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## Effect of Everolimus on Bone Marker Levels and Progressive Disease in Bone in BOLERO-2

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**Background** Breast Cancer Trials of Oral Everolimus 2 (BOLERO-2), a phase III study in postmenopausal women with estrogen receptor–positive breast cancer progressing despite nonsteroidal aromatase inhibitor therapy, showed statistically significant benefits with adding everolimus to exemestane. Moreover, in preclinical studies, mammalian target of rapamycin inhibition was associated with decreased osteoclast survival and activity. Exploratory analyses in BOLERO-2 evaluated the effect of everolimus on bone marker levels and progressive disease in bone.

**Methods** Patients were treated with exemestane (25 mg/day) and randomized (2:1) to everolimus (10 mg/day; combination) or placebo (exemestane only). Exploratory endpoints included changes in bone turnover marker levels vs baseline and progressive disease in bone, defined as unequivocal progression of a preexisting bone lesion or the appearance of a new bone lesion.

**Results** Baseline disease characteristics were well balanced between arms (N = 724); baseline bisphosphonate use was not (43.9% combination vs 54.0% exemestane only). At a median of 18 months of follow-up, median progression-free survival (primary endpoint) was statistically significantly longer with the combination vs exemestane only (Cox proportional hazard ratio = 0.45, 95% confidence interval = 0.38 to 0.54; log-rank, 1-sided  $P < .0001$ ). Bone marker levels at 6 and 12 weeks increased with exemestane only, as expected, but decreased with the combination. The cumulative incidence rate of progressive disease in bone was lower in the combination arm. Bone-related adverse events occurred with similar frequency in both arms (3.3% combination vs 4.2% exemestane only).

**Conclusion** These exploratory analyses suggest that everolimus has beneficial effects on bone turnover and progressive disease in bone in patients receiving exemestane for hormone receptor–positive breast cancer progressing during/after nonsteroidal aromatase inhibitor therapy.

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Maintaining bone health is of critical importance for patients with breast cancer because the disease itself, in addition to anti-cancer therapies, can adversely affect bone. Interactions between breast cancer cells and bone cells result in an intercellular signaling loop that promotes growth and spread of bone metastases (1). This destructive cycle occurs when growth factors that promote development or progression of metastases by stimulating dormant cancer cell proliferation (eg, endothelin 1 and transforming growth factor beta family members) are released from the bone matrix during bone remodeling (1). In addition, breast cancer cells can secrete factors that promote further osteolysis, thereby resulting in a vicious cycle of bone destruction and tumor growth (1). Because breast cancer often metastasizes to bone, this painful and potentially debilitating complication develops in 65% to 75% of patients with advanced breast cancer (1,2). Endocrine therapies used to

treat breast cancer also can have detrimental effects on bone health. Several local and systemic factors, including estrogen, influence normal bone homeostasis, which is maintained through a continuous remodeling process involving bone resorption by osteoclasts and formation by osteoblasts (3). However, endocrine therapies for breast cancer suppress estrogen, thereby potentially leading to subsequent bone loss (4–11).

Nonsteroidal aromatase inhibitors (ie, anastrozole and letrozole) are often the initial endocrine therapy used in patients with hormone receptor–positive breast cancer. However, the profound estrogen depletion achieved with aromatase inhibitor therapy has been associated with decreased bone mineral density and increased fracture risk (9,12–14). Exemestane is a steroidal aromatase inhibitor used to treat patients in the advanced setting whose disease has progressed on nonsteroidal aromatase

inhibitors. Although preclinical studies suggest that exemestane may have androgenic effects (15–18), the implied protective effect on bone with such activity has not been demonstrated in clinical studies. In fact, in the phase III trial reporting the efficacy of exemestane vs megestrol acetate, androgenic adverse events of all grades and causes were not reported because they occurred in only 1% or less of the study population (18,19). Furthermore, exemestane also has been associated with increases in bone resorption and formation marker levels (4,6,8) and higher fracture rates vs tamoxifen or placebo (20).

Everolimus is an oral inhibitor of mammalian target of rapamycin (mTOR), a serine–threonine kinase that regulates cell growth, angiogenesis, and survival (21). Notably, everolimus recently was approved by the US Food and Drug Administration for treating patients with hormone receptor–positive advanced breast cancer progressing during/after nonsteroidal aromatase inhibitor therapy, based on interim analysis from the BOLERO-2 trial (22). Activation of the mTOR signaling pathway is a key adaptive change associated with endocrine resistance (23–27). Moreover, preclinical evidence also indicates that mTOR signaling is involved in osteoclast survival and osteoblast differentiation (28), and mTOR pathway inhibition has been shown to decrease bone resorption in animal models (29,30). Preclinical studies using mouse models have shown that mTOR inhibition decreases osteoclast maturation and increases osteoclast apoptosis (29). Furthermore, rat studies have shown that everolimus treatment decreases bone loss associated with estrogen deprivation (30). Together, these studies provide the rationale for examining the bone effects of everolimus in patients with advanced breast cancer.

Previous reports from BOLERO-2 showed that adding everolimus to exemestane treatment statistically significantly improved progression-free survival (PFS) in postmenopausal women with hormone receptor–positive breast cancer progressing on prior nonsteroidal aromatase inhibitor therapy (31–33). The objectives of the current exploratory analyses from BOLERO-2 are to evaluate the effects of everolimus plus exemestane vs exemestane only on bone marker levels and progressive disease in bone in patients with advanced breast cancer progressing during or after nonsteroidal aromatase inhibitor therapy.

