Received: 10 February 2021 | Revised: 1 April 2021 | Accepted: 13 April 2021

DOI: 10.1002/ijc.33613

CANCER THERAPY AND PREVENTION

IJC International Journal of Cancer

Final results of the randomized phase 2 LEO trial and bone protective effects of everolimus for premenopausal hormone receptor-positive, HER2-negative metastatic breast cancer

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Funding information
Dongkook Pharma Co, Ltd.; Novartis

Abstract

The phase 2 LEO study showed that everolimus (EVE) plus letrozole (LET) with ovarian suppression increased progression-free survival (PFS) in tamoxifen-exposed premenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer with visceral metastases. Here we report final survival outcomes from the LEO study, and the results of exploratory analyses of bone turnover marker changes and bone-specific progressive disease. Patients who were exposed to or progressed on tamoxifen as adjuvant/palliative treatments were randomly assigned (2:1) to the EVE (leuprorelin + LET + EVE, n = 92) or LET (leuprorelin + LET, n = 45) arm. In a median 51-months of follow-up, the median PFS was 17.5 and 13.8 months in the EVE and LET arms, respectively ($P = .245$). Patients in the EVE arm with baseline visceral (median PFS 16.4 vs 9.5 months, $P = .040$) and bone (median PFS 17.1 vs 10.9, $P = .003$) metastases had greater PFS compared to the LET arm. No differences in overall survival (OS) were observed (median OS, 48.3 vs 50.8 months, $P = .948$). The 1-year cumulative incidences of bone-specific disease progression were 6.0% and 23.4% in the EVE and LET arms, respectively (hazard ratio 0.26, $P < .001$). Bone turnover markers at 6 and 12 weeks after treatment decreased in the EVE arm but were increased or stationary in the LET arm. Skeletal-related events occurred in 6.5% and 11.1% of patients in the EVE and LET arms, respectively. EVE + LET with ovarian suppression prolonged PFS in patients with baseline visceral or bone metastases and offered bone-protective effects in the overall study population. However, these clinical benefits did not translate into an OS benefit.

KEYWORDS
bone turnover markers, breast cancer, everolimus, hormone receptor-positive, premenopausal women

Abbreviations: BSAP, bone-specific alkaline phosphatase; CDK 4/6, cyclin-dependent kinase 4 and 6; CTX, serum c-terminal telopeptide; EVE, everolimus; GnRH, gonadotropin-releasing hormone; HER2, human epidermal growth factor receptor 2; HR, hormone-receptor; LET, letrozole; LEUP, leuprorelin; mTOR, mammalian target of rapamycin; OS, overall survival; P1NP, serum amino-terminal propeptide of type I collagen; PFS, progression-free survival; SRE, skeletal-related events.

Hyehyun Jeong and Jae Ho Jeong contributed equally to this study.

1 | INTRODUCTION

For premenopausal patients with advanced hormone-receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2−) breast cancer, treatment decisions are

primarily based on the extrapolation of data from studies conducted in postmenopausal women as many trials have not included premenopausal patients.[1,2] This is also true for everolimus (EVE)-based therapy in patients with HR+, HER2− metastatic breast cancer who progressed on prior endocrine therapy. While the previous phase 3 BOLERO-2 trial showed that adding EVE to exemestane resulted in significant improvements in progression-free survival (PFS) in this patient population, the study included postmenopausal women alone.[3] However, up to half of Asian patients with breast cancer are premenopausal and evidence suggests that their clinicopathological and molecular features differ from those of postmenopausal women.[4-9]

Therefore, in the phase 2 LEO study, we investigated the effectiveness of EVE in combination with the aromatase inhibitor letrozole (LET) and gonadotropin-releasing hormone (GnRH) agonist leuprorelin (LEUP) in tamoxifen-exposed premenopausal women with HR+, HER2− metastatic breast cancer.[10] We observed improved PFS in patients with visceral metastases, along with a numerically greater PFS in the overall study population.

An exploratory analysis of the BOLERO-2 study showed that the addition of EVE to exemestane resulted in significant reductions in bone-specific disease progression, as well as reductions in bone turnover markers.[11] Since the use of aromatase inhibitors in patients with breast cancer and ovarian suppression in premenopausal women are well-known risk factors for decreased bone mineral density,[12-17] the bone-protecting effects of EVE in premenopausal patients with breast cancer deserve further investigation.

Therefore, the present study reported final survival outcomes from the LEO study with approximately 20 months of additional follow-up. Additionally, the results of exploratory analyses evaluating the effects of adding EVE to LET and LEUP on the changes in bone turnover markers, the risk for progressive diseases in bone and the incidence of skeletal-related events (SREs) during treatment in tamoxifen-exposed premenopausal women with HR+, HER2− metastatic breast cancer were also investigated.

