study to analyze SRE, PFS and OS. Patients who withdraw consent or withdraw from the study due to toxicity will continue to be followed for SRE and PFS, even if they begin another therapy. The Kaplan-Meier product-limit method will be used to estimate the time to SRE, OS and PFS. The log-rank test will be used to compare the two treatment arms on time to SRE, OS and PFS. Further, the Chi-square test will be used to compare the two arms on the proportion of patients with grade 3 or higher toxicity. In addition, the proportional hazards model will be used to assess the importance of the treatment arm in predicting time to SRE, adjusting on patient characteristics, intermittent therapy use, and other important covariates, such as LDH, PSA, and alkaline phosphatase.

We expect that less than 20% of the patients enrolled will have received intermittent androgen deprivation (IAD) treatment. Data on intermittent

androgen deprivation (yes or no) or continuous use will be collected every cycle on the follow-up form. The potential confounding effect of intermittent androgen therapy (including those patients enrolled on SWOG 9346) will be explored. IAD will be treated as a time-dependent covariate in the proportional hazards model.

**15.2.6. Accrual and Follow-up:** The target sample size is 680 and assuming that CALGB institutions will enroll about 14 patients/month, accrual will be completed in about 48 months. All patients will be followed for time to SRE and PFS for a maximum period of 36 months and will be followed for survival for a maximum period of 10 years following randomization.

### 15.3 Statistical Considerations for the Correlative Science Companion Study

**15.3.1 Hypothesis:** In men receiving primary hormonal therapy for metastatic prostate cancer, baseline serum concentrations of N-telopeptide, a specific marker of osteoclast activity, predicts independently overall survival and the risk of SREs.

**15.3.2 Power computations:** The primary objectives of this correlative science study are to determine the prognostic importance of serum N-telopeptide concentrations on overall survival and time to first SRE. For the power calculations, serum N-telopeptide levels will be dichotomized at the median level and patients will be classified as having either low (below or equal the median) or high (above the median) N-telopeptide levels. Because we are testing two primary hypotheses, each hypothesis will be tested with a significance level of 2.5%. Assuming that the median survival (or median time to SRE) in the low N-telopeptide group = 30 months, the power is 80% to detect a hazard ratio of 1.33. The power computations are based on the following assumptions: the survival time (and time to SRE) follows an exponential distribution, an accrual rate of 680 patients/48 months period, 36 months post-accrual follow-up, a two-sided significance level of 0.025 and the median survival in the low N-telopeptide group = 30 months.

**15.3.3 Data Analyses:** The Kaplan-Meier product-limit method will be used to estimate the OS and time to SRE by the two N-telopeptide groups. The log-rank test will be used to compare these two groups. Further, the proportional hazards model will be used to examine the effect of N-telopeptide treated as a categorical or continuous variable in univariate and multivariate analysis adjusting on other baseline factors. Because of the multiplicity of analysis and endpoints, we will use the Bonferroni correction to adjust the type I error rate. A type I error rate of 2.5% will be used for the primary analyses based on OS and time to SRE as the endpoints patients will be classified by the median N-telopeptide levels as either low or high levels. However, an alpha level = 0.01 will be used as a substitute for formal tests of significance to perform exploratory analyses (N-telopeptide levels are considered as a continuous factor in univariate or multivariate analyses). Information on N-telopeptide obtained from sequential samples (at 6 and 12 months and at open-label) will be used for exploratory analyses.

### 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 beginning April 1, 2011.

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.**

The reporting of adverse events described in the table below is in addition to and does not supplant the reporting of adverse events on study-specific adverse event forms (see Section 6.6 for required CALGB forms).