## Methods

### BOLERO-2 Study Design

Breast Cancer Trials of Oral Everolimus 2 (BOLERO-2) (ClinicalTrials.gov identifier NCT00863655) (34) is an international, phase III, multicenter, randomized, double-blind, placebo-controlled trial designed by the academic investigators and representatives of the sponsor, Novartis. The protocol has been described previously (31). See [Supplementary Methods](#) (available online) for additional study details.

**Patient Population.** Patients were postmenopausal women with metastatic or locally advanced, estrogen receptor–positive, human epidermal growth factor receptor 2 nonamplified breast cancer that was not amenable to curative surgery or radiotherapy and that was progressing despite prior letrozole or anastrozole therapy. Other eligibility criteria have been described previously (31).

The institutional review board at each participating center approved the study, and it was conducted in accordance with Good Clinical Practice principles, the Declaration of Helsinki, and applicable local regulations. A steering committee supervised the conduct of the study, and an independent data and safety monitoring committee performed semiannual safety reviews and reviewed interim efficacy results. All patients provided written informed consent. Subset analyses by race/ethnic group were completed, as described previously (31,33).

**Treatment and Dose Modification.** Patients received exemestane (25 mg/day) and were randomly assigned (2:1) to receive everolimus (10 mg/day; combination arm) or placebo (exemestane-only arm) daily. Stratification and dose adjustments were performed as described previously (31).

**Efficacy and Safety Assessments.** The primary endpoint was PFS, defined as time from randomization to first documentation of progressive disease as assessed by the local investigator according to Response Evaluation Criteria in Solid Tumors (35) or death from any cause for patients without progressive disease, whichever occurred first.

### Bone Marker Assessments

Percentage change for bone-specific alkaline phosphatase (BSAP), amino-terminal propeptide of type 1 collagen (P1NP), and C-terminal cross-linking telopeptide of type 1 collagen (CTX) at 6 and 12 weeks vs baseline (investigator assessed) was a protocol-specified exploratory endpoint. The bone markers chosen allowed assessment of osteoclast metabolism (BSAP), bone formation (P1NP), and bone resorption (CTX). Blood samples (8.5 mL, fasting preferred) were collected at baseline and 6 and 12 weeks (visits 5 and 6) after treatment initiation. Specimen collection methods were consistent across study visits. See [Supplementary Methods](#) (available online) for additional details.

### Exploratory Analyses for Progressive Disease in Bone

Cumulative incidence of progressive disease in bone (investigator assessed) was compared between the two arms as ad hoc exploratory analyses. Progressive disease in bone (first documented progression event in bone, with or without concurrent progression outside of bone) was defined as unequivocal progression of a preexisting bone lesion or the appearance of a new bone lesion at the time of documented progressive disease. A bone scan or skeletal survey was performed at baseline, within 6 weeks before randomization. Patients with bone metastases identified at baseline also were assessed by x-ray, computed tomography scan with bone windows, or magnetic resonance imaging before randomization and every 6 weeks thereafter using the same modality until disease progression or new anticancer therapy was started. Additional bone scans or skeletal surveys were performed if clinically indicated per the local investigator's discretion.

### Statistical Analyses

For the primary endpoint of PFS, hazard ratios (HRs) and associated 95% confidence intervals (CIs) were estimated using a stratified Cox regression model (1-sided *P* value, 2.5% significance

level) as described previously (31); additional details are available in the [Supplementary Methods](#) (available online). Differences in percentage change in bone turnover marker levels from baseline are exploratory; all *P* values are two-sided, with *P* less than .05 considered statistically significant.

Differences in progressive disease in bone event rates between treatment groups were evaluated using Gray's test to compare cumulative incidence curves (see [Supplementary Methods](#), available online, for additional details) and to check for equality of incidence across groups (36,37). *P* values are two-sided, with *P* less than .05 considered statistically significant.