What's New?

In the phase 2 LEO study, women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with visceral metastases who were previously treated with tamoxifen, experienced significant improvements in progression-free survival following combination therapy with the protein kinase inhibitor everolimus and the aromatase inhibitor letrozole. This report describes final survival outcomes from the LEO study. Patients with visceral or bone metastases treated with combined leuprorelin, letrozole, and everolimus survived longer with progression-free disease compared to women who received leuprorelin and letrozole. Regimens employing everolimus were associated with reductions in bone turnover, bone-specific disease progression, and skeletal-related events, suggesting a role for everolimus in bone protection.

2 | MATERIALS AND METHODS

2.1 | Patients and study design

Details on the randomized, open-label, multicenter, phase 2 LEO trial have been previously reported.[10] The LEO trial enrolled premenopausal patients with HR+, HER2− metastatic breast cancer who progressed on or were exposed to tamoxifen, with or without sequential/concurrent GnRH agonist, as adjuvant treatment or for metastatic disease.

The key eligibility criteria of the study included (a) an Eastern Cooperative Oncology Group performance status of 0-2, (b) tamoxifen treatment duration of ≥3 months and (c) one measurable lesion or mainly lytic bone lesions in the absence of measurable disease. One line of chemotherapy for metastatic disease was permitted. The key exclusion criteria included (a) prior treatment with an aromatase inhibitor, fulvestrant, or mammalian target of rapamycin (mTOR) inhibitor; and (b) the presence of extensive symptomatic visceral metastases, lymphangitic carcinomatosis involving >50% of the lungs or brain metastases. Written informed consent was obtained from all patients. The study protocol was approved by the institutional review boards of all participating institutions.

2.2 | Procedures and assessments

The participants were randomized (2:1) into the EVE (EVE 10 mg plus LET 2.5 mg daily orally) or LET (LET 2.5 mg daily orally) arm, with 3.75 mg LEUP administered subcutaneously every 28 days in both arms. The stratification factors were the presence of visceral metastases and sensitivity to endocrine therapy (defined as ≥24 months of adjuvant endocrine therapy before recurrence, or response or stabilization for ≥24 weeks of endocrine therapy for advanced disease). Tumor response was assessed by the investigator per the Response Evaluation Criteria in Solid Tumors version 1.1 every 8 weeks for 12 months and every 12 weeks thereafter until disease progression. Repeated imaging was conducted at any time if progressive disease was clinically suspected.

2.3 | Endpoints

The primary endpoint was the investigator-assessed PFS, defined as the time from treatment initiation to disease progression or death from any cause, whichever occurred first. The secondary endpoints were overall response rate (complete and partial responses), clinical benefit rate (complete response, partial response or stable disease for

≥6 months) and overall survival (OS), defined as the time from treatment initiation to death from any cause.

2.4 | Exploratory analyses for progressive disease in bone, bone turnover markers and skeletal-related events

Progressive disease in bone was defined as an unequivocal progression of pre-existing bone metastases or the development of new bone metastases at the time of progressive disease, as assessed by computed tomography, magnetic resonance imaging, or bone scans.[11] The cumulative incidences of progressive disease in bone were compared between arms. The concentrations of bone turnover markers (ie, bone-specific alkaline phosphatase [BSAP], serum amino-terminal propeptide of type I collagen [P1NP] and serum c-terminal telopeptide [CTX]) were measured in blood samples collected at baseline (within 3 weeks of treatment) and at 6 and 12 weeks after treatment, until the end of the study. The percent changes in bone turnover markers from baseline to 6 and 12 weeks were assessed and compared between arms in both the overall study population and subgroups, according to the presence of baseline bone metastases and bisphosphonate use. SREs included pathologic bone fracture, any radiotherapy or surgery for bone metastases and spinal cord compression due to bone metastases.

2.5 | Statistical analyses

The Kaplan-Meier method was used to measure PFS, OS and cumulative incidence of progressive disease in bone, and the log-rank test was used for comparison between arms. Hazard ratios (HRs) were estimated by a Cox proportional hazards model. A two-sided *P*-value of <.05 was considered statistically significant. Changes in bone turnover markers were presented as medians and interquartile ranges (IQRs) for percent changes and compared between groups using Mann-Whitney *U* tests.

