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Effect of visceral metastases on the efficacy and safety of everolimus in postmenopausal women with advanced breast cancer: Subgroup analysis from the BOLERO-2 study ☆

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KEYWORDS
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Abstract ***Background:*** Everolimus (EVE; an inhibitor of mammalian target of rapamycin [mTOR]) enhances treatment options for postmenopausal women with hormone-receptor-positive (HR^+), human epidermal growth factor receptor-2-negative ($HER2^-$) advanced breast cancer (ABC) who progress on a non-steroidal aromatase inhibitor (NSAI). This is especially true for patients with visceral disease, which is associated with poor prognosis. The BOLERO-2 (Breast cancer trial of OraL EveROlimus-2) trial showed that combination treatment with EVE and exemestane (EXE) versus placebo (PBO) + EXE prolonged progression-free survival (PFS) by both investigator (7.8 versus 3.2 months, respectively) and independent (11.0 versus 4.1 months, respectively) central assessment in postmenopausal women with HR^+, $HER2^-$ ABC recurring/progressing during/after NSAI therapy. The BOLERO-2 trial included a substantial proportion of patients with visceral metastases (56%).
Methods: Prespecified exploratory subgroup analysis conducted to evaluate the efficacy and safety of EVE + EXE versus PBO + EXE in a prospectively defined subgroup of patients with visceral metastases.
Findings: At a median follow-up of 18 months, EVE + EXE significantly prolonged median PFS compared with PBO + EXE both in patients with visceral metastases ($N = 406$; 6.8 versus 2.8 months) and in those without visceral metastases ($N = 318$; 9.9 versus 4.2 months). Improvements in PFS with EVE + EXE versus PBO + EXE were also observed in patients with visceral metastases regardless of Eastern Cooperative Oncology Group performance status (ECOG PS). Patients with visceral metastases and ECOG PS 0 had a median PFS of 6.8 months with EVE + EXE versus 2.8 months with PBO + EXE. Among patients with visceral metastases and ECOG PS $\geqslant 1$, EVE + EXE treatment more than tripled median PFS compared with PBO + EXE (6.8 versus 1.5 months).
Interpretation: Adding EVE to EXE markedly extended PFS by $\geqslant 4$ months among patients with HR^+ $HER2^-$ ABC regardless of the presence of visceral metastases.
Funding: Novartis.

1. Introduction

Endocrine therapy (ET) is the cornerstone of systemic treatment for patients with hormone-receptor-positive (HR^+) advanced breast cancer (ABC). Endocrine treatment with third-generation aromatase inhibitors (letrozole, anastrozole and exemestane) has improved overall survival (OS) and has become the standard first-line treatment option for postmenopausal women.[1,2] Despite the documented benefits of ET in breast cancer, intrinsic and acquired resistance remains a common feature that limits the success of this therapeutic strategy.[3] The treatment options for patients with progression on ET offer limited clinical benefit and poor survival outcomes, leading to the need for new therapeutic strategies to enhance the efficacy of ET.[4] Recent years have seen major advances in understanding the mechanisms of resistance to ET, including up-regulation of the phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (PI3K/Akt/mTOR) signalling pathway, which is a key regulator of tumour cell growth, proliferation and metabolism.[5–8] Hyperactivation of this pathway has been linked to breast cancer pathogenesis, progression and resistance to endocrine therapy.

Everolimus (EVE; Afinitor®, Novartis) is an oral mTOR inhibitor that acts by binding to mTOR complex 1 and has been approved for treating advanced renal cell carcinoma, progressive neuroendocrine pancreatic tumours and, most recently, ABC progressing after non-steroidal aromatase inhibitors (NSAIs).[9,10] In preclinical studies, use of EVE in combination with ET resulted in synergistic inhibition of proliferation, induction of apoptosis and restoration of tumour endocrine sensitivity.[11–13] This concept was recently confirmed in the randomised, placebo-controlled, phase 3 BOLERO-2 (Breast cancer trial of OraL EveROlimus-2) study that evaluated the efficacy and safety of the combination of EVE and exemestane (EXE) in postmenopausal women with HR^+ ABC progressing/recurring after NSAIs.[14] Based on investigator assessment, EVE + EXE improved progression-free survival (PFS) compared with placebo (PBO)+EXE (median PFS 7.8 versus 3.2 months, respectively).[9] These results were consistent with those based on independent central assessment (median PFS 11.0 versus 4.1 months for EVE + EXE and PBO + EXE, respectively).[9]