## Results

### Patient Characteristics

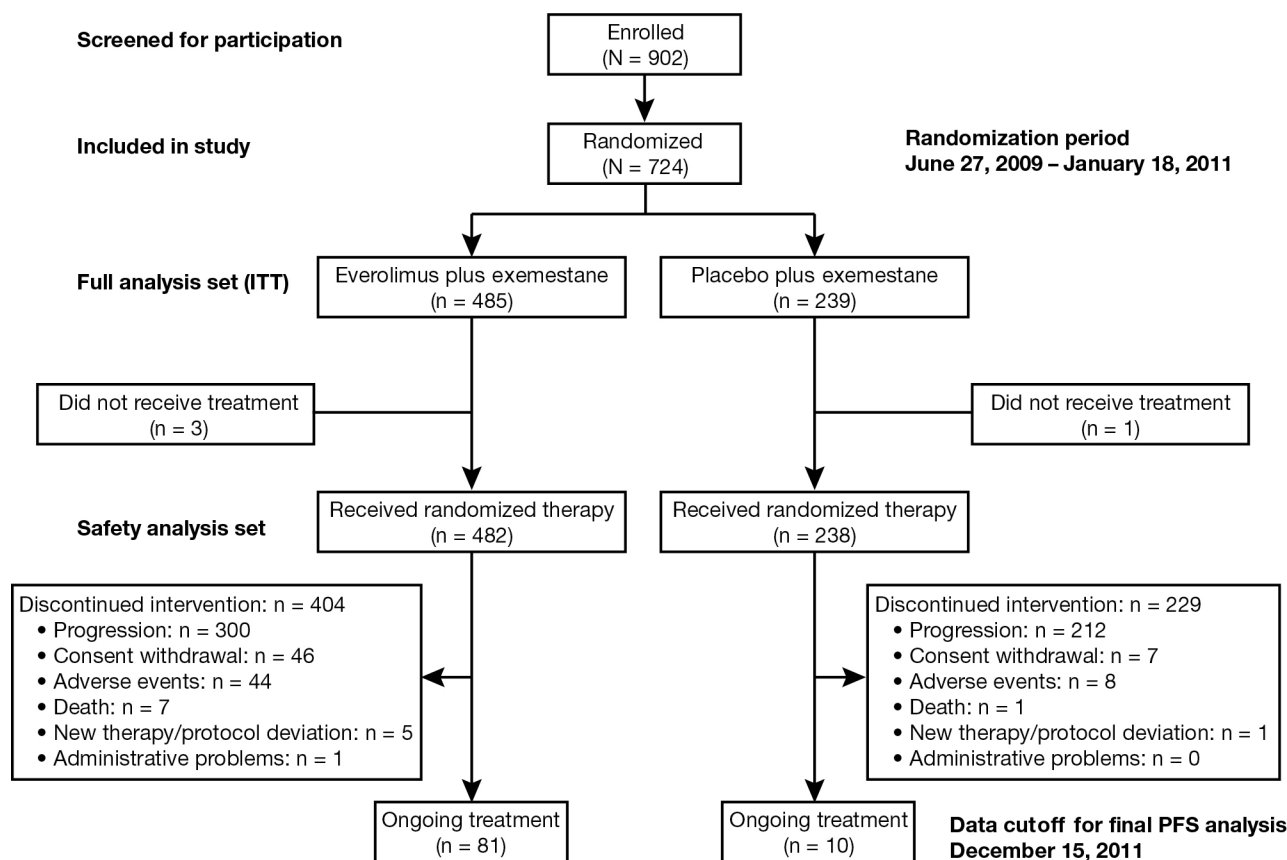
A total of 724 patients (intent-to-treat population) receiving exemestane were randomly assigned to also receive everolimus (*n* = 485; combination arm) or placebo (*n* = 239; exemestane-only arm) from June 2009 to January 2011 ([Figure 1](#)). Median duration of follow-up for bone-related analyses (cutoff date December 15, 2011) was 18 months. Median treatment exposures to exemestane were 29.5 and 14.1 weeks for the combination and exemestane-only arms, respectively; median exposure to everolimus was 23.9 weeks. Baseline patient disease characteristics were well balanced between treatment groups, including median age (61 years) and presence of bone metastases at baseline (76.5% in the combination arm

and 77.4% in the exemestane-only arm) ([Table 1](#)). However, baseline bisphosphonate use was less frequent in the combination arm (43.9%) vs the exemestane-only arm (54.0%). Types of bisphosphonates used at baseline in the combination and exemestane-only arms included zoledronic acid (29.3% vs 33.6%), pamidronate (6.2% vs 6.7%), ibandronate (4.8% vs 6.3%), and clodronate (1.7% vs 3.8%).

### Efficacy

**Progression-Free Survival.** Efficacy results have been reported previously for BOLERO-2 (33). By local assessment (primary endpoint), median PFS at 18 months of follow-up was more than twice as long for the combination arm vs the exemestane-only arm (Cox proportional HR = 0.45, 95% CI = 0.38 to 0.54; *P* < .0001, log-rank, 1-sided). Central assessment confirmed these results (33).

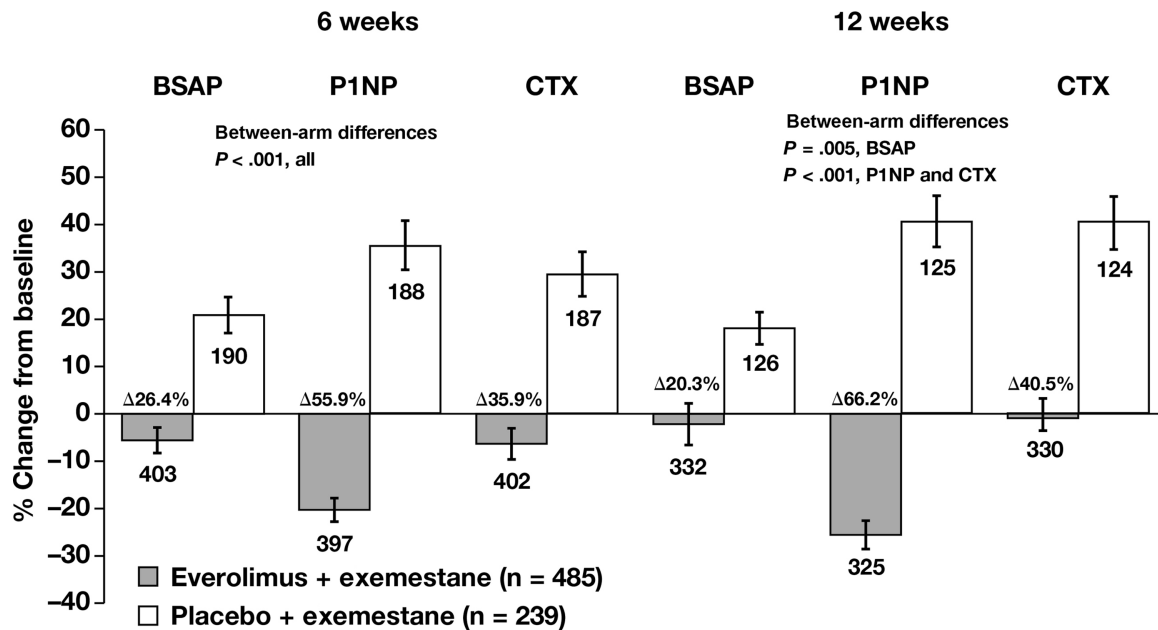
**Bone Marker Assessments.** In the overall patient population, bone marker (BSAP, P1NP, and CTX) levels increased at 6 and 12 weeks relative to baseline in the exemestane-only arm, as expected from prior observations ([Figure 2](#)). In contrast, adding everolimus to exemestane in the combination arm decreased bone marker levels at 6 and 12 weeks relative to baseline ([Figure 2](#)), with statistically significant differences in changes from baseline to week 6 between treatment arms (26.4% for BSAP, 55.9% for P1NP, and 35.9% for CTX; *P* < .001 for all; *n* = 593 evaluable patients at week 6). Data at 12 weeks demonstrated similar trends, with differences in changes from baseline to week 12 between treatment arms of