3 | RESULTS

3.1 | Patients

A total of 137 patients from four institutions across South Korea were randomly assigned to the EVE (n = 92) or LET (n = 45) arm. The baseline demographics and clinicopathologic characteristics were well-balanced between arms.[10] At data cutoff (26 October 2020), 12 patients in the EVE arm (13.0%) and 6 patients in the LET arm (13.3%) remained on study treatment (Figure 1).

3.2 | Survival outcomes

The median follow-up duration was 51.3 months (IQR: 40.1-65.9). At data cutoff, 75 patients (81.5%) in the EVE arm and 37 patients (82.2%) in the LET arm experienced PFS-related events (disease progression or death). The median overall PFS was 17.5 months (95% confidence interval [CI]: 13.8-24.0) in the EVE arm and 13.8 months (95% CI: 5.5-19.8) in the LET arm ($P = .245$; Figure 2A).

PFS analysis in stratified subgroups (the presence of visceral metastases and sensitivity to endocrine therapy) revealed a median PFS of 16.4 months (95% CI: 10.5-27.3) and 9.5 months (95% CI: 1.8-16.9) in the EVE and LET arms, respectively, among the 83 patients with visceral metastases ($P = .040$; Figure 2B). Among the 54 patients without visceral metastases, the median PFS in the EVE and LET arms was 18.1 months (95% CI: 13.9-25.4) and 15.6 months (95% CI: 10.9-53.1), respectively ($P = .487$; Figure 2C). Of the 102 patients with prior endocrine sensitivity, the median PFS in the EVE and LET arms was 18.6 months (95% CI: 13.9-27.3) and 13.8 months (95% CI: 5.5-20.0), respectively ($P = .100$). Among the 35 patients with prior endocrine resistance, the median PFS was 13.8 months (95% CI: 7.5-24.0) and 10.9 months (95% CI: 0.9-53.1) ($P = .555$), respectively.

At data cutoff, 42 patients (45.7%) in the EVE arm and 21 patients (46.7%) in the LET arm had died. The median overall OS was 48.3 months (95% CI: 36.9-not estimated [NE]) in the EVE arm and 50.8 months (95% CI: 38.0-NE) in the LET arm ($P = .948$; Figure 2D). No statistically significant differences in OS were observed in stratified subgroup analyses.

3.3 | Exploratory subgroup analyses

The results of an exploratory subgroup analysis that assessed PFS and OS according to patient baseline characteristics and previous treatment are shown in Figure 3. In patients with bone metastases at baseline, PFS significantly favored the EVE arm over the LET arm (median PFS, 17.1 months [95% CI: 12.5-20.8] and 10.9 months [95% CI: 3.7-13.8], respectively, $P = .003$, log-rank test). However, no statistically significant differences in OS were observed in this subgroup (Figure 3).

3.4 | Effect on progressive disease in bone

Exploratory analyses on bone-specific disease progression showed that 66 patients (71.7%) in the EVE arm and 32 patients (71.1%) in the LET arm had bone metastases and 53 patients (57.6%) in the EVE arm and 21 patients (46.7%) in the LET arm were on bisphosphonate therapy at baseline. During follow-up, 12 patients in the EVE arm (13.0%) and 17 patients in the LET arm (37.8%) experienced progressive bone disease. The 6-month, 12-month and 18-month cumulative incidences of progressive disease in bone were, respectively, 4.7%, 6.0% and 10.2% in the EVE arm and 13.9%, 23.4% and 43.6% in the LET arm (HR 0.26 [95% CI: 0.12-0.55], $P < .001$). In patients with baseline bone metastases, the 6-month, 12-month and 18-month cumulative incidences of progressive disease in bone were, respectively, 6.7%, 8.5% and

