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CLINICAL TRIAL

# Everolimus plus exemestane as first-line therapy in HR$^+$, HER2$^-$ advanced breast cancer in BOLERO-2

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**Abstract** The present exploratory analysis examined the efficacy, safety, and quality-of-life effects of everolimus (EVE) + exemestane (EXE) in the subgroup of patients in BOLERO-2 whose last treatment before study entry was in the (neo)adjuvant setting. In BOLERO-2, patients with hormone-receptor-positive (HR$^+$), human epidermal growth factor receptor-2-negative (HER2$^-$) advanced breast cancer recurring/progressing after a nonsteroidal aromatase inhibitor (NSAI) were randomly assigned (2:1) to receive EVE (10 mg/day) + EXE (25 mg/day) or placebo (PBO) + EXE. The primary endpoint was progression-free survival (PFS) by local assessment. Overall, 137 patients received first-line EVE + EXE ($n = 100$) or PBO + EXE ($n = 37$). Median PFS by local investigator assessment nearly tripled to 11.5 months with EVE + EXE from 4.1 months with PBO + EXE (hazard ratio = 0.39; 95 % CI 0.25–0.62), while maintaining quality of life. This was confirmed by central assessment (15.2 vs 4.2 months; hazard ratio = 0.32; 95 % CI 0.18–0.57). The marked PFS improvement in patients receiving EVE + EXE as first-line therapy for disease recurrence during or after (neo)adjuvant NSAI therapy supports the efficacy of this combination in the first-line setting. Furthermore, the results highlight the potential benefit of early introduction of EVE + EXE in the management of

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$HR^+$, $HER2^-$ advanced breast cancer in postmenopausal patients.

**Keywords** BOLERO-2 · Breast cancer · Everolimus · First-line therapy · Metastatic disease · mTOR inhibition

**Abbreviations**

| | |
|---|---|
| ABC1 | 1st International Consensus Conference for Advanced Breast Cancer |
| AE | Adverse event |
| AGO | Arbeitsgemeinschaft Gynäkologische Onkologie e.V |
| AI | Aromatase inhibitor |
| AKT | Protein kinase B |
| ANA | Anastrozole |
| CI | Confidence interval |
| ECOG | Eastern Cooperative Oncology Group |
| ESMO | European Society for Medical Oncology |
| EVE | Everolimus |
| EXE | Exemestane |
| $HER2^-$ | Human epidermal growth factor receptor-2-negative |
| LET | Letrozole |
| HR | Hazard ratio |
| $HR^+$ | hormone-receptor-positive |
| HRQoL | Health-related quality of life |
| LHRHa | Luteinizing hormone-releasing hormone analogue |
| mTOR | Mammalian target of rapamycin |
| NCCN | National Comprehensive Cancer Network |
| NSAI | Nonsteroidal aromatase inhibitor |
| PBO | Placebo |
| PFS | Progression-free survival |
| PI3K | Phosphatidylinositol 3-kinase |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| TDD | Time to definitive deterioration |
| TTP | Time to progression |

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## Introduction

The majority of breast cancers are hormone-receptor-positive ($HR^+$), with up to 75 % expressing estrogen receptors and/or progesterone receptors [1, 2], whereas human epidermal growth factor receptor-2 (HER2) is overexpressed in approximately 15–23 % of breast cancers [3]. Thus, the majority of breast cancers are $HR^+$ and HER2-negative ($HER2^-$). Endocrine therapy, particularly aromatase inhibitors (AIs), represents the principal systemic therapy for postmenopausal women with $HR^+$, $HER2^-$ breast cancer in both the adjuvant and advanced settings [4, 5]. Nonetheless, disease progression may occur despite continued endocrine therapy (also referred to clinically as endocrine resistance) [6, 7], and has been attributed, among other mechanisms, to the cross-talk between estrogen receptor signaling and the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway, which is essential for breast cancer growth, progression, and insensitivity to endocrine interventions [7–9]. Thus, co-targeting both signaling pathways may enhance the effectiveness of endocrine therapy and improve outcomes in patients with $HR^+$, $HER2^-$ advanced breast cancer [7, 10].