**Figure 1.** Breast Cancer Trials of Oral Everolimus 2 (BOLERO-2) trial flow diagram showing design, enrollment, and outcome. ITT = intent-to-treat population; PFS = progression-free survival.

**Table 1.** Baseline bone metastases and bisphosphonate use

Baseline characteristics	Everolimus + exemestane	Placebo + exemestane
Overall population, No. (%)	n = 485	n = 239
Baseline bone metastases	371 (76.5)	185 (77.4)
Baseline bisphosphonate use	213 (43.9)	129 (54.0)
Presence of bone metastases at baseline in patients, No. (%)	n = 371	n = 185
With baseline bisphosphonate use	199 (53.6)	121 (65.4)
Without baseline bisphosphonate use	172 (46.4)	64 (34.6)
Rates of bisphosphonate use at baseline in patients, No. (%)	n = 213	n = 129
With baseline bone metastases	199 (93.4)	121 (93.8)
Without baseline bone metastases	14 (6.6)	8 (6.2)



**Figure 2.** Changes in bone turnover marker levels at 6 and 12 weeks vs baseline in the overall population. The percentage change in bone turnover marker levels was calculated from the differences at 6 and 12 weeks vs baseline (investigator-assessed, protocol-specified exploratory endpoint). Blood samples (8.5 mL, fasting preferred) were collected at baseline and at 6 and 12 weeks (visits 5 and 6) after treatment initiation. Serum bone-specific alkaline phosphatase (BSAP) was measured with an immunochemiluminescence assay using the Ostase reagent on

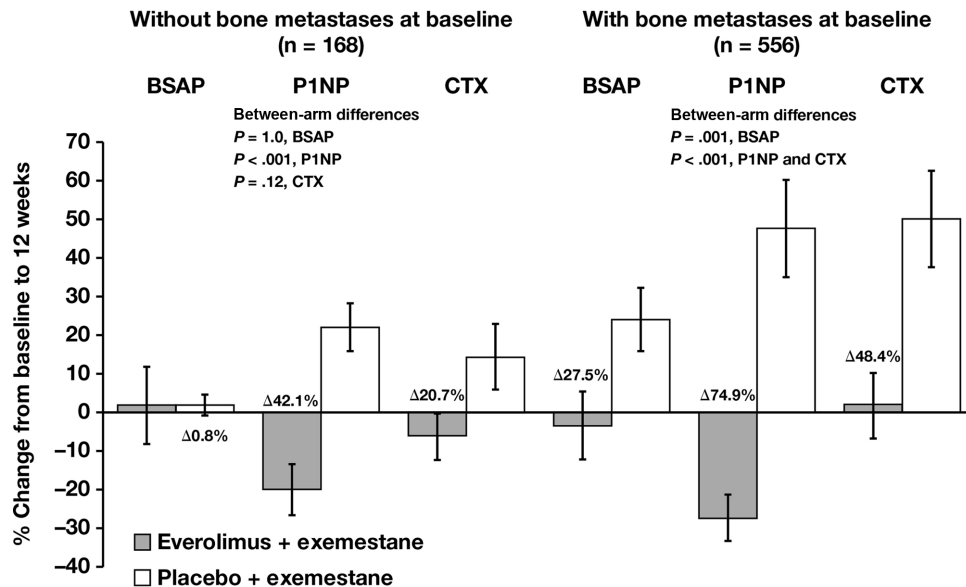
an automatic analyzer. Serum amino-terminal propeptide of type 1 collagen (P1NP) was measured with a two-site immunoassay using monoclonal antibodies against purified human P1NP to detect both intact monomeric and trimeric forms, but not fragments. Serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) was measured with a two-site assay using monoclonal antibodies against an eight amino acid sequence from the C-telopeptide of human type 1 collagen. Error bars are standard error of the mean. *P* values are two-sided.

20.3% for BSAP ( $P = .005$ ), 66.2% for P1NP ( $P < .001$ ), and 40.5% for CTX ( $P < .001$ ).

