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Media Contact:
Jeremy Moore
(215) 446-7109
Jeremy.Moore@aacr.org
In San Antonio:
(210) 582-7021

Zoledronic Acid Shows Long-Term Benefit in Survivorship for Premenopausal ER-Positive Breast Cancer

- Zoledronic acid and endocrine treatment improved survivorship in early-stage, premenopausal ER-positive breast cancer.
- Risk for recurrence decreased by 28 percent, and risk for death decreased by 36 percent.
- No patients have experienced osteonecrosis of the jaw or renal failure.

SAN ANTONIO — Researchers have proven the continuing effectiveness of treating patients with estrogen receptor-positive premenopausal breast cancer with adjuvant zoledronic acid in addition to adjuvant endocrine treatment including ovarian function suppression.

Data from the Austrian Breast & Colorectal Cancer Study Group (ABCSG-12), reported at the 2011 CTRC-AACR San Antonio Breast Cancer Symposium, held Dec. 6-10, 2011, confirmed and extended data reported at 48 months and 62 months of follow-up. Now at 84 months of follow-up, patients are experiencing drastically fewer recurrences of breast cancer and improved rates of survivorship without toxic side effects.

“We have confirmed what this trial showed initially, which was both exciting and surprising,” said Michael Gnant, M.D., professor of surgery and president of the ABCSG at the Medical University of Vienna. “The continued success of this treatment means we can intervene early and still observe persistence of the benefit of treatment.”

In the four-arm trial, researchers randomly assigned 1,803 premenopausal patients with early-stage, estrogen receptor (ER)-positive breast cancer to receive tamoxifen or anastrozole or each of these two treatments with zoledronic acid for three years. In the initial report, presented in 2008, Gnant and his colleagues reported significantly improved disease-free survival.

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The most recent long-term data, at 84 months after treatment, revealed a 28 percent reduced risk for recurrence and a 36 percent reduction in risk for death among patients treated with zoledronic acid. Also, no patients experienced osteonecrosis of the jaw or renal failure — thus, Gnant said, proving the safety of the treatment seven years later.

Researchers also found that patients aged older than 40 years with presumed complete ovarian blockade had a 34 percent reduced risk for recurrence and a 44 percent reduced risk for death. They found no significant survival benefits among patients aged younger than 40 years.

Gnant and his team said these data, considered with previously demonstrated bone-protective effects of zoledronic acid, suggest that adding zoledronic acid to adjuvant endocrine therapy including ovarian function suppression should be considered for premenopausal women with ER-positive early breast cancer.

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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: Michael Gnant, M.D.

Abstract Number: S1-2

Title: Long-Term Follow-Up in ABCSG-12: Significantly Improved Overall Survival with Adjuvant Zoledronic Acid in Premenopausal Patients with Endocrine-Receptor-Positive Early Breast Cancer.

Author Block: M Gnant¹, B Mlineritsch², G Luschin-Ebengreuth³, H Stoeger³, P Dubsky¹, R Jakesz¹, C Singer¹, H Eidtmann⁴, C Fesl⁵, W Eiermann⁶, C Marth⁷ and R Greil². ¹Medical University of Vienna, Vienna, Austria; ²Paracelsus Medical University Salzburg, Salzburg, Austria; ³Medical University of Graz, Graz, Austria; ⁴University of Schleswig-Holstein, Kiel, Germany; ⁵Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria; ⁶Red Cross Women's Hospital, Munich, Germany and ⁷Medical University of Innsbruck, Innsbruck, Austria.

Background: We have previously reported significantly improved disease-free survival (DFS) in premenopausal patients with endocrine-responsive early breast cancer receiving adjuvant zoledronic acid (ZOL) in ABCSG-12 (Gnant M, et al. *NEJM*. 2009;360:679-91). Other trials, such as ZO-FAST and the postmenopausal (>5 yr) subset analysis of AZURE, have demonstrated similar anticancer effects with ZOL. Now with >6 yr of follow-up in ABCSG-12, we report an overall survival (OS) benefit and preplanned subgroup analyses that more precisely define interactions between the ZOL benefit and patient/tumor characteristics.

Methods: Premenopausal women with endocrine-receptor-positive early stage breast cancer (N = 1,803) were randomized to ovarian function suppression with goserelin (3.6 mg q28d) and tamoxifen (TAM; 20 mg/d) or anastrozole (ANA; 1 mg/d) □ } ZOL (4 mg q6mo) for 3 yr. Endpoints included DFS and OS, both analyzed using log-rank test and Cox models.

Results: At median follow-up of 76 mo, patients receiving ZOL had a significant 27% reduction in the risk of DFS events (HR = 0.73; Cox *P* = .022) and a significant 41% reduction in the risk of death (HR = 0.59; Cox *P* = .027) vs no ZOL. Multivariate analyses showed a strong interaction between ZOL and patient age, but did not show any interactions between ZOL and ANA/TAM or any classic tumor parameter (eg, T, N, grade, ER). Among patients > 40 yr of age (n = 1,390) with presumed complete ovarian blockade, ZOL significantly reduced the risk of DFS events by 34% (HR = 0.66; Cox *P* = .014) and the risk of death by 49% (HR = 0.51; Cox *P* = .020); however, there were no significant DFS or OS benefits in patients <40 yr of age. Currently, all patients have completed 3 yr of ZOL and are in the follow-up phase with no reported cases of osteonecrosis of the jaw or renal failure. Additional analyses at a median follow-up of approximately 84 mo are planned for late 2011 and will be presented, providing additional insights into disease recurrence patterns with and without ZOL.

Conclusions: Long-term follow-up of ABCSG-12 (76 months) confirms and extends previous results seen at 48 mo and 62 mo follow-up, and suggests that anticancer benefits of adjuvant ZOL result in highly significant DFS and OS benefits mainly in patients with a low-estrogen environment (ie, ovarian suppression and age >40 yr). These results are consistent with the significant DFS and OS improvements seen in the postmenopausal (>5 yr) cohort of the AZURE trial, and suggest that both estrogen deprivation and reduction of bone-turnover-derived growth factors in the bone marrow microenvironment are needed for sufficient suppression of dormant

micrometastases. Taken together with the previously demonstrated bone-protective effects of ZOL, these DFS and OS benefits strongly suggest that adding ZOL to adjuvant endocrine therapy should be considered for premenopausal women with endocrine-receptor-positive early breast cancer.