The mTOR inhibitor everolimus (EVE) in combination with exemestane (EXE) was recently approved for the treatment of postmenopausal women with $HR^+$, $HER2^-$ advanced breast cancer whose disease recurred or progressed during or after nonsteroidal AI (NSAI) therapy [11]. This approval was based on the results of the pivotal BOLERO-2 trial, wherein EVE + EXE more than doubled median progression-free survival (PFS) versus placebo (PBO) plus EXE at 18 months median follow-up [12], while maintaining health-related quality of life (HRQoL) [13]. Moreover, consistent efficacy results were observed in all predefined subgroups [12], including patients with visceral metastases, patients with bone disease, elderly patients, and Asian patients [14–17].

The present exploratory analyses evaluated the efficacy, safety, and HRQoL effects of EVE + EXE in the subgroup of patients in the BOLERO-2 trial who received this regimen as first-line therapy for advanced disease.

## Methods

### Study design and patient population

The BOLERO-2 trial is an international, phase 3, multicenter, randomized, double-blind, PBO-controlled trial (ClinicalTrials.gov identifier NCT00863655) that has been described in detail previously [18]. In brief, postmenopausal women with $HR^+$, $HER2^-$, unresectable, locally

advanced or metastatic breast cancer recurring or progressing during or after letrozole or anastrozole were randomized at a 2:1 ratio to receive either EVE (10 mg daily) or matching PBO in a blinded manner, with open-label EXE (25 mg daily). For simplicity, the PBO + EXE arm will henceforth be referred to as the control arm. Randomization was stratified by the presence or absence of visceral metastases and sensitivity to prior endocrine therapy [18]. Treatment continued until disease progression, development of unacceptable toxicity, or withdrawal of consent. Written informed consent was obtained from all patients before enrollment; trial-related approvals were obtained from the institutional review boards of participating centers, and the trial was conducted in accordance with the Good Clinical Practice guidelines, Declaration of Helsinki, and local regulations. The present analyses included patients who received EVE + EXE as first-line therapy for advanced disease. Patients in this subset may have received (neo)adjuvant and adjuvant therapy, or adjuvant therapy only as last therapy before study entry.

### Primary and secondary endpoints

Here we report the results of a retrospective and exploratory analysis from the BOLERO-2 trial. The primary endpoint of BOLERO-2 was investigator-assessed PFS (defined as time from randomization to first documented progression or death from any cause) per Response Evaluation Criteria in Solid Tumors (RECIST), v1.0. Secondary endpoints included safety, and HRQoL using European Organization for Research and Treatment of Cancer QLQ-C30 and BR23 questionnaires [18]. The present analysis evaluated investigator-assessed and centrally assessed PFS according to RECIST, v1.0. As with the overall study, adverse events (AEs) were recorded throughout the trial and were graded according to the Common Terminology Criteria for Adverse Events, v3.0.

### Statistical analyses

The subset analyses reported in this manuscript are retrospective and exploratory. Estimates of PFS were obtained by Kaplan–Meier method, and hazard ratios and 95 % confidence intervals (CIs) were calculated using an unstratified Cox proportional hazards model. Time to definitive deterioration (TDD) of the Global Health Status was defined as a 5 % decrease in HRQoL relative to baseline, with no subsequent increase above this threshold, and was estimated by Kaplan–Meier method; hazard ratios and 95 % CIs were calculated using an unstratified Cox proportional hazards model. All analyses were conducted using SAS® for Windows, v9.2 (SAS Institute, Cary, NC, USA). All analyses were based on data at 18 months median follow-up.

## Results

### Demographics and disposition

Between June 2009 and January 2011, 724 women across 189 centers in 24 countries were randomized to the BOLERO-2 trial treatment arms (EVE + EXE, $n = 485$; control, $n = 239$) [18]. Patient baseline characteristics were well balanced between treatment groups and have been reported previously [18]. Overall, 19 % of patients (137 of 724) entered the trial having received (neo)adjuvant therapy as their last systemic treatment before study entry. These patients received EVE + EXE (100 of 485) or control (37 of 239) as first-line treatment for advanced breast cancer. Baseline characteristics were well balanced between the two treatment arms in this subset, including the presence of visceral metastases (EVE + EXE, 50 %; control, 43 %), bone metastases (EVE + EXE, 65 %; control, 70 %), and bone-only metastases (EVE + EXE, 29 %; control, 24 %) at baseline (Table 1).