The reductions in bone marker levels reported in the combination arm were observed irrespective of the presence of bone metastases (Figure 3). Notably, in patients with bone metastases at baseline ( $n = 556$ ), bone marker levels were markedly lower in the combination arm vs the exemestane-only arm, with differences in the change from baseline to week 12 between treatment arms of 27.5% for BSAP ( $P = .001$ ), 74.9% for P1NP ( $P < .001$ ), and 48.4% for CTX ( $P < .001$ ). Additionally, in patients with baseline bone metastases, the reduction in bone marker levels observed in the combination arm occurred despite less frequent baseline bisphosphonate use (55.2%) vs the exemestane-only arm (66.9%). Although the group of patients without bone metastases at baseline was much smaller ( $n = 168$ ), the differences in bone marker level changes from baseline to week 12 between treatment arms

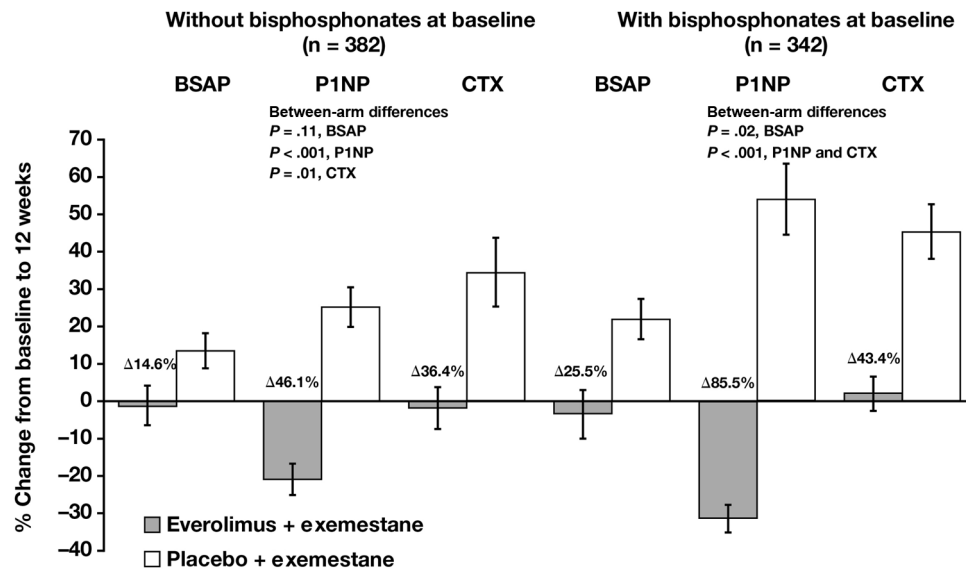
were still notable (stable BSAP:  $P = 1.0$  [not statistically significant]; 42.1% P1NP:  $P < .001$ ; and 20.7% CTX:  $P = .12$  [not statistically significant]) within this group.

The influence of bisphosphonate use on bone marker level changes was also examined in both treatment arms. At 12 weeks, bone marker levels were lower in the combination arm vs the exemestane-only arm, and differences in changes from baseline to week 12 between treatment arms at this timepoint were consistent with possibly larger differences in patients who received baseline bisphosphonates ( $n = 342$ ; 25.5% BSAP:  $P = .02$ ; 85.5% P1NP:  $P < .001$ ; 43.4% CTX:  $P < .001$ ) vs those who did not ( $n = 382$ ; 14.6% BSAP:  $P = .11$  [not statistically significant]; 46.1% P1NP:  $P < .001$ ; 36.4% CTX:  $P = .01$ ) (Figure 4). Although baseline bisphosphonate use was not balanced between treatment arms (43.9% combination vs 54.0% exemestane only), the beneficial effects of everolimus on bone marker levels were observed regardless of baseline bisphosphonate use.



**Figure 3.** Changes in bone turnover marker levels at 12 weeks vs baseline in patients with or without bone metastases at baseline. The percentage change in bone turnover marker levels was calculated from the difference at 12 weeks vs baseline for patients with or without bone metastases at baseline. Blood samples (8.5 mL, fasting preferred) were collected at baseline and at 6 and 12 weeks (visits 5 and 6) after treatment initiation. Serum bone-specific alkaline phosphatase (BSAP) was measured with an immunochemiluminescence assay using the Ostase

reagent on an automatic analyzer. Serum amino-terminal propeptide of type 1 collagen (P1NP) was measured with a two-site immunoassay using monoclonal antibodies against purified human P1NP to detect both intact monomeric and trimeric forms, but not fragments. Serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) was measured with a two-site assay using monoclonal antibodies against an eight amino acid sequence from the C-telopeptide of human type 1 collagen. Error bars are standard error of the mean. *P* values are two-sided.



**Figure 4.** Changes in bone turnover marker levels at 12 weeks vs baseline in patients with or without bisphosphonate use at baseline. The percentage change in bone turnover marker levels was calculated from the difference at 12 weeks vs baseline for patients with or without baseline bisphosphonate use. Blood samples (8.5 mL, fasting preferred) were collected at baseline and at 6 and 12 weeks (visits 5 and 6) after treatment initiation. Serum bone-specific alkaline phosphatase (BSAP) was measured with an immunochemiluminescence assay using the Ostase

reagent on an automatic analyzer. Serum amino-terminal propeptide of type 1 collagen (P1NP) was measured with a two-site immunoassay using monoclonal antibodies raised against purified human P1NP to detect both intact monomeric and trimeric forms, but not fragments. Serum C-terminal cross-linking telopeptide of type 1 collagen (CTX) was measured with a two-site assay using monoclonal antibodies against an eight amino acid sequence from the C-telopeptide of human type 1 collagen. Error bars are standard error of the mean. *P* values are two-sided.