The prognosis of patients with HR^+ ABC depends on the pattern and extent of metastatic tumour spread. Notably, two fundamental patterns of metastatic spread have been recognised: one with the involvement of soft tissues and/or bone metastases and one with visceral organ involvement, including lung, liver, peritoneum or pleura. Patients with visceral metastases have worse prognosis than patients without visceral disease (median survival 18–24 months versus ~40 months in early clinical trials of first-line NSAI therapy).[15–17] Unfortunately,

treatment options are limited in patients with visceral metastases who have progressed during/after NSAI treatment. Current treatment guidelines recommend endocrine therapy unless the patient has extensive visceral disease and the need for rapid symptom control; in these cases chemotherapy is recommended.[1,18] However, in contrast with the current guidelines, most patients with visceral metastases may be treated with cytotoxic chemotherapy regardless of their disease burden, predominantly because of concerns regarding the longer time needed for response to ET compared with chemotherapy.[19] In fact, a substantial proportion of patients with visceral disease who are not in visceral crisis (and therefore not in need of immediate symptom control) could benefit from continued ET, thereby delaying the need for chemotherapy and its associated toxicities. The prespecified exploratory subgroup analyses presented here evaluate the efficacy and safety of EVE + EXE in the prospectively defined subgroup of patients with visceral metastases in the BOLERO-2 study.

2. Methods

2.1. Trial design

BOLERO-2 is an international, phase 3, multicentre, randomised, double-blind, placebo-controlled trial including patients from 189 centres in 24 countries. The study was designed by the academic investigators and by representatives of the sponsor, Novartis (ClinicalTrials.gov identifier NCT00863655).[20] Full details have already been reported.[14]

2.2. Patients

Postmenopausal women with HR^+, human epidermal growth factor receptor-2-negative ($HER2^-$) metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy, who had progressed on prior anastrozole or letrozole (recurrence during/within 12 months after adjuvant treatment or progression during/within 1 month after treatment for advanced disease), were enrolled in the study. Patients had baseline Eastern Cooperative Oncology Group performance status (ECOG PS) $\leqslant 2$ with adequate organ and haematologic functions and at least one measurable lesion or mainly lytic bone lesions in the absence of measurable disease. Patients who had received prior ET and a single prior chemotherapy regimen for advanced disease were also eligible. Key exclusion criteria were HER2 overexpression; a history of brain metastases; prior treatment with EXE or mTOR inhibitors and bilateral diffuse lymphangitic carcinomatosis. Patients with massive lung (>50%) or liver (>1/3) involvement by sonogram and/or computed tomographic scan (i.e. disease burden that may constitute a visceral crisis) were initially excluded; however, a protocol amendment in February 2010 removed this language and appreciation of massive visceral involvement in the lung or liver was left to investigator discretion. Adequate liver function was required for study entry. Enrolment began in June 2009 and continued until January 2011.

The Institutional Review Board at each participating centre 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 (IDMC) performed semiannual safety reviews and reviewed the interim efficacy results. Written informed consent was obtained from all patients before enrolment.

2.3. Randomisation and masking

Patients were randomised (at a 2:1 ratio in favour of EVE + EXE group) to oral EVE (10 mg/day) or matching PBO, both plus EXE (25 mg/day). Randomisation was stratified by the presence of visceral metastases (yes versus no) and documented sensitivity to prior ET (yes versus no). Visceral metastases included pulmonary, hepatic, pleural, pleural effusions, peritoneal and ascites involvement. Any other sites of metastasis (e.g. bone, lymph nodes, skin) were considered non-visceral. Patients with visceral metastases irrespective of the presence of any other metastatic sites (e.g. bone) were categorised as visceral. All other patients without visceral metastases were categorised as non-visceral. Endocrine sensitivity was defined as either objective response or stable disease lasting $\geqslant 24$ weeks after hormonal therapy for advanced disease or $\geqslant 24$ months of adjuvant hormonal therapy before disease recurrence.

2.4. Treatment

Patients were treated until disease progression, development of unacceptable toxicity or withdrawal of consent. Everolimus dose interruptions or reductions were permitted for the management of adverse events (AEs). The initial dose reduction allowed in the protocol was 5 mg daily and a subsequent reduction to 5 mg every other day.[14]

Computed tomographic scanning or magnetic resonance imaging of chest, abdomen and pelvis was performed to assess tumours at baseline and every 6 weeks until disease progression. The primary endpoint was PFS, defined as time from randomisation to first documentation of disease progression by the local investigator according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0, unequivocal progression of existing bone lesions, appearance of

new lesions or death from any cause. Secondary endpoints included OS, overall response rate, clinical benefit rate (CBR), time to deterioration of ECOG PS, safety and quality of life. Clinical benefit rate was defined as complete response, partial response or stable disease for ⩾24 weeks. Adverse events were monitored throughout the study and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.[21]