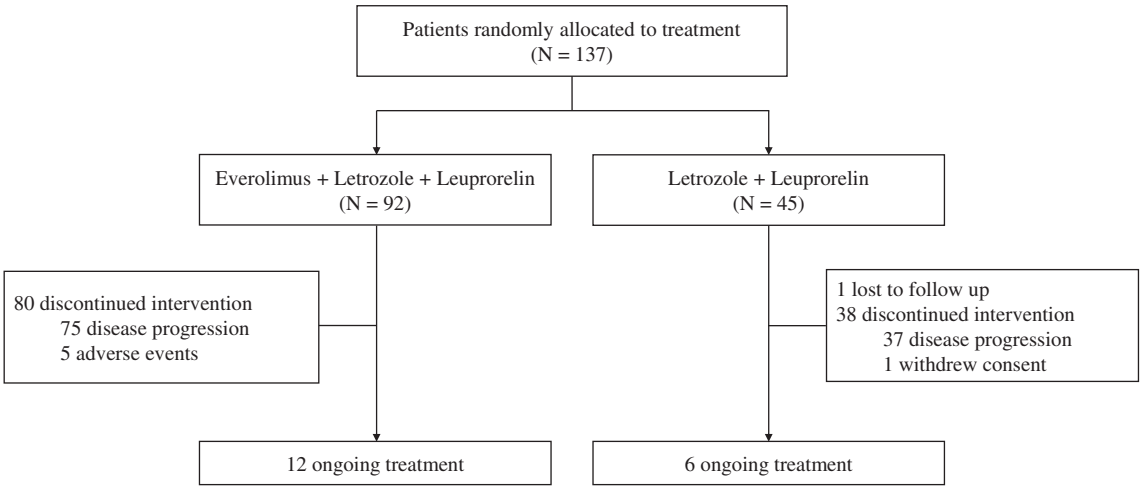

FIGURE 1 LEO study flow diagram

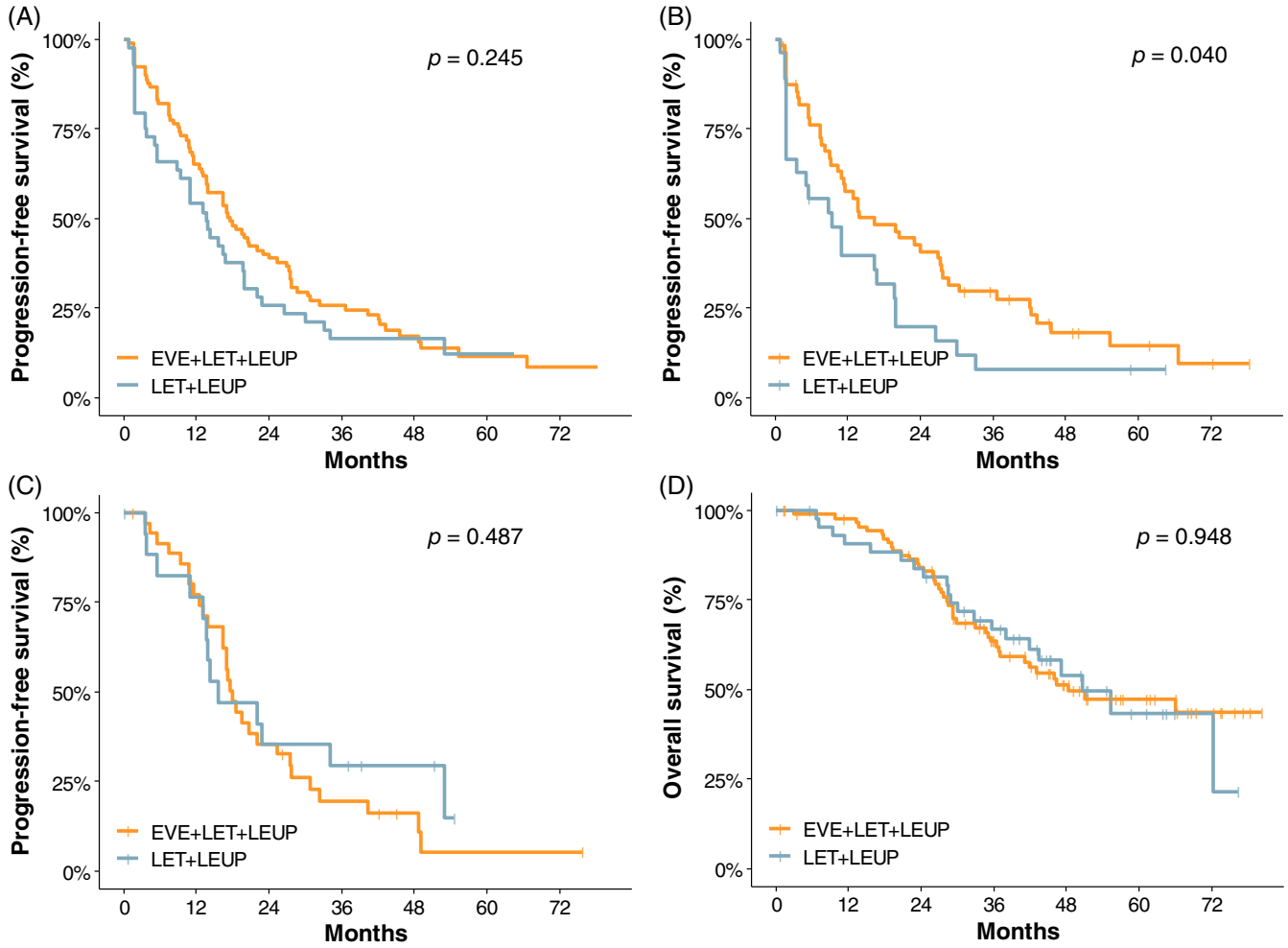

FIGURE 2 Survival outcomes. A, Progression-free survival (PFS) in the entire study population. B, PFS in patients with visceral metastases. C, PFS in patients without visceral metastasis. D, Overall survival in the entire study population. EVE, everolimus; LET, letrozole; LEUP, leuprorelin