**CALGB 90202 Reporting Requirements**

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND or non-CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent

|                            | Grade 1                 | Grade 2          | Grade 2      | Grade 3                         |                         | Grade 3                       |                         | Grades 4 & 5 <sup>2</sup> | Grades 4 & 5 <sup>2</sup> |
|----------------------------|-------------------------|------------------|--------------|---------------------------------|-------------------------|-------------------------------|-------------------------|---------------------------|---------------------------|
|                            | Unexpected and Expected | Unexpected       | Expected     | Unexpected with Hospitalization | without Hospitalization | Expected with Hospitalization | without Hospitalization | Unexpected                | Expected                  |
| Unrelated Unlikely         | Not Required            | Not Required     | Not Required | 10 Calendar Days                | Not Required            | 10 Calendar Days              | Not Required            | 10 Calendar Days          | 10 Calendar Days          |
| Possible Probable Definite | Not Required            | 10 Calendar Days | Not Required | 10 Calendar Days                | 10 Calendar Days        | 10 Calendar Days              | Not Required            | 24-Hrs; 5 Calendar Days   | 10 Calendar Days          |

<sup>1</sup> Adverse events with attribution of possible, probable, or definite that occur greater 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 24-hour notification followed by complete report within 5 calendar days for:  
 • Grade 4 and Grade 5 unexpected events  
 AdEERS 10 calendar day report:  
 • Grade 3 unexpected events with hospitalization or prolongation of hospitalization  
 • Grade 5 expected events

<sup>2</sup> Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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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:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.



- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND or non-CTEP IND.
- 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 Phase 2 and 3 Trials Utilizing an Agent under a CTEP-IND or non-CTEP IND:**

- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- CALGB holds the IND for zoledronic acid for this study. The expedited reporting requirements in the table above apply to this study.
- A list of specific expected adverse events can be found in Section 11.0 (Drug Formulation, Availability and Preparation).
- AdEERS reports are to be submitted electronically (<http://ctep.info.nih.gov/reporting/adeers.html>) to the CALGB Central Office ([calgb@uchicago.edu](mailto: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).
- 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-1104.

**17.0 REFERENCES**

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**18.0 MODEL CONSENT FORM:**

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III  
STUDY OF EARLY VERSUS STANDARD ZOLEDRONIC ACID TO  
PREVENT SKELETAL RELATED EVENTS IN MEN WITH PROSTATE  
CANCER METASTATIC TO BONE**

This is a clinical trial (a type of research study). Clinical trials include only patients who choose to take part. Please take your time to make your decision. Discuss it with your friends, family, and your health care providers caring for you.

*[Attach NCI booklet "Taking Part in Clinical Trials: What Cancer Patients Need To Know"]*

You are being asked to take part in this study because you have prostate cancer 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. In addition, hormonal treatment may cause bone loss and contribute to your risk of fracture.

**WHY IS THIS STUDY BEING DONE?**

The purpose of this study is to compare the effects (good and bad) of early treatment with zoledronic acid (Zometa) compared to standard treatment with zoledronic acid.

We know that treatment with zoledronic acid decreases the risk of certain skeletal (bone) related events in men with prostate cancer AFTER the cancer has spread to the bones and continues to grow even with hormonal therapy (standard treatment). This research is being done because we do not know whether earlier treatment with zoledronic acid (started BEFORE the cancer grows with hormonal therapy) is better or worse than standard treatment.

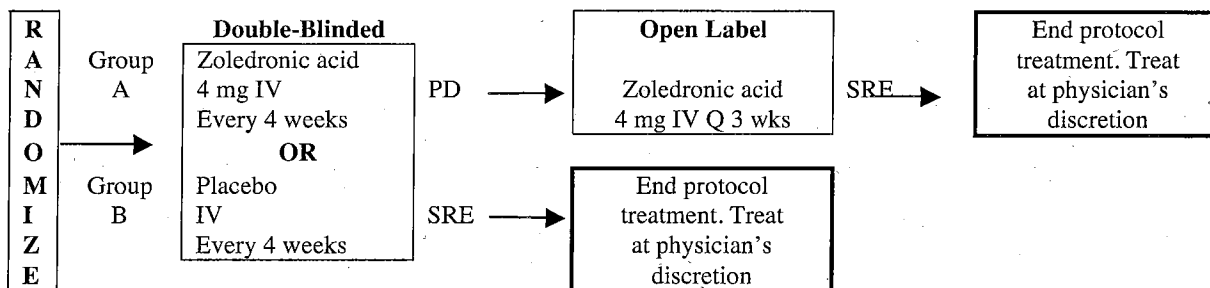
**HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?**

About 680 men will take part in this study.

