

CLINICAL TRIALS Broadcast

In Focus: Metastatic Prostate Cancer

CALGB 90202:

A Randomized Double-Blind, Placebo-Controlled Phase III Study of Early vs Standard Zoledronic Acid to Prevent Skeletal-Related Events in Men With Prostate Cancer Metastatic to the Bone

Background

Bone metastases are present in over 80% of men with metastatic prostate cancer, and in the majority of individuals who die of prostate cancer. Pain, fractures, spinal cord compression, and myelophthisis are among the clinical manifestations of bone metastases.

Zoledronic acid is approved to treat men with prostate cancer and bone metastases with disease progression after first-line hormone therapy. The bisphosphonate zoledronic acid was found to significantly decrease the occurrence of skeletal-related events among men with prostate cancer metastatic to the bone after primary treatment with hormonal therapy.¹ As a result, the US Food and Drug Administration approved this agent for the treatment of such patients after failure of primary hormonal therapy. This placebo-controlled study of 643 patients found that zoledronic acid significantly increased the mean time to the first skeletal-related event compared with the placebo (500 vs 329 days, respectively; $P=.011$). The proportion of men experiencing any skeletal-related event at 15 months was 44% versus 33% ($P=.02$), respectively.

The role of zoledronic acid in the treatment of men with hormone-sensitive prostate cancer and bone metastases has not yet been studied. The question of whether or not this agent may be beneficial when given earlier is particularly important given the high rate of response—80%—and duration of response—approximately 18 months—to primary hormonal therapy among prostate cancer patients with bone metastases.

This phase III study will compare the efficacy of early versus delayed zoledronic acid in delaying skeletal-related events in patients with prostate cancer metastatic to the bone. Patients will be randomized to receive either zoledronic acid or placebo. Those who fail primary hor-

monal treatment prior to experiencing a skeletal-related event will receive open-label treatment with zoledronic acid. Positive findings from this study may lead to earlier administration of zoledronic acid with primary hormonal therapy as part of routine clinical practice. Alternatively, negative or neutral findings from the study would lead to standard use of zoledronic acid only in men with disease progression after primary hormone therapy and, thus, avoidance of the cost, inconvenience, and potential adverse effects of earlier treatment.

Bisphosphonates have been studied in men receiving initial androgen-deprivation therapy for metastatic prostate cancer in only one previous clinical trial (Medical Research Council Pr05).² In this study, patients receiving primary androgen-deprivation therapy plus either oral clodronate (a second-generation bisphosphonate) or placebo. Clodronate was associated with non-statistically significant improvements in the primary endpoints: skeletal disease progression or prostate cancer death. The clodronate group also had a non-statistically significant lower risk of all-cause death. Clodronate is a relatively weak bisphosphonate with poor bioavailability after oral administration. Despite these limiting factors and the small sample size of this study, the findings provide important background data for CALGB 90202, which is designed to overcome these impediments.

There are several important features of this study. The randomized design will enable clear determination of whether early administration of zoledronic acid further decreases the risk of skeletal-related events. During the blinded portion of the study, the agent will be given on a 4-week schedule; dose-finding studies suggest that efficacy will be maintained with this schedule. The open-label portion of CALGB 90202 will employ the every-3-week schedule used in the clinical trial that led to regulatory approval so that the data can be clearly compared with the best arm of the previous clinical trial. Other important elements of this study include the measurement of outcome according to skeletal-related events, treatment with zoledronic acid after disease progression or first skeletal-related event, and a substantial interval between early and delayed treatment.

References

1. Saad F, Gleason M, Murray R, et al. Zoledronic acid reduces skeletal complications in patients with hormone-refractory prostate carcinoma metastatic to bone: a randomized placebo-controlled trial. *J Natl Cancer Inst.* 2002;94:1458-1468.
2. Dearnaley DP, Sydes MR. Preliminary evidence that oral clodronate delays symptomatic progression of bone metastases from prostate cancer: first results of the MRC Pr05 trial. *Proc Am Soc Clin Oncol.* 2001;20:174a.

Objectives

- Primary: 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: To compare the effect of treatment with zoledronic acid to placebo on overall survival, progression-free survival, and toxicity in men receiving androgen deprivation therapy for metastatic prostate cancer

Eligibility Criteria

- Histologic documentation of prostate adenocarcinoma
- ≥ 1 bone metastasis by radiographic imaging
- Patients must receive androgen-deprivation therapy for treatment of prostate cancer
- No hormone therapy at any point prior to 6 months before enrollment
- Duration of prior hormone therapy of ≤ 6 months and discontinued ≤ 6 months prior to study entry

- No prior bisphosphonates or radiopharmaceuticals and ≥ 4 weeks since completion of prior radiation therapy
- Eastern Cooperative Oncology Group performance status 0–2

Targeted Accrual

680 patients (340 per treatment arm) within 4 years

Contact Information

CALGB

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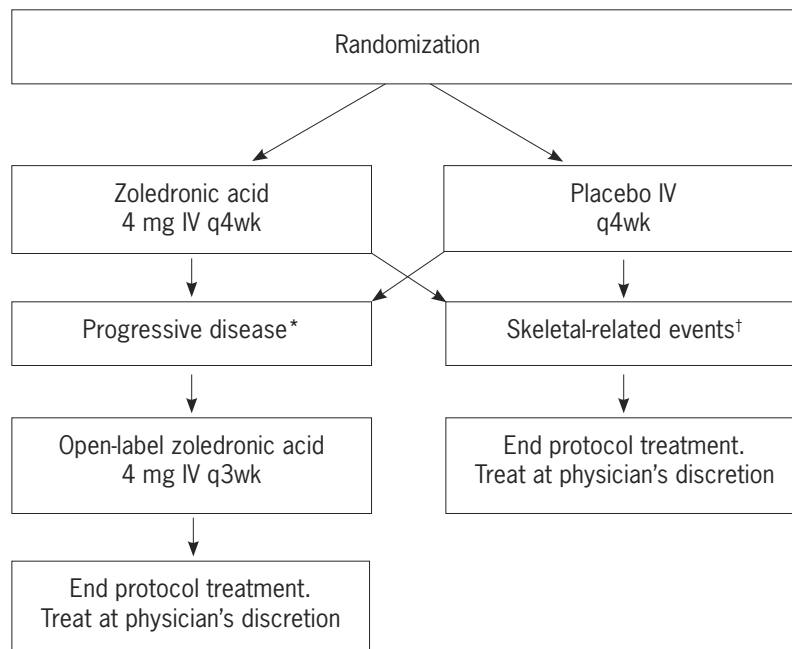
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Schema



* Progressive disease is defined as new bone metastases or three consecutive rises in prostate-specific antigen (PSA) with each PSA measurement at least 2 weeks apart and at least one PSA value >4.0 ng/mL.

† Skeletal-related events are defined as radiation to bone, clinical fracture, surgery to bone, or spinal cord compression.