14.6% in the EVE arm and 21.8%, 36.4%, 68.2% in the LET arm (HR 0.16 [95% CI: 0.07-0.36], $P < .001$). Among patients on bisphosphonate at baseline, the 6-month, 12-month and 18-month cumulative incidences of progressive disease in bone were, respectively,

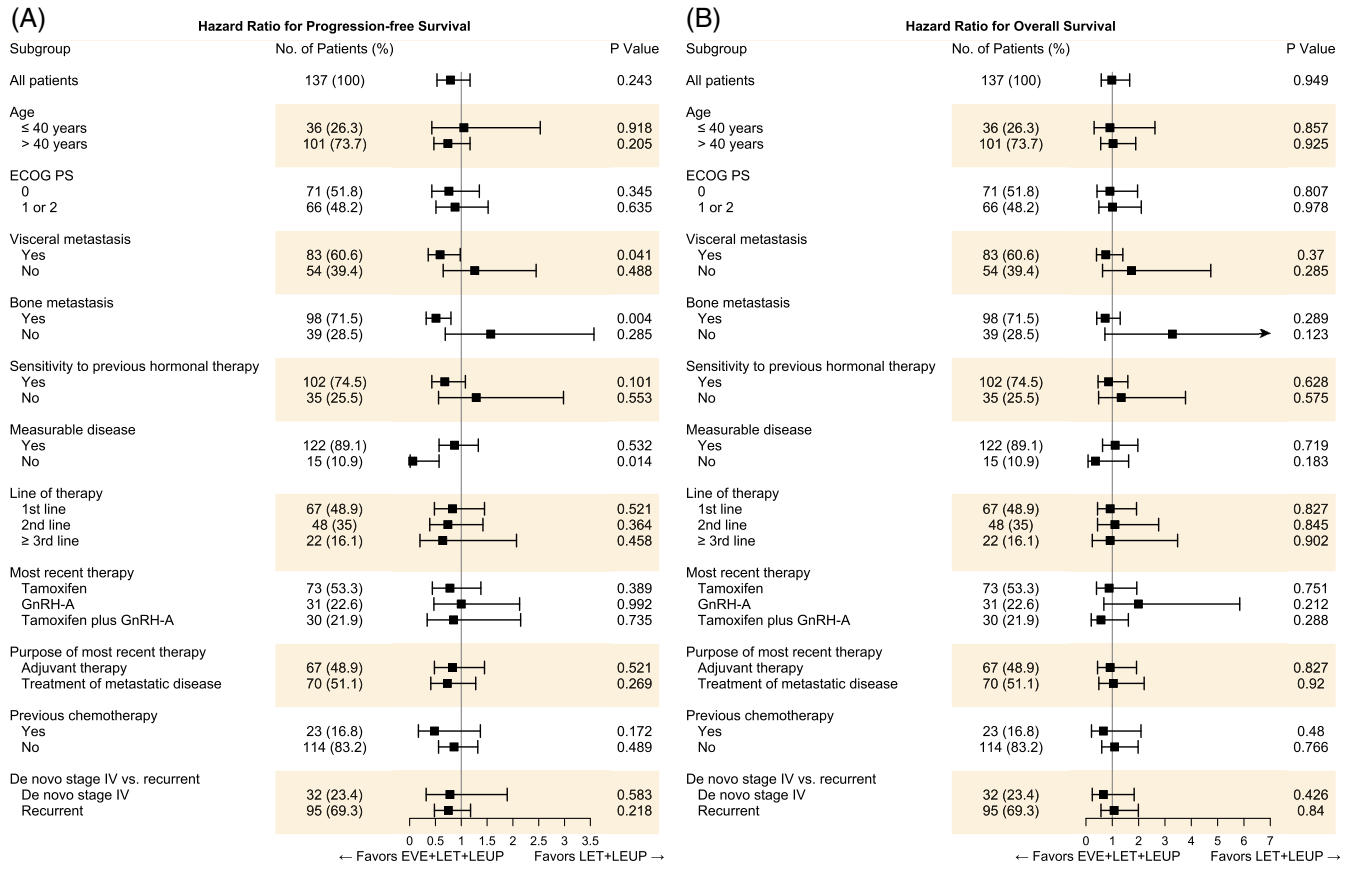

FIGURE 3 Forest plots for subgroup analyses. A, Progression-free survival; B, overall survival. ECOG PS, Eastern Cooperative Oncology Group performance status; EVE, everolimus; LET, letrozole; LEUP, leuprorelin [Color figure can be viewed at wileyonlinelibrary.com]

6.5%, 8.8% and 16.8% in the EVE arm and 17.5%, 30.2% and 61.9% in the LET arm (HR 0.19 [95% CI: 0.08-0.45], $P < .001$; Figure 4).