### Efficacy

The efficacy data from this subset were consistent with outcomes in the overall trial population [12, 13]. Median PFS was nearly tripled with EVE + EXE versus control by local investigator assessment (11.5 vs 4.1 months, respectively; hazard ratio = 0.39; 95 % CI 0.25–0.62) in patients whose disease recurred during or after (neo)adjuvant therapy. Median PFS assessed by independent central review (15.2 vs 4.2 months, respectively; hazard ratio = 0.32; 95 % CI 0.18–0.57) was consistent with local assessment (Fig. 1a, b).

### Quality of life

In patients who received EVE + EXE as first-line therapy for advanced disease, baseline mean Global Health Status scores were similar between treatment arms (62.8 vs 63.4). Median TDD in Global Health Status was numerically longer with EVE + EXE versus control (11.1 vs 7.2 months, respectively; hazard ratio = 0.69; 95 % CI 0.39–1.22; Fig. 2).

### Safety

The safety profile of EVE + EXE in this subset analysis was consistent with that of the overall patient population [12]. The majority of AEs were mild to moderate in intensity (i.e., grade 1 or 2) and manageable. The most frequently reported AEs of any grade with EVE + EXE were stomatitis (68 %), diarrhea (40 %), and rash (37 %; Table 2). Among the most frequently reported any grade

**Table 1** Baseline characteristics in patients whose disease recurred during or after adjuvant therapy

| Characteristics | Patients (%) | |
|---|---|---|
| | EVE + EXE ($n = 100$) | Control (PBO + EXE) ($n = 37$) |
| Median age, years (range) | 62 (45–83) | 61 (50–82) |
| Race | | |
| Caucasian | 68 | 62 |
| Asian | 31 | 32 |
| Black | 0 | 3 |
| Other | 1 | 3 |
| ECOG performance status[a] | | |
| 0 | 70 | 70 |
| 1 | 29 | 24 |
| 2 | 0 | 3 |
| Missing | 1 | 3 |
| Measurable disease[b] | 67 | 68 |
| Metastatic site | | |
| Visceral[c] | 50 | 43 |
| Lung | 26 | 22 |
| Liver | 25 | 30 |
| Lung and liver | 5 | 11 |
| Bone | 65 | 70 |
| Bone only | 29 | 24 |
| Other | 47 | 57 |
| Prior NSAI | | |
| LET only | 25 | 24 |
| ANA only | 69 | 70 |
| LET and ANA | 6 | 5 |
| ANA or LET as most recent treatment | 98 | 100 |
| Prior endocrine therapy other than NSAI[d,e] | | |
| Prior tamoxifen | 21 | 22 |
| Prior toremifene | 1 | 3 |
| Prior LHRHa | 0 | 3 |
| Prior chemotherapy [(neo)adjuvant only][e] | 74 | 76 |
| Prior radiotherapy[e] | 74 | 78 |
| Number of prior therapies[f] | | |
| 1 or 2 | 58 | 57 |
| ≥3 | 42 | 43 |

Includes patients who also received (neo)adjuvant therapy

*ANA* Anastrozole, *ECOG* Eastern Cooperative Oncology Group, *EVE* everolimus, *EXE* exemestane, *LET* letrozole, *LHRHa* luteinizing hormone-releasing hormone analogue, *NSAI* nonsteroidal aromatase inhibitor, *PBO* placebo

[a] No patients in this subset had ECOG performance status ≥3

[b] Measurable disease includes patients with ≥1 target lesion; all other patients had ≥1 mainly lytic bone lesion

[c] Visceral includes lung, liver, pleural, pleural effusion, peritoneum, and ascites

[d] No patients received prior fulvestrant, consistent with its indication for metastatic disease

[e] Received in addition to NSAI in the (neo)adjuvant setting

[f] Includes all previous treatment modalities

AEs, the most common AEs of grade 3 or 4 intensity with EVE + EXE were hyperglycemia (8 %), stomatitis (4 %), diarrhea (4 %), and fatigue (3 %). Treatment discontinuation due to AEs was slightly higher with EVE + EXE (10 %) compared with control (8 %). In the EVE + EXE arm, 74 % of patients had one or more EVE dose reductions or interruptions and 23 % had one or more EXE dose reductions or interruptions. In the control arm, 32 % of patients had one or more PBO dose reductions or interruptions and 19 % had one or more EXE dose reductions or interruptions. The majority of dose reductions or interruptions for both EVE and EXE were due to AEs.