## WHAT IS INVOLVED IN THE STUDY?

You will be “randomized” into one of the two study groups described below. Randomization means that you are put into a group by chance. Your assignment is chosen by a computer. You will have an equal chance of being put into either of the two groups. Neither you nor your doctor will choose or know which treatment you will receive. When neither the doctor nor the patient knows what the treatment is, this is called a “double blind” study. However, your treatment information will be available to your doctor in case of an emergency.

### Treatment Plan



**Progressive disease (PD)** is defined as new bone metastases or three consecutive rises in PSA with each PSA measurement at least two weeks apart and at least one PSA value > 4.0 ng/mL.

**Skeletal-related events (SRE)** are defined as radiation to bone, clinical fracture, surgery to bone, or spinal cord compression (see Section 13.1).

**Group A:** Men randomized to Group A will receive zoledronic acid by intravenous infusion (IV) over 15 minutes once every 4 weeks. This is done through a needle placed in a vein in your arm at the doctor’s office or an outpatient clinic.

**Group B:** Men randomized to Group B will receive placebo (salt and water) by intravenous infusion (IV) over 15 minutes once every 4 weeks. This is done through a needle placed in a vein in your arm at the doctor’s office or an outpatient clinic. The placebo contains no medication and is used to compare the effects of early treatment with zoledronic acid to no early treatment with zoledronic acid in an unbiased way. It is used so that neither you nor your doctor will know what you are receiving.

If your doctor finds evidence of cancer growth, you will stop the double-blinded part of the study and will receive “open label” zoledronic acid by intravenous infusion over 15 minutes once every 3 weeks. This means that you and doctor will no longer be “blinded” and you will know that you are receiving zoledronic acid.

If you experience a skeletal related event (bone fracture, spinal cord compression, or surgery or radiation to your bones) you will be removed from this study at which time you and your doctor will decide what treatment is best for you.

Daily calcium and vitamin D are recommended to maintain strong bones. All participants in the study will be asked to take supplemental calcium (500 mg daily) and a multivitamin containing 400 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.

- Various blood tests every few months.

You will also have the following procedures done because you are in this study:

- Blood tests every 3-4 weeks to measure your PSA and kidney functioning

Several of these tests will be repeated during the study. 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. You will need to see your health care provider every 3 or 4 weeks for the blood tests to measure your PSA and kidney functioning.

### HOW LONG WILL I BE IN THE STUDY?

We think you will receive the study treatment until you experience a skeletal related event, which may not occur for several years. After the treatment has been completed, your doctor will follow your medical condition for up to 10 years from the time you started the study.

The study doctor may decide to take you off this study if 1) continued participation is thought not to be in your medical best interest, 2) funding for the study is stopped, 3) the drug supply is insufficient, 4) health conditions occur which would make your participation possibly dangerous, 5) new information relevant to this study becomes available

You can stop participating at any time. If you choose to stop participating in the study, your medical care will not be affected in any way. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor and your health care providers caring for you first.

### WHAT ARE THE RISKS OF THE STUDY?

While on the study, you are at risk for these side effects. You should discuss these with the study doctor and/or your health care providers caring for you. There also may be other side effects that we cannot predict. Other drugs will be given to make side effects less serious and uncomfortable. Many side effects go away shortly after the intervention/drugs are stopped, but in some cases side effects can be serious, long lasting, permanent, or life-threatening. Generally, the use of zoledronic acid has mild to moderate side effects.

**Risks of Zoledronic acid**

**LIKELY:**

- Fever
- Fatigue (tiredness)
- 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
- Anorexia or loss of appetite

**LESS LIKELY:**

- Headaches
- Insomnia
- Anxiety
- Stomach irritation
- Bone, back, muscle, and joint pain
- Nausea, vomiting, constipation, and /or abdominal pain
- Low red blood cell counts which may cause tiredness, shortness of breath or fatigue
- 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.
- Abnormal heart rhythms
- Abnormal kidney function tests
- Diarrhea
- Tingling in the fingers and toes

**RARE BUT SERIOUS**

- Kidney failure
- Severe allergic reactions
- Permanent damage to the jawbone 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. In addition, zoledronic acid will stay in bones for a very long time. If you see a dentist, you should inform him or her that you have received zoledronic acid.