**Progressive Disease in Bone.** The proportion of PFS events (progressive disease and death before progression) as reported by the investigator was 63.9% in the combination arm and 83.7% in the exemestane-only arm (Table 2). Progressive disease occurred in 60.6% (combination arm) vs 82.8% of patients (exemestane-only

arm). Progressive disease in bone occurred in 13.0% (combination arm) vs 18.8% of patients (exemestane-only arm). Rates of overall progressive disease and progressive disease in bone were similar in patients with baseline bone metastases (64.4% combination arm vs 81.6% exemestane-only arm; HR = 0.43, 95% CI = 0.35 to 0.53)

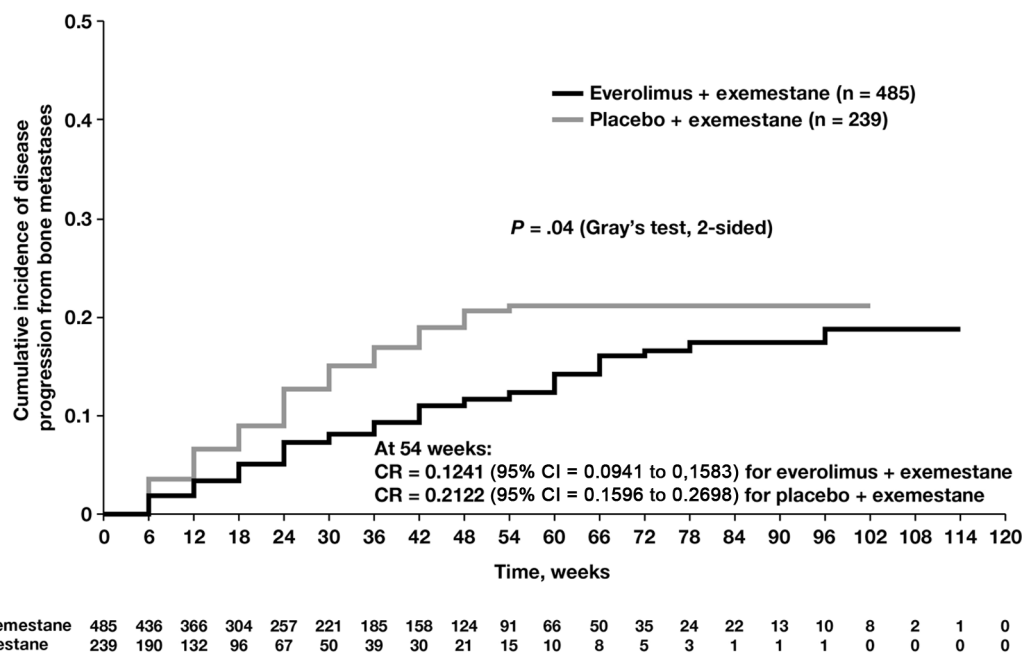


**Table 2.** Summary of progression-free survival

Characteristics	Everolimus + exemestane	Placebo + exemestane
Overall population, No. (%)	n = 485	n = 239
Total number of PFS events*	310 (63.9)	200 (83.7)
Deaths before progression	16 (3.3)	2 (0.8)
Progressive disease	294 (60.6)	198 (82.8)
Progressive disease in bone†	63 (13.0)	45 (18.8)
Patients with baseline bone metastases, No. (%)	n = 371	n = 185
Progressive disease	239 (64.4)	151 (81.6)
Progressive disease in bone†	60 (16.2)	43 (23.2)
Patients with baseline bisphosphonate use, No. (%)	n = 213	n = 129
Progressive disease	141 (66.2)	108 (83.7)
Progressive disease in bone†	33 (15.5)	30 (23.3)

\* Includes deaths before progression (n = 16 [3.3%] combination arm and n = 2 [0.8%], exemestane-only arm). PFS = progression-free survival.

† Defined as the first documented progression event; includes patients with concurrent progression in and outside of bone.



**Figure 5.** Progressive disease in bone in the overall population (N = 724). Progressive disease in bone (first documented progression event in bone, with or without concurrent progression outside of bone) was defined as unequivocal progression of a preexisting bone lesion or the appearance of a new bone lesion at the time of documented