Notably, the median duration of exposure to EVE in this subset was 31.1 weeks (range 1.0–109.4 weeks), which is substantially longer than the median duration of exposure of 23.9 weeks in the overall patient population (range 1.0–123.3 weeks) [12]. However, the median relative dose intensity of EVE in this subset (85 %) was comparable to that in the overall population (86 %).

## Discussion

In the overall BOLERO-2 trial population, EVE + EXE more than doubled the median PFS compared with control (local assessment 7.8 vs 3.2 months, respectively; hazard ratio = 0.45; log-rank $P < 0.0001$) without compromising HRQoL (confirmed by central assessment 11.0 vs 4.1 months, respectively; hazard ratio = 0.38; log-rank $P < 0.0001$) [12]. The present subset analysis from BOLERO-2 demonstrated that EVE + EXE as first-line therapy for advanced breast cancer nearly tripled PFS in patients with $HR^+$, $HER2^-$ advanced breast cancer previously treated with (neo)adjuvant NSAIs.

Notably, guidelines from the 1st International Consensus Conference for Advanced Breast Cancer (ABC1), European Society for Medical Oncology (ESMO), and National Comprehensive Cancer Network (NCCN) generally recommend multiple lines of endocrine therapy before switching to chemotherapy for patients with $HR^+$ advanced breast cancer [4, 5, 19]. The German Arbeitsgemeinschaft Gynäkologische Onkologie e.V. (AGO) and Canadian consensus guidelines specifically recommend EVE + EXE, fulvestrant, tamoxifen, or EXE for patients who have recurred during or after adjuvant AI therapy, with EVE + EXE reserved for shorter treatment-free intervals (i.e., no longer endocrine sensitive) [20, 21].

First-line treatment of advanced breast cancer with AIs (EXE, letrozole, or anastrozole) has demonstrated superior efficacy compared with tamoxifen, substantially prolonging median time to progression (TTP)/PFS durations (9.9/10.7 vs 5.8/6.4 months) in postmenopausal women with $HR^+$ or hormone-receptor status unknown, locally advanced or

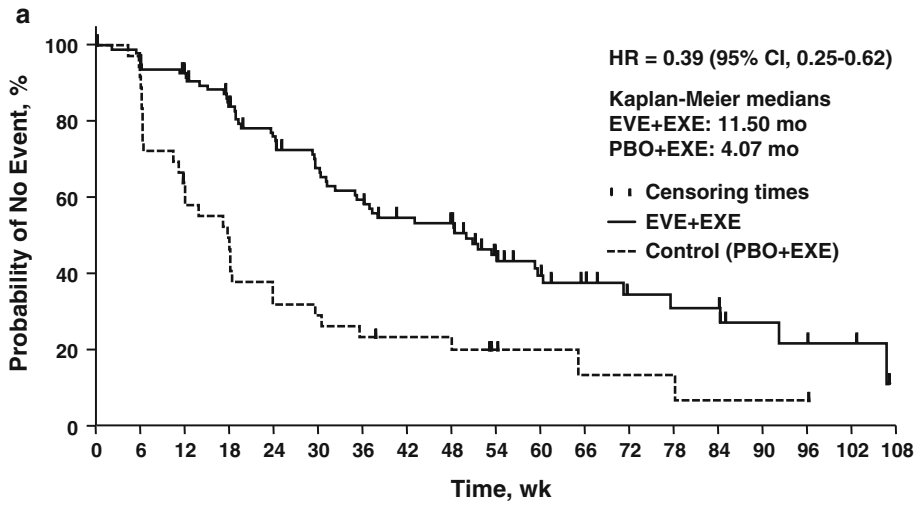
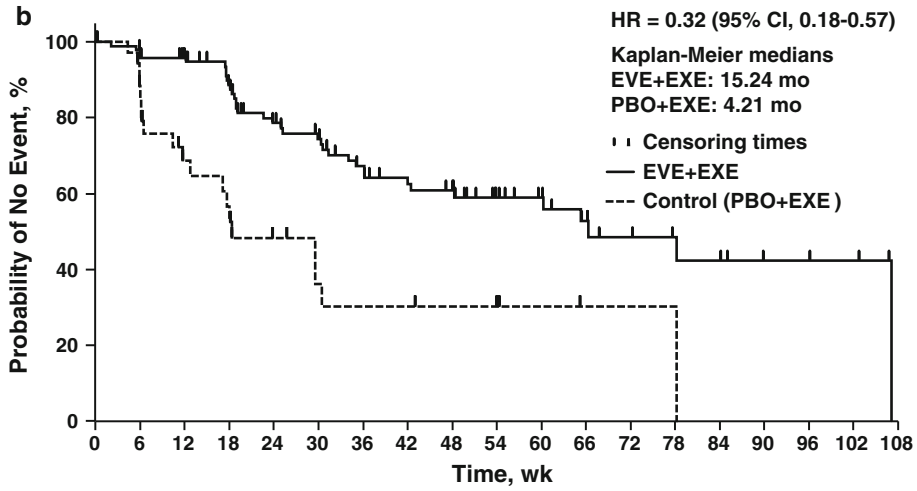