2.5. Statistical analysis

The primary efficacy analysis of PFS was assessed using a log-rank test stratified according to visceral metastases and previous hormone sensitivity, and was estimated between treatment groups using the Kaplan–Meier method. Hazard ratios and associated 95% confidence intervals (CIs) were assessed by the Cox proportional hazards method as previously described.[14] All analyses were conducted using SAS® for Windows, Version 9.2 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics and disposition

Between June 2009 and January 2011, 724 women across 189 centres in 24 countries were randomised to study treatments ($N = 485$; EVE + EXE, $N = 239$; PBO + EXE). Table 1 shows baseline demographics and patient characteristics with regard to visceral involvement. Visceral involvement was reported in 406 patients (56%) and was balanced between treatment arms. The mean age of patients (~62 years) was similar regardless of visceral involvement. The majority of patients (>60%) with visceral involvement had ECOG PS 0 at baseline. The time between initial diagnosis and first recurrence/metastasis was ⩾6 months for the majority of patients (~70%) with or without visceral disease. The majority of patients had invasive ductal carcinoma irrespective of visceral involvement. Among patients with visceral involvement, 84% had two or more metastatic sites and 50% had three or more

Table 1
Patient demographics and baseline disease characteristics.[a]

Characteristic	Everolimus + exemestane		Placebo + exemestane	
	Visceral ($N = 271$)	Non-visceral ($N = 214$)	Visceral ($N = 135$)	Non-visceral ($N = 104$)
Mean age, years (SD)	62.7 (10.3)	62.2 (10.3)	61.3 (9.9)	61.1 (9.6)
⩾65 years	42%	38%	35%	32%
ECOG PS				
0	61%	60%	62%	56%
1	35%	37%	33%	38%
2	2%	1%	2%	4%
Unknown	2%	2%	2%	3%
Time between initial diagnosis and first recurrence/metastasis				
<3 months	19%	22%	21%	15%
3 to <6 months	2%	1%	2%	2%
⩾6 months	72%	71%	70%	77%
Unknown	7%	7%	7%	6%
Histology/cytology				
Invasive ductal carcinoma	80%	73%	80%	71%
Invasive lobular carcinomas	9%	19%	13%	22%
Other	9%	7%	7%	7%
Not applicable	2%	1%	1%	0%
Number of metastatic sites involved				
1	19%	49%	11%	47%
2	33%	27%	36%	34%
3	26%	15%	29%	13%
4	14%	6%	18%	6%
5	6%	2%	4%	1%
>5	2%	1%	2%	0%
Key metastatic sites[b]				
Lung	43%	12%	47%	14%
Liver	51%	12%	47%	9%
Lung and liver	13%	5%	16%	4%
Bone	71%	83%	73%	84%

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; SD, standard deviation.

[a] Percentages are rounded to the nearest whole number.

[b] 75 patients were mis-stratified as not having visceral disease at randomisation, which accounts for the small percentages of patients with lung and/or liver metastases in the 'no visceral metastases at baseline' columns.