**Risks of Placebo**

**LESS LIKELY:**

- A reaction at the injection site, which might include pain, redness, tenderness, swelling, and/or bruising.

**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. For example, low potassium can be seen with water pills such as Furosemide and low calcium can be seen with antibiotics such as Gentamicin. In addition, you should not take calcium and tetracycline antibiotics at the same time because the calcium will lessen the effectiveness of tetracycline.

**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 can affect an unborn baby, you should not father a baby while on this study. Ask about counseling and more information about preventing pregnancy. [Include a statement about possible sterility when appropriate.]

For more information about risks and side effects, ask the study doctor or contact  
\_\_\_\_\_.

## ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other patients with prostate cancer in the future.

## WHAT OTHER OPTIONS ARE THERE?

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

- You may choose to have treatment with zoledronic acid when there is evidence of cancer growth despite hormonal therapy.
- You may choose not to receive treatment with zoledronic acid.
- You may choose to receive hormone therapy outside this study.

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

## WHAT ABOUT CONFIDENTIALITY?

Efforts will be made to keep your personal information confidential. We cannot guarantee absolute confidentiality. Your personal information may be disclosed if required by law.

Organizations that may inspect and/or copy your research records for quality assurance and data analysis include groups such as:

- The Cancer and Leukemia Group B,
- the National Cancer Institute or its authorized representatives,
- the Food and Drug Administration,
- the Clinical Trials Support Unit (CTSUS is a clinical trials mechanism sponsored by the NCI to provide greater access to phase III trials), and
- the NCI Central Institutional Review Board (CIRB), for patients enrolled at institutions for whom the CIRB is the IRB of record, and
- Novartis Pharmaceuticals Company, the makers of zoledronic acid (Zometa®).

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?

Taking part in this study will lead to added costs to you or your insurance company no matter to which group you are randomized due to the need for additional blood tests and the IV for either zoledronic acid or placebo every four weeks. While zoledronic acid or placebo will be provided free of charge by the drug company, you or your insurance company will have to pay for all other costs associated with your outpatient visits. You will also have to pay for your calcium and vitamin pills. Please ask about any expected added costs or insurance problems.

In the case of injury or illness resulting from this study, emergency medical treatment is available but will be provided at the usual charge. No funds have been set aside to compensate you in the event of injury.

You or your insurance company will be charged for continuing medical care and/or hospitalization. Medicare should be considered a health insurance provider.

You will receive no payment for taking part in this study.

You may find a National Cancer Institute guide: "Clinical Trials and Insurance Coverage - a Resource Guide" helpful in this regard. You may ask your doctor for a copy, or it is available on the world wide web at <http://cancer.gov/clinicaltrials/insurance> (and click on printable version)



Although no funds have been set aside to compensate you for injury or illness related to the study treatment or procedures, you do not give up any of your legal rights for compensation by signing this form.

## WHAT ARE MY RIGHTS AS A PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or may leave the study at any time. Leaving the study will not result in any penalty or loss of benefits to which you are entitled.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

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

## 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 NCI's **Cancer Information Service** at **1-800-4-CANCER (1-800-422-6237)** or **TTY: 1-800-332-8615**

**Visit the NCI's Web sites...**

For comprehensive clinical trials information go to <http://cancer.gov/clinicaltrials>

For accurate cancer information go to <http://cancer.gov/cancerinformation>

**You will get a copy of this form. You may also request a copy of the protocol (full study plan).**

**SIGNATURE**

I agree to take part in this study.

Participant \_\_\_\_\_ Date \_\_\_\_\_

**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

Approximately 2 additional teaspoons of blood would be collected at the beginning of the study and after 6 and 12 months and if you switch to "open label" treatment with zoledronic acid at the times when your other routine tests are done. The serum (the fluid portion of the blood in which the different blood cells are suspended) will be separated from the sample, frozen, and sent to a central laboratory for analysis.

These tests may provide additional information that will be helpful in understanding prostate cancer or response to treatment. 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 serum 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.

I agree that my blood may be used for research studies to learn about the effects that the experimental treatment may be having.

Yes  No

Participant \_\_\_\_\_ Date \_\_\_\_\_

### 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 of cancer 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.

My blood may be kept for future unknown use in research to learn about, prevent, treat, or cure cancer.

