# 5 Minute JournalClub

*Key SABCS Presentations*
Issue 2, 2011

# ZO-FAST Study of the Effect of Zoledronic Acid on Aromatase Inhibitor-Associated Bone Loss in Early Breast Cancer

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

The annual San Antonio Breast Cancer Symposium (SABCS) is unmatched in its significance with regard to the advancement of breast cancer treatment. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results from a plethora of ongoing clinical trials lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across all breast cancer subtypes. In order to offer optimal patient care — including the option of clinical trial participation — the practicing medical oncologist must be well informed of the rapidly evolving data sets in breast cancer. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest SABCS meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for breast cancer.

## LEARNING OBJECTIVE

- Compare the effects of immediate versus delayed therapy with zoledronic acid on bone mineral density, disease-free survival and safety for patients with Stage I to IIIA breast cancer who received letrozole for five years.

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No real or apparent conflicts of interest to disclose.

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To go directly to slides and commentary, **click here**.

On June 1, 2008, Martine Piccart-Gebhart served as the discussant for Mike Gnant's historic ASCO plenary presentation of the Austrian ABCSG-12 study documenting a disease-free survival advantage with adjuvant zoledronate (ZDA) in premenopausal women with ER-positive breast cancer. Martine's eloquent review of the topic and her explanation of the so-called "seed and soil" hypothesis made these findings even more provocative. Yet when it came down to the bottom line, she urged the audience to hold off on using bisphosphonates outside a protocol setting and to wait a few more months until another major trial, the AZURE study, was reported. Like many recent adjuvant trials, AZURE had fewer events than anticipated, and it was not until the recent San Antonio meeting, more than two years later, that Rob Coleman **presented the data** in an unplanned early analysis.

Overall, the study struck out cold (hazard ratio of 0.98 for its primary endpoint, disease-free survival), making Martine's cautious approach truly prescient. However, from the podium Dr Coleman suggested that there might be more to this story — specifically, a planned subset analysis demonstrated that the postmenopausal women in the trial (only about a third) had fewer recurrences on bisphosphonates (odds ratio of 0.76). This seems somewhat in line with the Austrian study, which was restricted to premenopausal women with suppressed ovarian function and raises the possibility that low estrogen levels in the bone microenvironment may be contributing to the benefit of ZDA. There were several other important but difficult-to-decipher aspects of these studies, including that very few of the patients on the Austrian trial received chemo, whereas more than 90 percent of those in AZURE did, and the incidence of ONJ was quite different (zero cases in the Austrian study and 17 in AZURE).

To further complicate the issue, an update of the **Austrian study** was also reported at this year's meeting and demonstrated continued improvement in DFS and OS with more follow-up (median 62 months). Similarly, the **ZO-FAST trial** — part of a trio of studies evaluating ZDA in postmenopausal women on adjuvant letrozole — was also presented in San Antonio and continued to demonstrate better bone density and slightly fewer recurrences.

Two major US cooperative group trials investigating this question have yet to report — NSABP-B-34, evaluating the oral agent clodronate, and SWOG-S0307, comparing zoledronate to clodronate to ibandronate. Although on the SWOG study all patients receive a bisphosphonate, it is worth remembering that a recently reported MRC study in multiple myeloma reported greater survival with up-front ZDA than with clodronate.

Up until now, no one has known what to do clinically about this confusing situation, and our **Patterns of Care studies** have demonstrated that approximately a quarter of oncologists have been offering adjuvant bisphosphonates to premenopausal patients off study since the data were initially presented at ASCO 2008. This has likely come to a grinding halt, closing that chapter for now with a resounding thud. But is this really the end of adjuvant bisphosphonates? Or down the road some time, might we learn that this interesting story has a very different ending?

Next up in this series, select San Antonio papers on a suddenly exciting part of the field — triple-negative breast cancer.

