



Embargoed for Release:
9:45 a.m. CT, Dec. 7, 2011

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Immediate Bisphosphonate Use With Endocrine Therapy Reduced Recurrence, Increased Survival in Postmenopausal Early Breast Cancer

- Long-term data confirm overall survival benefit with zoledronic acid.
- Women five years postmenopause had greatest benefit.
- Even delayed use of zoledronic acid reduced recurrence vs. no use.

SAN ANTONIO — The addition of zoledronic acid to adjuvant endocrine therapy increased bone mineral density and reduced the risk for disease recurrence among postmenopausal women with early hormone receptor-positive breast cancer, according to new data from the ZO-FAST trial.

Richard de Boer, M.D., of the Royal Melbourne Hospital in Victoria, Australia, presented long-term data from the Zometa-Femara Adjuvant Synergy Trial (ZO-FAST) at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011.

De Boer and colleagues explored adding zoledronic acid, an intravenous bisphosphonate, to adjuvant endocrine therapy to reduce bone mineral density loss seen with aromatase inhibitors and to improve survival outcomes.

When he presented initial data from ZO-FAST at the 2010 CTRC-AACR San Antonio Breast Cancer Symposium, de Boer indicated that early zoledronic acid resulted in a significantly improved bone mineral density and an improved disease-free survival. At this year's symposium, he reported long-term data and data on the effect of menopausal status at breast cancer diagnosis on disease-free survival.

Researchers randomly assigned 1,065 patients who were about to commence letrozole, an aromatase inhibitor, to receive immediate zoledronic acid every six months or to a delayed group where zoledronic acid was started at a later time only if the patient experienced a fracture or a documented fall in bone mineral density.

After 60 months of follow-up, “the primary endpoint of the trial was successfully achieved — up-front zoledronic acid significantly decreased bone mineral density loss in both the lumbar spine and the hip,” de Boer said. “The secondary endpoint of an improvement in disease-free survival was also met with a 34 percent decrease in disease recurrence in the patients receiving the up-front zoledronic acid.”

Researchers conducted an exploratory subgroup analysis based on menopausal status at the time of breast cancer diagnosis. Data indicated that in women who were truly menopausal at diagnosis, immediate treatment with zoledronic acid reduced the risk for disease recurrence by 29 percent and improved overall survival by 35 percent.

“In addition, patients in the delayed group, who did not start with zoledronic acid but who switched to start at a later time, also appeared to benefit from the zoledronic acid with an improvement in disease outcomes compared with those women who never started the bisphosphonate,” de Boer said.

Additional studies are needed to fully define the patient populations most likely to benefit from adjuvant zoledronic acid in this setting.

Until then, “patients with hormone receptor-positive breast cancer who are postmenopausal and about to commence letrozole have the option of considering the addition of zoledronic acid — primarily to maintain bone mineral density but also with the aim of reducing the risk for disease recurrence,” de Boer said.

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The mission of the CTRC-AACR San Antonio Breast Cancer Symposium is to produce a unique and comprehensive scientific meeting that encompasses the full spectrum of breast cancer research, facilitating the rapid translation of new knowledge into better care for patients with breast cancer. The Cancer Therapy & Research Center (CTRC) at The University of Texas Health Science Center at San Antonio, the American Association for Cancer Research (AACR) and Baylor College of Medicine are joint sponsors of the San Antonio Breast Cancer Symposium. This collaboration utilizes the clinical strengths of the CTRC and Baylor and the AACR’s scientific prestige in basic, translational and clinical cancer research to expedite the delivery of the latest scientific advances to the clinic. The 34th annual symposium is expected to draw nearly 8,000 participants from more than 90 countries.

Presenter: Richard de Boer, M.D.

Abstract Number: S1-3

Title: Long-Term Survival Outcomes among Postmenopausal Women with Hormone Receptor-Positive Early Breast Cancer Receiving Adjuvant Letrozole and Zoledronic Acid: 5-Year Follow-Up of ZO-FAST.

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Introduction: Recent clinical trials suggest potential anticancer activity for bisphosphonates combined with adjuvant endocrine therapy in patients with hormone receptor-positive (HR+) early breast cancer (EBC). Data from the interim analysis of AZURE suggest that the benefits of adding zoledronic acid (ZOL) may be greatest in patients with low estrogen levels (Coleman RE, et al. SABCs 2010). In ZO-FAST, we have previously demonstrated that adding ZOL to adjuvant therapy significantly improved bone mineral density (BMD) and prolonged disease-free survival (DFS) vs delayed ZOL (de Boer R, et al. SABCs 2010). We report here the effect of time since menopause at breast cancer diagnosis (ie, baseline menopausal status) on DFS benefits with ZOL.

Methods: Postmenopausal women with HR+ EBC receiving letrozole (LET; 2.5 mg qd × 5 yr) with a BMD T-score ≥ -2 (N=1065) were randomized to ZOL (4 mg q6mo): immediate (IMZOL) or delayed (DZOL; initiated for postbaseline T-score < -2 or nontraumatic/asymptomatic fracture). Patients were followed for disease recurrence and overall survival (OS) for 5 years. Patients were eligible for the study if they had established menopause at the time of diagnosis, or if they became menopausal because of chemotherapy or ovarian suppression (ie, recently postmenopausal). The effect of baseline menopausal status on DFS was examined in Cox regression analyses.

Results: At 60 months' follow-up in the overall population (N=1065), IMZOL significantly reduced the risk of a DFS event by 34% vs DZOL (hazard ratio [HR]=0.66; 95% confidence interval [CI], 0.44-0.97; $P=.034$). In exploratory analyses of women who were postmenopausal for >5 years or >60 years old at study entry (n=670), IMZOL improved DFS (HR=0.63; 95% CI, 0.39-1.01; $P=.052$) and significantly prolonged OS (HR=0.50; 95% CI, 0.27-0.92; $P=.022$) vs DZOL. Additional subgroup analyses including patterns of breast cancer recurrence will be presented. During 5 years of treatment, osteonecrosis of the jaw (ONJ) was reported in 4/669 patients (0.6%) who received ZOL, and there was no increase in renal adverse events (AEs) in the ZOL-treated patients. Overall, AEs were consistent with the known safety profiles of both study drugs.

Conclusions: Long-term follow-up in ZO-FAST confirms the overall survival benefits of adding ZOL (4 mg q6mo) to adjuvant LET therapy for EBC. However, subset analyses suggest that women with established postmenopausal status may benefit from ZOL therapy more than others.

These results are consistent with observations in the AZURE trial, and support potentially greater ZOL benefits in a low-estrogen environment. Additional studies are needed to fully define the patient populations most likely to benefit from adjuvant ZOL in this setting.