Yes  No Participant \_\_\_\_\_ Date \_\_\_\_\_

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 \_\_\_\_\_

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 \_\_\_\_\_

APPENDIX I

**PROVISIONS FOR THE USE OF ZOLEDRONIC ACID**

The agent, zoledronic acid (Zometa®), (hereinafter referred to as "Agent"), used in this protocol is provided to your institution by Novartis Pharmaceuticals Corporation (hereinafter referred to as "Collaborator").

For this study, to be conducted under the CALGB IND with the Collaborator's Agent, the following provisions apply:

1. Agent may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Neither the institution nor the investigator shall charge any third party payer or patient enrolled in the study for the Agent, nor shall the institution or investigator include the cost of such drug in any cost report to third party payers.
2. Collaborator data for Agent are confidential and proprietary to Collaborator and shall be maintained as such by the investigators. Collaborator Confidential Information includes any scientific, technical, trade or business information provided, directly or indirectly, by Collaborator which is treated by Collaborator as confidential or proprietary, which is labeled or identified as "Confidential." Confidential Information is to be used solely for the purpose of conducting the research described in the protocol. Information not disclosed in writing, or disclosed in writing and not marked as confidential at the time of disclosure shall be considered Confidential Information if reduced to written summary and marked as such within thirty (30) days of disclosure.
3. The provisions in the "Intellectual Property Option to Collaborator" terms of award modifications apply to the use of the Agent in this study. These award modifications can be found at <http://ctep.info.nih.gov/industry/ipo.html> and are included below, for ease of reference:

Institution agrees to promptly notify the NCI and "Collaborator" in writing of any inventions, discoveries or innovations made by the Institution's principal investigator or any other employees or agents of Institution, whether patentable or not, which are conceived and/or first actually reduced to practice in the performance of this study using Collaborator's Study Drug (hereinafter "Institution Inventions").

Institution agrees to grant to Collaborator: (i) a paid-up nonexclusive, nontransferable, royalty-free, world-wide license to all Institution Inventions for research purposes only; and (ii) a time-limited first option to negotiate an exclusive, world-wide royalty-bearing license for all commercial purposes, including the right to grant sub-licenses, to all Institution Inventions on terms to be negotiated in good faith by Collaborator and Institution. Collaborator shall notify Institution, in writing, of its interest in obtaining an exclusive license to any Institution Invention within six (6) months of Collaborator's receipt of notice of such Institution Invention(s). In the event that Collaborator fails to so notify Institution, or elects not to obtain an exclusive license, then Collaborator's option shall expire with respect to that Institution Invention, and Institution will be free to dispose of its interests in such Institution Invention in accordance with Institution's policies. If Institution and Collaborator fail to reach agreement within ninety (90) days, (or such additional period as Collaborator and Institution may agree) on the terms for an exclusive license for a particular Institution Invention, then for a period of six (6) months thereafter Institution shall not offer to license the

Institution Invention to any third party on materially better terms than those last offered to Collaborator without first offering such terms to Collaborator, in which case Collaborator shall have a period of thirty (30) days in which to accept or reject the offer.

Institution agrees that notwithstanding anything herein to the contrary, any inventions, discoveries or innovations; whether patentable or not, which are not Subject Inventions as defined in 35 USC 201(e),\* arising out of any unauthorized use of the Collaborator's Study drug and/or any modifications to the Study Drug, shall be the property of the Collaborator (hereinafter "Collaborator Inventions"). Institution will promptly notify the Collaborator in writing of any such Collaborator Inventions and, at Collaborator's request and expense, Institution will cause to be assigned to Collaborator all right, title and interest in and to any such Collaborator Inventions and provide Collaborator with reasonable assistance to obtain patents (including causing the execution of any invention assignment or other documents). Institution may also be conducting other more basic research using the Study Drug under the authority of a separate Material Transfer Agreement (MTA), or other such agreement with the Collaborator. Inventions arising thereunder shall be subject to the terms of the MTA, and not to this clause.

\* 35 USC(e):(e) The term "subject invention" means any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement: Provided, That in the case of a variety of plant, the date of determination (as defined in section 41(d) (FOOTNOTE 1) of the Plant Variety Protection Act (7 U.S.C. 2401(d))) must also occur during the period of contract performance.