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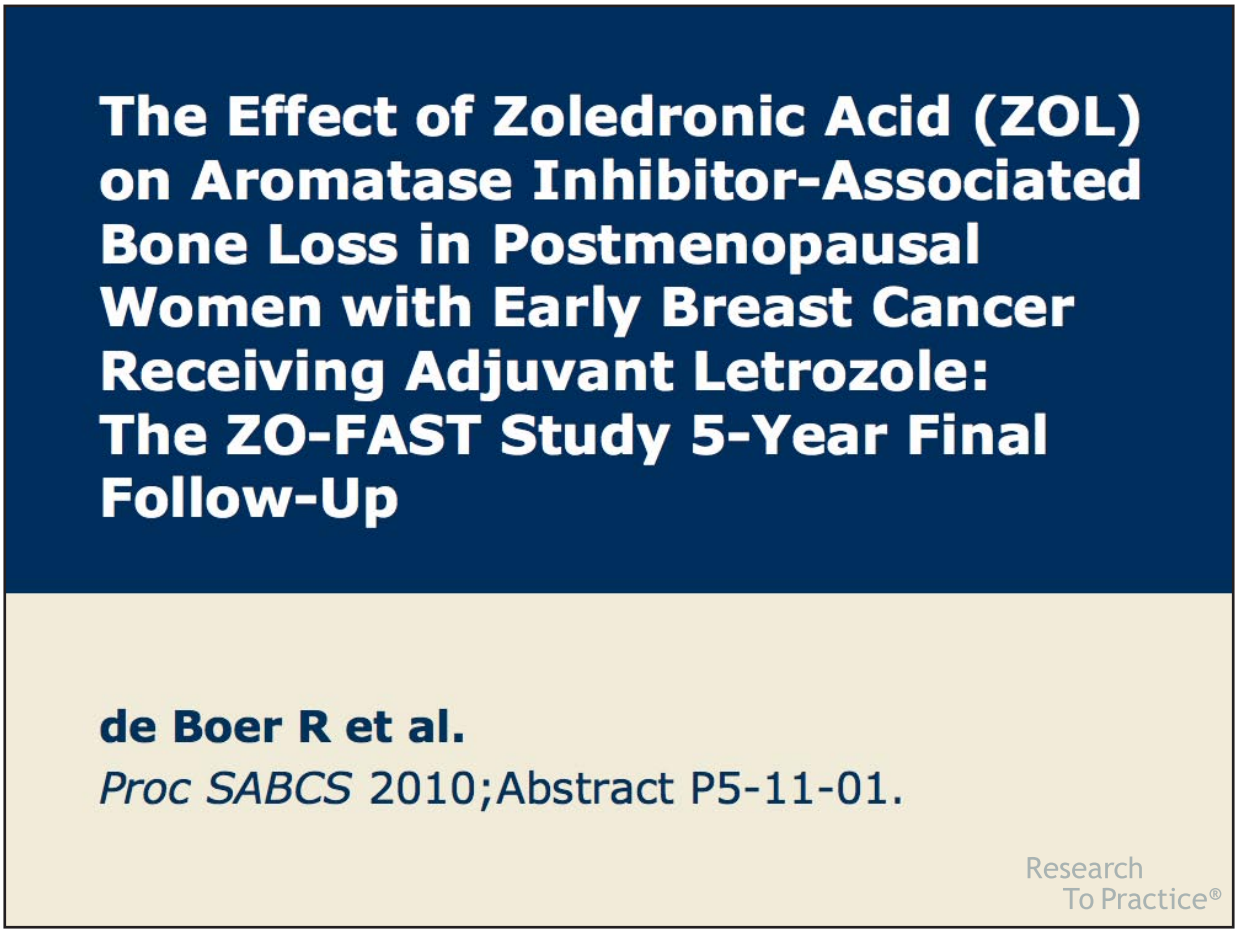
# ZO-FAST Study of the Effect of Zoledronic Acid on Aromatase Inhibitor-Associated Bone Loss in Early Breast Cancer

## Presentation discussed in this issue

deBoer R et al. **The effect of zoledronic acid on aromatase inhibitor associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole: The ZO-FAST study 5-year final follow-up.** San Antonio Breast Cancer Symposium 2010;**Abstract P5-11-01**.