**Fig. 1** Kaplan–Meier curves of PFS in patients whose disease recurred during/after adjuvant therapy [includes patients who also received (neo)adjuvant therapy] by **a** local assessment and **b** central assessment. *CI* Confidence interval, *EVE* everolimus, *EXE* exemestane, *HR* hazard ratio, *mo* month(s), *PBO* placebo, *wk* week(s)



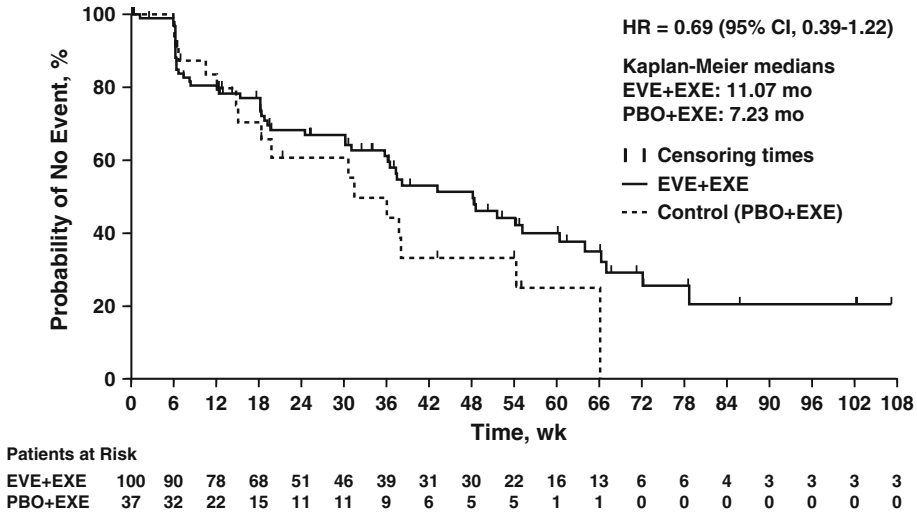




**Fig. 2** Kaplan–Meier curves of TDD (5 % decrease in HRQoL relative to baseline) in Global Health Status in patients whose disease recurred during/after adjuvant therapy [includes patients who also received (neo)adjuvant therapy]. *CI* Confidence interval, *EVE* everolimus, *EXE* exemestane, *HR* hazard ratio, *mo* month(s), *PBO* placebo, *wk* week(s)

recurrent disease without prior exposure to NSAIs [22–24]. However, endocrine therapy in patients with $HR^+$, $HER2^-$ advanced breast cancer previously exposed to NSAIs, whether in the adjuvant or advanced disease setting, generally results in shorter median TTP or PFS. For example, in the EFECT trial, median TTP was 3.7 months for both