3.5 | Effect on bone turnover markers and skeletal-related events

During study treatment, percent changes in the levels of bone turnover markers (ie, BSAP, P1NP and CTX) at 6 and 12 weeks from baseline were compared. At baseline, the levels of all three markers were within the reference range and did not differ between groups (BSAP, median 11.8 [IQR: 7.9-16.8] vs 12.9 [IQR: 9.9-18.4], $P = .137$; P1NP, median 51.7 [IQR: 27.7-83.7] vs 45.1 [IQR: 36.1-96.5], $P = .515$; CTX, median 0.2 [IQR: 0.1-0.5] vs 0.3 [IQR: 0.1-0.3], $P = .914$).[18] In the overall study population, the levels of P1NP and CTX had decreased at 6 weeks after treatment in the EVE arm (−31.8% and −31.0%, respectively) but had increased in the LET arm (+4.5% and +34.1%, respectively) ($P < .001$ for both). No differences in the percent changes in BSAP levels between arms were observed. Similar results were noted at 12 weeks (P1NP and CTX, −46.5% and −24.1%, respectively in the EVE arm; −2.7% and +64.9%, respectively, in the LET arm) (Figure 5). Reductions in the levels of bone turnover markers in the EVE arm were observed regardless of bone metastases or bisphosphonate use at baseline (Table S1; Figures S1 and S2).

SREs, including pathologic fracture, radiotherapy, surgery and spinal cord compression due to bone metastases, occurred in six (6.5%) and five (11.1%) patients in the EVE and LET arms, respectively (Table S2).

4 | DISCUSSION

The previous phase 2 LEO study showed that, in tamoxifen-exposed patients with HR+, HER2− premenopausal metastatic breast cancer, adding EVE to LET+LEUP resulted in numerically prolonged PFS and a higher clinical benefit rate in the overall study population, as well as a significant PFS benefit in patients with visceral metastases at baseline.[10] In this final analysis of the LEO trial with approximately 20 months of additional follow-up, results were consistent with the primary analysis with the PFS benefit in patients with visceral metastases and the numerically longer PFS in the overall study population. However, these clinical benefits did not confer an OS benefit. We also observed the bone-protective effect of EVE through the (a) reduced level of bone turnover markers, (b) lower risk for bone-specific disease progression and (c) lower incidence of skeletal-related events. No new safety issues were observed.

The bone-protective effect of EVE demonstrated in our study is consistent with the results of a previous sub-study of the phase