## Slides from a presentation at SABCS 2010 and transcribed comments from a recent interview with Harold J Burstein, MD, PhD (12/22/10)



# Endpoints

- Primary: Percent change in lumbar spine (L2-L4) bone mineral density (BMD) at 12 months in the immediate- and delayed-treatment groups
- Secondary:
  - Lumbar spine BMD assessments at 2, 3, 4, and 5 years
  - Percentage change in total hip BMD at each assessment
  - Fractures over 3 years
  - Time to recurrence
  - Overall survival (OS)
  - Safety

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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# Eligibility

- Post-menopausal women with ER+ and/or PR+ Stage I, II, or IIIA early breast cancer (BC)
- ECOG PS ≤ 2
- Baseline lumbar-spine and total-hip T-scores ≥ -2
- Completed surgical resection
- No residual disease after completion of chemotherapy followed by radiation therapy ≤12 weeks prior
- No clinical or radiologic evidence of distant metastases
- No existing lumbar-spine or hip fracture or a history of low-intensity fractures
- No diseases known to affect bone density

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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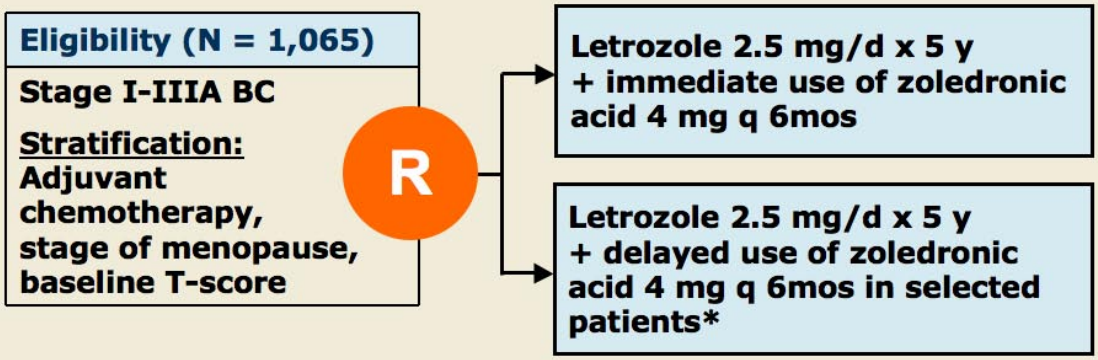
# Phase III Study Schema




* In patients with BMD T-score < −2.0; a clinical fracture; asymptomatic fracture at 36 mos

All patients also received calcium and vitamin D supplements.

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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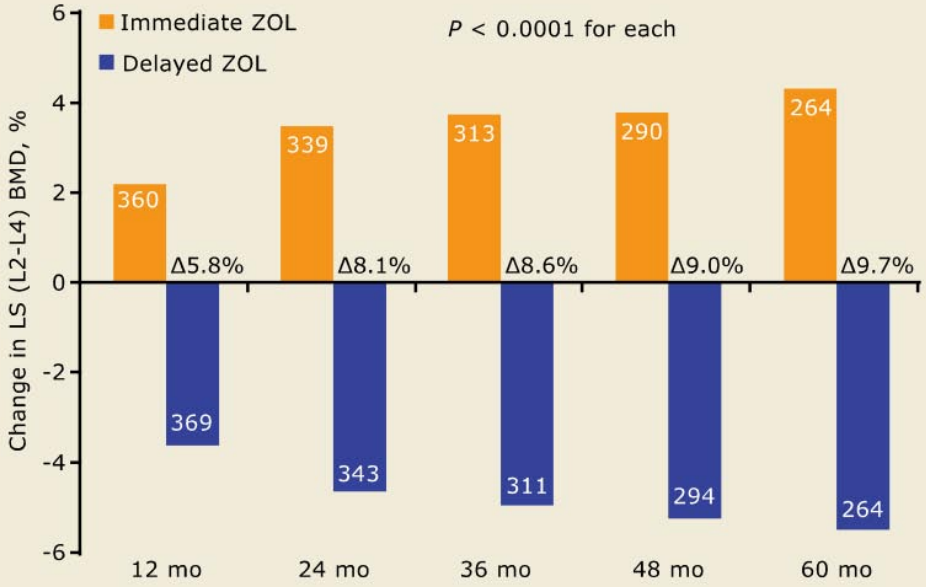
# Efficacy Results: Change in BMD