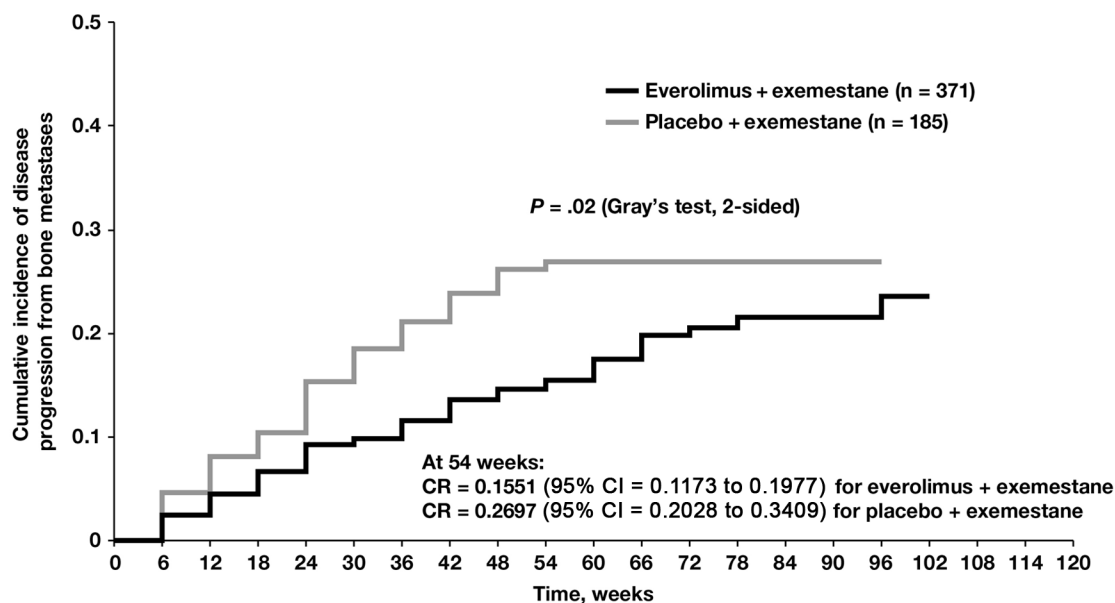
progressive disease as assessed by the investigator at the local site. Comparison of cumulative incidence of progression due to bone metastasis using competing risk methods by treatment;  $P = .04$  (Gray's test, 2-sided). CI = confidence interval; CR = competing risk estimate.

or baseline bisphosphonate use (66.2% combination arm vs 83.7% exemestane-only arm; HR = 0.41; 95% CI = 0.31 to 0.52) as in the overall patient population (Table 2).

Progression in bone (ie, progression of preexisting bone lesions or development of new bone lesions) was statistically significantly lower in the combination arm vs the exemestane-only arm ( $P = .04$ , Gray's test) in the overall patient population (N = 724) (Figure 5). Differences in the incidence of progressive disease in bone became evident between the treatment arms by week 12, with a lower cumulative incidence rate of progressive disease in bone for the combination arm (3.5%) vs the exemestane-only arm (6.6%) in the overall population. Progressive disease in bone remained nearly twofold lower in the combination arm vs the exemestane-only arm through week 30 (8.1% vs 15.0%, respectively), and similar trends

continued beyond 30 weeks. Notably, concomitant bisphosphonate use during the study continued to be less frequent in the combination arm (52.5%) vs the exemestane-only arm (58.8%).

**Progressive Disease in Bone in Patients With Bone Metastases at Baseline.** Patients with baseline bone metastases (n = 556) had higher rates of on-study bone disease progression vs the overall population; nonetheless, incidence rates for progressive disease in bone remained lower with the combination of everolimus plus exemestane versus exemestane only (Figure 6) ( $P = .02$ , Gray's test) in this subset (4.5% vs 8.1%, respectively, at week 12). Again, the difference in incidence rates of progressive disease in bone remained nearly twofold lower in the combination arm through week 30 vs the exemestane-only arm (9.9% vs 18.5%, respectively). Similar



Patients at risk	
Everolimus + exemestane	371 327 278 230 200 172 144 122 95 69 50 35 25 15 13 8 6 5 0 0 0
Placebo + exemestane	185 135 91 69 47 36 26 20 13 10 5 3 3 2 1 1 1 0 0 0 0

**Figure 6.** Progressive disease in bone in the subgroup of patients with bone metastases at baseline (n = 556). Progressive disease in bone (first documented progression event in bone, with or without concurrent progression outside of bone) was defined as unequivocal progression of a preexisting bone lesion or the appearance of a new bone lesion at the

time of documented progressive disease as assessed by the investigator at the local site. Comparison of cumulative incidence of progression due to bone metastasis using competing risk method by treatment for subgroup of patients who had bone metastasis at baseline;  $P = .02$  (Gray's test, 2-sided). CI = confidence interval; CR = competing risk estimate.

trends continued beyond 30 weeks. These data suggest that everolimus in the combination arm delayed the worsening of existing bone lesions in addition to delaying the development of new bone lesions.

### Safety

The general safety profile from the BOLERO-2 study has been reported previously (33). Briefly, the most common adverse events were stomatitis, rash, fatigue, diarrhea, decreased appetite, nausea, decreased weight, and cough (33). Grade 3/4 adverse events were uncommon and manageable. Thus, the safety profile for the addition of everolimus to exemestane in the combination arm was manageable and consistent with prior experience with mTOR inhibitors in the oncology setting (38).

Bone-related adverse events included fractures, osteonecrosis (of the jaw or at other sites), and osteoporosis (Table 3). Rates of bone-related adverse events were low and largely similar across treatment arms (3.3% combination arm vs 4.2% exemestane-only arm). Notably, fewer fractures were reported in the combination arm vs the exemestane-only arm (2.3% vs 3.8%, respectively). No grade 3/4 fractures were reported in the combination arm, whereas four grade 3 events (1 pathologic fracture, 2 femur fractures, 1 hip fracture) were reported in the exemestane-only arm. Osteonecrosis of the jaw occurred in 0.4% of patients in both treatment arms.