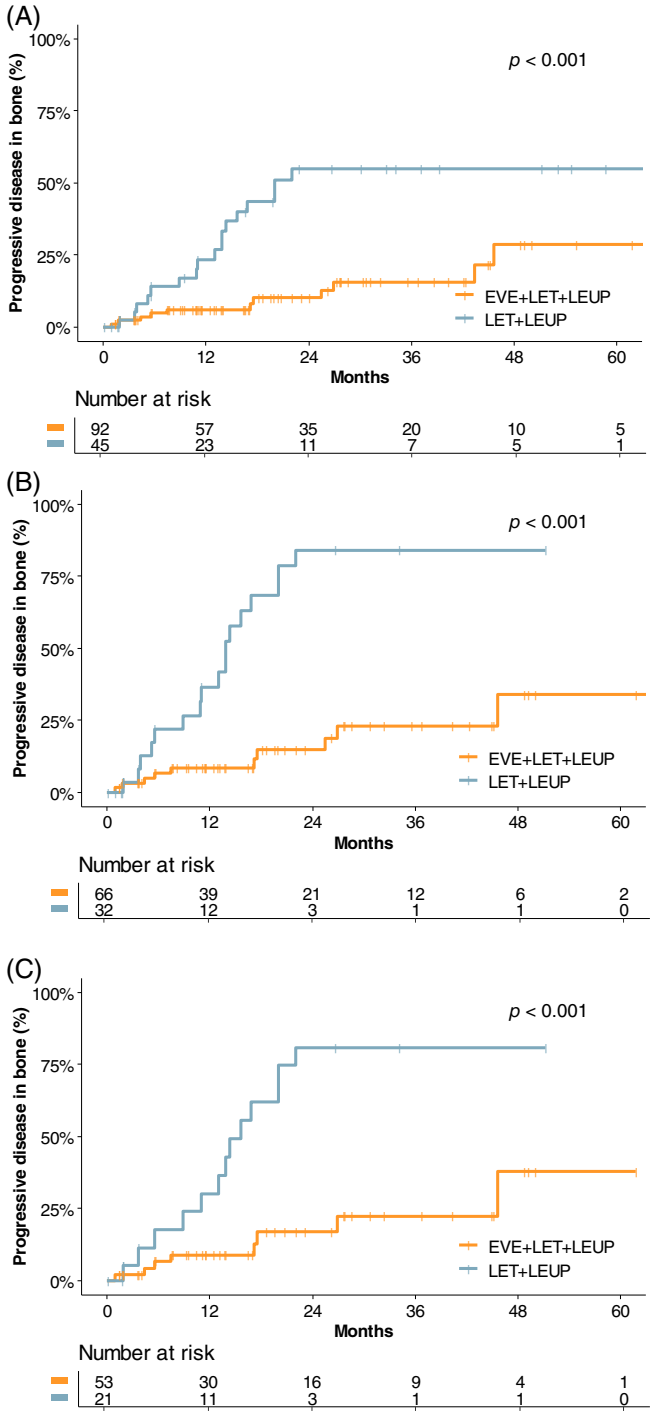

FIGURE 4 Cumulative incidences of progressive bone disease. A, Overall population; B, patients with bone metastasis at baseline and C, patients on bisphosphonate. EVE, everolimus; LET, letrozole; LEUP, leuprorelin. Progressive disease in bone was defined as unequivocal progression of pre-existing bone metastases or development of new bone metastases at the time of progressive disease, assessed by CT, MRI or bone scans. The log-rank test was used for comparison

3 BOLERO-2 trial, which explored the bone-protective effects of EVE added to exemestane in postmenopausal women.[11] High levels of bone turnover markers are associated with increased fracture risk and the fragility of bone architecture. Given that ovarian function suppression and aromatase inhibitor treatment induce estrogen deficiency in premenopausal patients, our finding of an overall increase in the levels of bone turnover markers in patients treated with LET+LEUP alone was as expected.[12-17] However, patients in the EVE arm showed a marked decrease in the levels of bone turnover markers irrespective of the presence of the bone metastasis or bisphosphonate use.

Several preclinical studies suggest the mechanism for this bone-protective effect of EVE that inactivation of mTOR signaling inhibits the differentiation and survival of osteoclasts—which play an important role in estrogen-deficient osteoporosis.[19-21] Not only the osteoclasts mediate bone resorption, they also interact with tumor cells and regulate osteolytic bone metastasis.[22] In our study, the cumulative incidence of bone-specific disease progression was also low with the addition of EVE. The protective effect of EVE on bone-specific progression was more prominent in the subgroup of patients with bone metastases at baseline (HR 0.16, a 1-year intergroup absolute difference of 27.9%) and those on bisphosphonate treatment (HR 0.19, a 1-year intergroup absolute difference of 21.4%). Although additional studies are needed, the increased protective effect of EVE on bone-specific disease progression in patients taking bisphosphonate may be attributed to the demonstrated synergistic effects of bisphosphonate on mTOR inhibition.[23] Taken together, these results suggest that adding EVE provided a bone-protective effect on ovarian suppression and aromatase inhibitor treatment in premenopausal women. These bone-protective effects of EVE could be of particular interest in these premenopausal population considering that they are at high risk of bone loss with ovarian suppression and their prolonged survival with the recent advances in treatment.

In our study, the PFS benefit with the addition of EVE was observed in patients with visceral or bone metastases at baseline. However, in the entire study population, the numerically longer PFS in the EVE arm (17.1 months vs 13.8 months in the EVE and LET arms, respectively) did not reach statistical significance in our study, unlike in the BOLERO-2 study. Although the reason for this discrepancy between the current study and BOLERO-2 study remains unclear, multiple factors might have contributed to these results, including the underlying biologic difference between premenopausal and postmenopausal breast cancer, imbalances in the proportions of the patients with "bone-only" metastases at baseline, relatively small sample size in the LEO trial based on sample estimations made in reference to the BOLERO-2 trial and improvement of PFS in the control arm, which was consistent with the results of control arms treated with a single endocrine agent from recently published trials for cyclin-dependent kinase 4 and 6 (CDK 4/6) inhibitors.[24,25] However, including the subgroups that showed a statistically significant PFS benefit with the addition of EVE, a benefit in OS was not observed, consistent with the results in the postmenopausal population from the BOLERO-2 trial.[26]