BMD = bone mineral density; LS = lumbar spine; ZOL = zoledronic acid (4 mg q 6 months)

With permission from de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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# Efficacy Results: DFS and Recurrence

| | Immediate ZOL (n = 532) | Delayed ZOL (n = 533) | HR (*p*-value) |
|---|---|---|---|
| **Disease-free survival** | 91.9% | 88.3% | 0.66 (0.0375) |
| **Disease recurrence** | | | |
| Distant | 5.5% | 8.8% | — |
| Local | 0.94% | 2.3% | |
| Total | 6.4% | 9.9% | |

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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# Adverse Events (AEs)*

| | Immediate ZOL n = 525 | Delayed ZOL n = 535 |
|---|---|---|
| Arthralgia | 49.0% | 46.9% |
| Hot flush | 29.0% | 30.5% |
| Bone pain | 18.5% | 12.1% |
| Fatigue | 17.7% | 17.8% |
| Pyrexia | 15.2% | 3.6% |
| Back pain | 15.0% | 15.1% |
| Headache | 14.5% | 12.0% |

* AE in >10% of patients in the overall safety population by treatment received; few fracture events reported, statistically similar in both arms (7.8%, immediate ZOL versus 7.1%, delayed ZOL)

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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# Adverse Events (cont'd)

| | Immediate ZOL n = 525 | Delayed ZOL n = 535 |
|---|---|---|
| Pain in extremity | 13.3% | 15.1% |
| Myalgia | 13.0% | 13.3% |
| Musculoskeletal pain | 11.0% | 8.6% |
| Hypercholesterolemia | 11.0% | 11.2% |
| Weight increase | 10.9% | 10.7% |
| Hypertension | 10.5% | 11.2% |
| Nausea | 10.3% | 10.3% |

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.



# Conclusions

- The use of immediate ZOL plus letrozole significantly reduced the rate of disease recurrence and DFS and improved BMD compared with delayed ZOL plus letrozole.
  - Mean change in lumbar spine BMD, +4.3% vs -5.4% at 5 years ($P < 0.0001$)
  - DFS, 91.9% vs 88.3% at 5 years ($P = 0.0375$)
- The differences in BMD between the immediate and delayed treatment groups were maintained over time.
- These 5-year data confirm the benefits of immediate ZOL on BMD shown at earlier time points.
- The immediate use of ZOL plus adjuvant letrozole was generally well tolerated.

de Boer R et al. *Proc SABCS* 2010;Abstract P5-11-01.

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## Investigator Commentary: Zoledronic Acid to Prevent Bone Loss in Patients Receiving an Adjuvant AI in ZO-FAST

ZO-FAST is a randomized study evaluating whether the early use of zoledronic acid versus its later use when patients became osteopenic would help prevent bone mineral density loss in women who were receiving adjuvant letrozole. In this updated analysis, the results were similar to previous reports in that the early use of zoledronic acid is associated with a greater likelihood of maintaining bone density. However, no difference was observed in the incidence of bone fracture between the early and delayed use of zoledronic acid, which is a more important endpoint for most patients. For most clinicians, the standard recommendation is to follow the WHO guidelines for the management of osteoporosis. We screen patients who are receiving aromatase inhibitors, and if the patients become osteopenic or osteoporotic then we institute effective therapy with bisphosphonates.

The ZO-FAST investigators continue to observe a small difference favoring the use of early bisphosphonate therapy in preventing breast cancer events. This observation is part of provocative literature that predated the AZURE trial, the results of which make it difficult to impart much clinical significance to this finding.

***Interview with Harold J Burstein, MD, PhD, December 22, 2010***