4. *Disclaimer: Novartis provides all materials hereunder, including study compound "as is" and makes no warranty of any kind, express or implied, concerning them or their merchantability or fitness thereof for any purpose, including but not limited to noninfringement of any third party intellectual property rights. Under no circumstances shall Novartis be liable in any manner for consequential, incidental, special, or indirect damages. Any advice furnished by Novartis is given gratis and Novartis assumes no obligation or liability for the advice given or the results obtained and any such advice shall not constitute a warranty as to any matter, all such advice being given and accepted at the recipient's risk.*
5. The results of Cancer and Leukemia Group B (CALGB) studies are published by the CALGB or its investigators in accordance with the "Guidelines for CALGB Publications" contained in the CALGB Policies and Procedures.

**APPENDIX II**

**CANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES**

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

|  |   |
|--|---|
| <p><b>To submit site registration documents:</b><br/>                 CTSU Regulatory Office<br/>                 1818 Market Street, Suite 1100<br/>                 Philadelphia, PA 19103<br/>                 Phone: 1-888-823-5923<br/>                 Fax: 215-569-0206</p> | <p><b>For patient enrollments:</b><br/>                 CTSU Data Operations Center<br/>                 Phone: 1-888-462-3009<br/>                 Fax: 1-888-691-8039<br/>                 Hours: 8:00 AM – 8:00 PM Eastern Time, Monday – Friday<br/>                 (excluding holidays)<br/>                 [For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]</p> |
|--|---|

**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 6.6 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 [ctscontact@westat.com](mailto:ctscontact@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-90202 Web page on the CTSU members' area of the website (<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-90202 site registration:**

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

**Prestudy requirements for patient enrollment on CALGB-90202:**

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms, and the patient decision whether to permit use of tissue for related studies and future studies has been documented.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

**CTSU PROCEDURES FOR PATIENT ENROLLMENT (SECTION 6.2)**

**Initial Registration:**

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. 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-90202 Eligibility Checklist
    - CALGB Registration Worksheet
  3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). Registration is limited to the operating hours of the CALGB Registration Office (9 AM - 5 PM 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 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**. The CTSU registrar will access the CALGB's on-line registration system, to obtain assignment of 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 14 days of randomization.
  - Registration to the companion study for those patients who have agreed to participate will be performed at the same time as registration to the treatment study.



**CTSU Instructions for Patient Re-registration at Disease Progression:**

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that a patient re-registration 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 (include patient id #)
  - CALGB 90202 Re-Registration Eligibility Checklist
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). Re-registration is limited to the operating hours of the CALGB Registration Office (9 AM – 5 PM 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 follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility, patient eligibility and patient id is confirmed, the CTSU registrar will contact the CALGB, **within the confines of CALGB's registration hours**. The CTSU registrar will access the CALGB's on-line registration system, and re-register the patient to open-label zoledronic acid. The CTSU registrar will confirm registration by fax.

*Open-label patient specific clinical supplies of zoledronic acid will be requested by the CALGB Statistical Center at the time of re-registration and should arrive at the clinical site within 7-10 days (see Section 11.2). The use of commercial zoledronic acid in the place of study-supplied open-label drug is a protocol violation*

**DATA SUBMISSION AND RECONCILIATION**

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the CALGB-90202 Web page located on the CTSU members' area of the website (<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 Statistical Center, [see contact table and Section 6.6 of protocol] 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 (via postal mail or fax) and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

### **SPECIAL MATERIALS OR SUBSTUDIES**

1. Serum Collection for Correlative Studies (Protocol Section 6.7)
  - Patient consent must be obtained.
  - 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 website (<https://www.ctsu.org>) or by selecting Adverse Event Reporting Forms from the document center drop down list on the protocol number 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):**

Investigational agent:                      Zoledronic Acid (Zometa)

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 Forms from the document center drop down list on the CCALGB-90202 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 issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

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

#### **Health Insurance Portability and Accountability Act of 1996 (HIPAA)**

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

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

#### **Clinical Data Update System (CDS) Monitoring**

This study will be monitored by the Clinical Data System (CDS-web). Cumulative CDS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDS data collected from the study-specific case report forms.