Although CDK 4/6 inhibitors have changed the paradigm of first-line and second-line treatments in the management of HR+ metastatic breast cancer, especially the OS survival benefit in

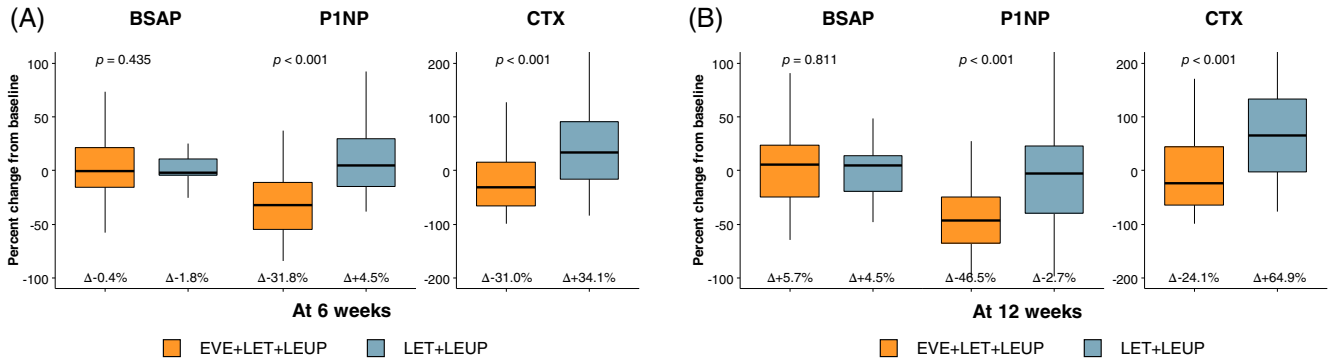

FIGURE 5 Percent changes in bone turnover markers in the overall study population. A, At 6 and B, 12 weeks from the start of treatment. BSAP, bone-specific alkaline phosphatase; CTX, serum c-terminal telopeptide; EVE, everolimus; LET, letrozole; LEUP, leuprorelin; P1NP, serum aminoterminal propeptide of type I collagen

pre/perimenopausal women first reported in the MONALEESA-7 trial,[27] the value of our study lies in the identification of subgroups benefiting from the addition of EVE, as well as the identification of the protective effect of EVE on progressive disease of bone and bone loss. Therefore, the results of the long-term follow-up analyses of our study suggest that EVE could be a useful treatment choice when there is limited access to CDK 4/6 inhibitors, especially in patients with visceral or bone metastases at baseline. It is worthy of further investigation if the addition of EVE might improve the quality-of-life of the breast cancer patients with bone metastasis and/or low bone mineral density, and although not included in the scope of the current study, if the EVE combination could be a useful choice after progression on the CDK 4/6 inhibitors.

In conclusion, the results of this updated analysis of the LEO study demonstrated that adding EVE to LET and LEUP in tamoxifen-treated premenopausal women yielded significant PFS benefits in patients with baseline visceral or bone metastases and also offered bone-protective effects in the overall study population. However, these clinical benefits did not translate into an OS benefit.

ACKNOWLEDGMENTS

This work was supported by Novartis and Dongkook Pharma Co, Ltd.

CONFLICT OF INTEREST

Kyung Hae Jung reports personal fees from AstraZeneca, Roche, Celgene, Novartis and Takeda, outside the submitted work. Keun Seok Lee reports personal fees from Roche, Lilly, Novartis, MSD and drug supply from Donga ST, outside the submitted work. Hyehyun Jeong, Jae Ho Jeong, Jeong Eun Kim, Jin-Hee Ahn, Su-Jin Koh, Jaekyung Cheon, Joohyuk Sohn, Gun Min Kim, Sung Hoon Sim, In Hae Park and Sung-Bae Kim declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

ETHICS STATEMENT

All patients provided written informed consent and the study protocol was approved by the institutional review boards of all participating institutions. This trial was registered at clinicaltrials.gov as #NCT02344550 (Date of registration: 26 January 2015).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Jeong H, Jeong JH, Kim JE, et al. Final results of the randomized phase 2 LEO trial and bone protective effects of everolimus for premenopausal hormone receptor-positive, HER2-negative metastatic breast cancer. *Int. J. Cancer*. 2021;149:917–924. https://doi.org/10.1002/ijc.33613