### Discussion

These exploratory analyses from BOLERO-2 suggest that adding everolimus to exemestane reduces the incidence of progressive disease in bone in postmenopausal women with advanced breast

cancer progressing despite nonsteroidal aromatase inhibitor therapy. Moreover, the overall incidence of bone-related adverse events was low (<5%) and similar across treatment arms. These results are consistent with the overall improvement in PFS observed in the primary analyses of this study (31,33). These data also suggest that everolimus might protect bone by reducing bone turnover and the rate at which breast cancer metastasizes to bone, thereby potentially reducing progressive disease in bone and improving patients' quality of life by mitigating painful debilitating complications.

Preclinical studies suggest that, in addition to inhibiting the mevalonate pathway, nitrogen-containing bisphosphonates may be associated with inhibiting the phosphatidylinositol 3-kinase/AKT/mTOR pathway (28,39,40). Furthermore, the combination of bisphosphonates and everolimus in human breast cancer or mouse osteosarcoma cells inhibits mTOR signaling to a greater extent than either agent alone (39,40). Although these preclinical data are intriguing and the beneficial effects of everolimus on bone marker levels were observed regardless of the imbalance in baseline bisphosphonate use (43.9% combination arm vs 54.0% exemestane-only arm), no definite conclusions about a potential interaction between bisphosphonates and everolimus can be drawn from the current subset analysis from BOLERO-2.

Previous studies have shown that exemestane therapy is associated with increased levels of bone resorption and bone formation markers (4,6,9,41). Preclinical data suggest that adding everolimus to exemestane in the combination arm could lead to a decrease in bone resorption marker levels. In fact, the exemestane-only arm showed a substantial increase in bone resorption (ie, CTX) and formation (ie, P1NP) marker levels at weeks 6 and 12 vs baseline



**Table 3.** Bone-related adverse events

Adverse event	Patients, No. (%)			
	Everolimus + exemestane (n = 482)		Placebo + exemestane (n = 238)	
	All grades	Grade 3†	All grades	Grade 3†
Any	16 (3.3)	0	10 (4.2)	4 (1.7)
Fractures				
Pathologic	0	0	3 (1.3)	1 (0.4)
Femur	0	0	2 (0.8)	2 (0.8)
Hip	0	0	1 (0.4)	1 (0.4)
Rib	7 (1.5)	0	1 (0.4)	0
Spinal	1 (0.2)	0	0	0
Spinal compression	2 (0.4)	0	0	0
Wrist	1 (0.2)	0	0	0
Pubis	0	0	1 (0.4)	0
Osteonecrosis	2 (0.4)	0	0	0
Osteonecrosis of the jaw*	2 (0.4)	0	1 (0.4)	0
Osteoporosis	2 (0.4)	0	0	0

\* One of 3 patients who developed osteonecrosis of the jaw had received bisphosphonate treatment.

† No grade 4 events were recorded.

in BOLERO-2. In contrast, in the combination arm there was a decrease in these bone marker levels at weeks 6 and 12 vs baseline, and the effects of everolimus were not influenced by baseline bisphosphonate use. The increase in bone marker levels observed in the exemestane-only arm suggests higher rates of bone turnover with exemestane therapy alone and is potentially consistent with earlier reports in postmenopausal women with breast cancer receiving adjuvant exemestane (4–8). These results suggest that everolimus may exert a protective effect on bone, potentially ameliorating negative effects on bone health associated with exemestane therapy.

Inhibiting the mTOR pathway with everolimus may have beneficial effects on bone metabolism, resulting in reduced bone resorption and contributing to a bone-sparing effect. Additionally, the observed reduction of progressive disease in bone with everolimus, including delaying progression of existing bone lesions, could be the net result of several mechanisms (eg, anticancer effect on bone metastases consistent with the overall substantial improvement in PFS and/or direct effects of mTOR inhibition on osteoclast survival and subsequent bone resorption) (28–30,42–44). However, translation of these findings to a definitive clinical benefit cannot be established on the basis of this single trial alone.

Because this report is a bone subset analysis from a large, randomized phase III study, it has some limitations. First, details from the local investigator of factors (eg, pain) used to determine whether additional imaging was clinically relevant were not recorded. Having this information would help clarify and improve interpretation of this subset analysis. Second, the relatively short follow-up duration (18 months) for assessing bone metastases in patients with hormone receptor-positive advanced breast cancer could limit broad interpretation. Subsequent analyses at later follow-up will improve the relevance of the current findings. However, the data from this subset analysis remain compelling and suggest that reducing bone turnover with everolimus may help patients with breast cancer maintain bone mineral density, thereby avoiding osteoporotic-type fractures and maintaining quality of life.

The potential protective effects of everolimus on bone distinguish it from other therapies for hormone receptor-positive breast cancer because some of these (particularly aromatase inhibitors) have a detrimental effect on bone. This is important because bone health is critical in patients with advanced breast cancer. Additionally, several adjuvant trial protocols are being developed and discussed by the global investigator community to evaluate the potential role of adjuvant everolimus in postmenopausal women with hormone receptor-positive breast cancer.

Bone marker data from these exploratory analyses of the BOLERO-2 trial suggest that everolimus suppresses bone turnover and reverses the increase in bone resorption associated with exemestane alone. Furthermore, adding everolimus to exemestane therapy also reduced the incidence of breast cancer progressive disease in bone in both the overall patient population and the subset of patients with baseline bone metastases. Therefore, everolimus might help preserve bone health in addition to improving PFS in patients with breast cancer who progress despite nonsteroidal aromatase inhibitor therapy.

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