**Table 2** Most commonly reported AEs in patients whose disease recurred during or after adjuvant therapy (incidence ≥25 % in the EVE + EXE arm)

| AE (preferred term) | Patients (%) | | | | | |
|---|---|---|---|---|---|---|
| | EVE + EXE ($n$ = 100) | | | Control (PBO + EXE) ($n$ = 37) | | |
| | Grade | | | Grade | | |
| | All | 3 | 4 | All | 3 | 4 |
| Stomatitis | 68 | 4 | 0 | 22 | 0 | 0 |
| Diarrhea | 40 | 3 | 1 | 22 | 0 | 0 |
| Rash | 37 | 0 | 0 | 8 | 0 | 0 |
| Fatigue | 32 | 3 | 0 | 16 | 3 | 0 |
| Weight decrease | 30 | 1 | 0 | 11 | 0 | 0 |
| Decreased appetite | 28 | 0 | 0 | 11 | 0 | 0 |
| Nausea | 28 | 0 | 1 | 30 | 3 | 0 |
| Cough | 26 | 0 | 0 | 8 | 0 | 0 |
| Pneumonitis[a] | 22 | 1 | 0 | 0 | 0 | 0 |
| Hyperglycemia[a] | 17 | 7 | 1 | 3 | 3 | 0 |

Includes patients who also received (neo)adjuvant therapy

*AE* Adverse event, *EVE* everolimus, *EXE* exemestane, *PBO* placebo

[a] Incidence <25 %, but AE of special interest

fulvestrant (250 mg q 4 weeks) and EXE ($P = 0.65$) [6]. In addition, median PFS was 3–5 months in the SoFEA trial (4.4 months for fulvestrant 250 mg q 4 weeks + anastrozole vs 4.8 months for fulvestrant 250 mg q 4 weeks vs 3.4 months for EXE; $P = 0.56$–$0.98$) and 6–7 months in CONFIRM (6.5 months for fulvestrant 500 mg q 4 weeks and 5.5 months for fulvestrant 250 mg q 4 weeks; $P = 0.006$) [25, 26]. Increasingly, NSAIs have become standard of care in the adjuvant setting. Thus, although both EXE and fulvestrant may be used for breast cancer recurring after adjuvant NSAI therapy, the efficacy of these treatments is limited, and additional effective first-line treatment options are needed for these patients, especially those whose disease progressed during/after NSAI therapy. In this context, data from the present subset analysis provide support for the efficacy of EVE + EXE as first-line therapy in $HR^+$, $HER2^-$ breast cancer progressing on adjuvant NSAIs, and suggest that earlier use of this strategy in the treatment course may lead to greater benefit.

Combinations of endocrine therapies with targeted agents in the first-line setting for advanced breast cancer progressing on NSAIs have shown mixed results. The histone deacetylate inhibitor entinostat plus EXE increased median PFS by 2 months versus EXE alone in patients whose disease recurred after adjuvant NSAI treatment or progressed after first-line NSAI (4.3 vs 2.3 months, $P = 0.055$) [27]. In the phase 3 HORIZON trial, temsirolimus, an mTOR inhibitor, plus letrozole versus letrozole alone failed to improve PFS as first-line therapy in patients with AI-naive advanced breast cancer [28]. It was suggested that the cyclic dosing regimen (30 mg/day for 5 days/2 weeks) used for oral temsirolimus [28] may not have achieved adequate suppression of mTOR activity as observed with a continuous dosing regimen [29]. In addition, the study populations in the BOLERO-2 and HORIZON trials had a different prior AI exposure. In fact, approximately 60 % of patients in HORIZON were endocrine therapy-naive at study entry [29]. In contrast, the TAMRAD (a phase 2 study of EVE plus tamoxifen vs tamoxifen alone in patients with $HR^+$, $HER2^-$ advanced breast cancer after AI therapy) and BOLERO-2 [8, 18] study populations only included patients who progressed on a prior AI.

The data presented here demonstrate that HRQoL is maintained even though a higher rate of AEs was observed with EVE + EXE compared with control. In addition, proactive monitoring and management of AEs are recommended in patients treated with EVE + EXE to help further optimize clinical benefit. Data from the present exploratory analysis indicate that EVE + EXE may be an effective and tolerable first-line therapy for advanced breast cancer after (neo)adjuvant NSAI treatment. Moreover, EVE + EXE could offer an additional first-line treatment option, providing PFS prolongation beyond the duration that would be expected with endocrine therapy alone, which is currently the recommended standard of care in this patient population [4, 5]. Limitations of this subset analysis include its retrospective and exploratory nature and modest sample size. Analysis of outcomes based on prior use of endocrine therapy only versus endocrine therapy plus chemotherapy in this subset also was not considered feasible because of the small sample size and the risk of creating an imbalance between treatment arms in further subanalyses.

These data raise a possible hypothesis that EVE + EXE combination therapy may be more effective in patients exposed to multiple lines of endocrine therapy, including those whose only prior therapy was an NSAI in the adjuvant setting. Specifically, the disease may be using alternative pathways, such as the mTOR pathway, to continue cancer cell growth and proliferation in the presence of endocrine interventions. These alternative pathways are less likely to be active in patients with minimal or no prior exposure to systemic endocrine therapy [29, 30]. Nonetheless, disease relapse during standard adjuvant endocrine therapy remains a concern, and might involve similar signaling pathways. Several prospective trials are also evaluating the effectiveness of EVE in improving disease-free survival and overall survival when used in combination with endocrine therapy in the adjuvant setting. For example, the SWOG/NSABP S1207 study is a phase 3 randomized trial that is evaluating the efficacy of 1 year of EVE plus endocrine

therapy in patients with high-risk early $HR^+$, $HER2^-$ breast cancer [31, 32]. The UNIRAD study by the UNICANCER group is evaluating the efficacy of EVE when administered concurrently with endocrine therapy after 3 years of adjuvant endocrine therapy in a similar study population [33, 34].

Based on data from BOLERO-2, recent NCCN and Canadian Consensus clinical practice guidelines have recommended EVE + EXE therapy for $HR^+$, $HER2^-$ advanced breast cancer recurring/progressing during or after an NSAI, even in the presence of visceral metastases [19, 21]; however, it should be noted that these guidelines are not specific to progression during or after adjuvant therapy. Furthermore, an ongoing multicenter, open-label, single-arm, phase 2 trial (BOLERO-4) is prospectively evaluating the efficacy of EVE plus letrozole as first-line therapy in patients with $HR^+$, $HER2^-$ advanced breast cancer [35], and may provide additional insight into the efficacy of EVE plus an AI as first-line treatment for advanced disease. Notably, BOLERO-4 also is evaluating measures to proactively manage common AEs (e.g., stomatitis) during EVE treatment to maintain continuity of therapy. In addition, the promising efficacy of EVE in managing advanced breast cancer has resulted in the ongoing SWOG and UNIRAD trials (discussed earlier) evaluating the efficacy of adding EVE to adjuvant endocrine therapy for reducing the risk of disease recurrence in patients with high-risk early breast cancer [31–34].

## Conclusions

In the BOLERO-2 trial, the benefit of adding EVE to EXE observed in the subset of patients whose disease progressed during or after (neo)adjuvant NSAI therapy was consistent with that observed in the overall population. Furthermore, the substantial improvement in PFS in this subset was accomplished while maintaining HRQoL. The safety and tolerability profile of EVE in this subset analysis also was similar to that observed in the overall BOLERO-2 population and with prior experience in the oncology setting. These data support the efficacy of EVE + EXE as first-line therapy for advanced breast cancer in patients with recurrence on adjuvant NSAI therapy.

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**Conflict of interest** T. Brechenmacher, M. El-Hashimy, S. Douma, and F. Ringeisen are employees of Novartis. M. Campone reports a consultant/advisory role with and remuneration/honoraria from Novartis. I. Deleu reports clinical trial funding from Novartis. L. Hart reports research funding to his institution from Novartis. D. Heng reports a consultant/advisory role with Novartis. G. Hortobagyi reports a consultant/advisory role with and research funding from Novartis. B. Melichar reports a consultant/advisory role with and remuneration/honoraria from Novartis. M. Piccart reports research funding from Novartis. B. Pistilli reports a consultant/advisory role with Novartis. The other authors report no competing interests.

**Ethical Standards** The BOLERO-2 trial was conducted in accordance with the Good Clinical Practice guidelines, the Declaration of Helsinki, and each country's laws and regulations.

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