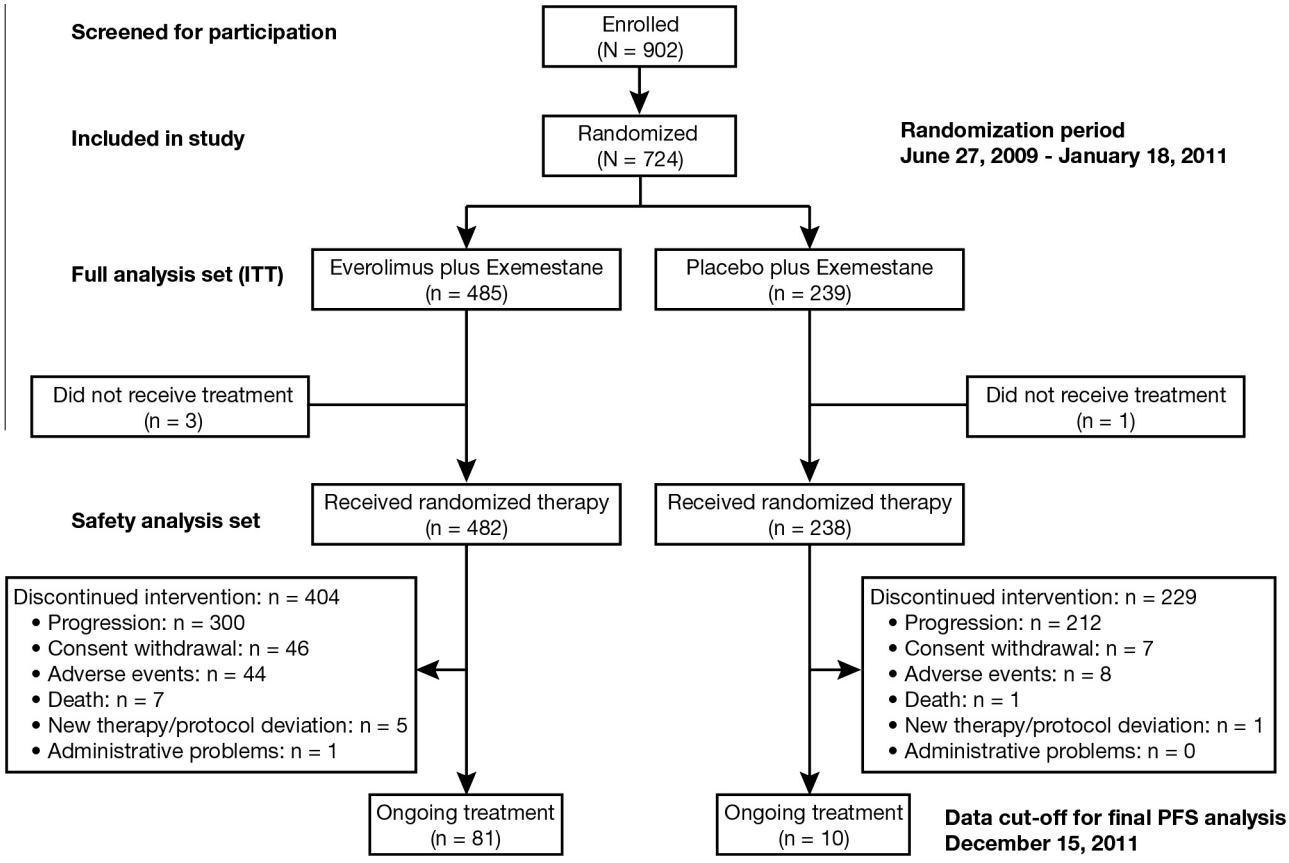

Fig. 1. Trial profile. *Abbreviation:* ITT, intent-to-treat population.

metastatic sites. For patients with visceral disease, approximately 45% had lung metastases, 50% had liver metastases and 14% had both lung and liver metastases. In patients without visceral disease (44% of the overall population), bone was the most common site of metastases (83%). The distribution of metastatic sites was well balanced across treatment arms. It is important to note that 75 patients were mis-stratified as not having visceral disease at randomisation; however, a sensitivity analysis for PFS using the stratification factor of visceral metastases based on patient medical records in the clinical report forms showed similar results as the analysis using the stratification factor based on randomisation (results not shown) (Fig. 1).

At a median follow-up of 18 months, 91 patients continued to receive study treatment: 81 (17%) in the EVE + EXE arm and 10 (4%) in the PBO + EXE arm. The most common reason for treatment discontinuation was disease progression (62% EVE + EXE; 89% PBO + EXE).

3.2. Efficacy

The trial met its primary end-point, PFS, which was significantly improved with EVE + EXE compared with PBO + EVE overall, and in all subgroups defined by stratification factors (i.e. sensitivity to prior hormonal therapy and the presence of visceral metastasis). Treatment with EVE resulted in significant improvement in PFS irrespective of visceral involvement. Among patients with visceral metastases, median PFS per local investigator assessment was 6.8 months in patients treated with EVE + EXE versus 2.8 months for those treated with PBO + EXE (hazard ratio 0.47; 95% CI 0.37–0.60; $p < 0.05$) (Fig. 2). Results based on central assessment for patients with visceral metastases treated with EVE + EXE versus PBO + EXE were consistent (8.3 versus 2.9 months; hazard ratio 0.46). Patients who did not have visceral metastases at baseline had a 5.7-month extension in median PFS per local investigator assessment with EVE + EXE versus PBO + EXE (9.9 versus 4.2 months; hazard ratio 0.41; 95% CI 0.31–0.55; $p < 0.05$) (Fig. 2).

Improvements in PFS with EVE + EXE versus PBO + EXE were also observed in all patients with visceral metastases regardless of ECOG PS. Patients who had visceral involvement at baseline with ECOG PS 0 had a median PFS of 6.8 months with EVE + EXE versus 2.8 months with PBO + EXE (hazard ratio 0.54, 95% CI 0.4–0.73, $p < 0.05$) (Table 2). Among patients with visceral involvement at baseline and ECOG PS $\geqslant 1$, EVE + EXE treatment also improved median

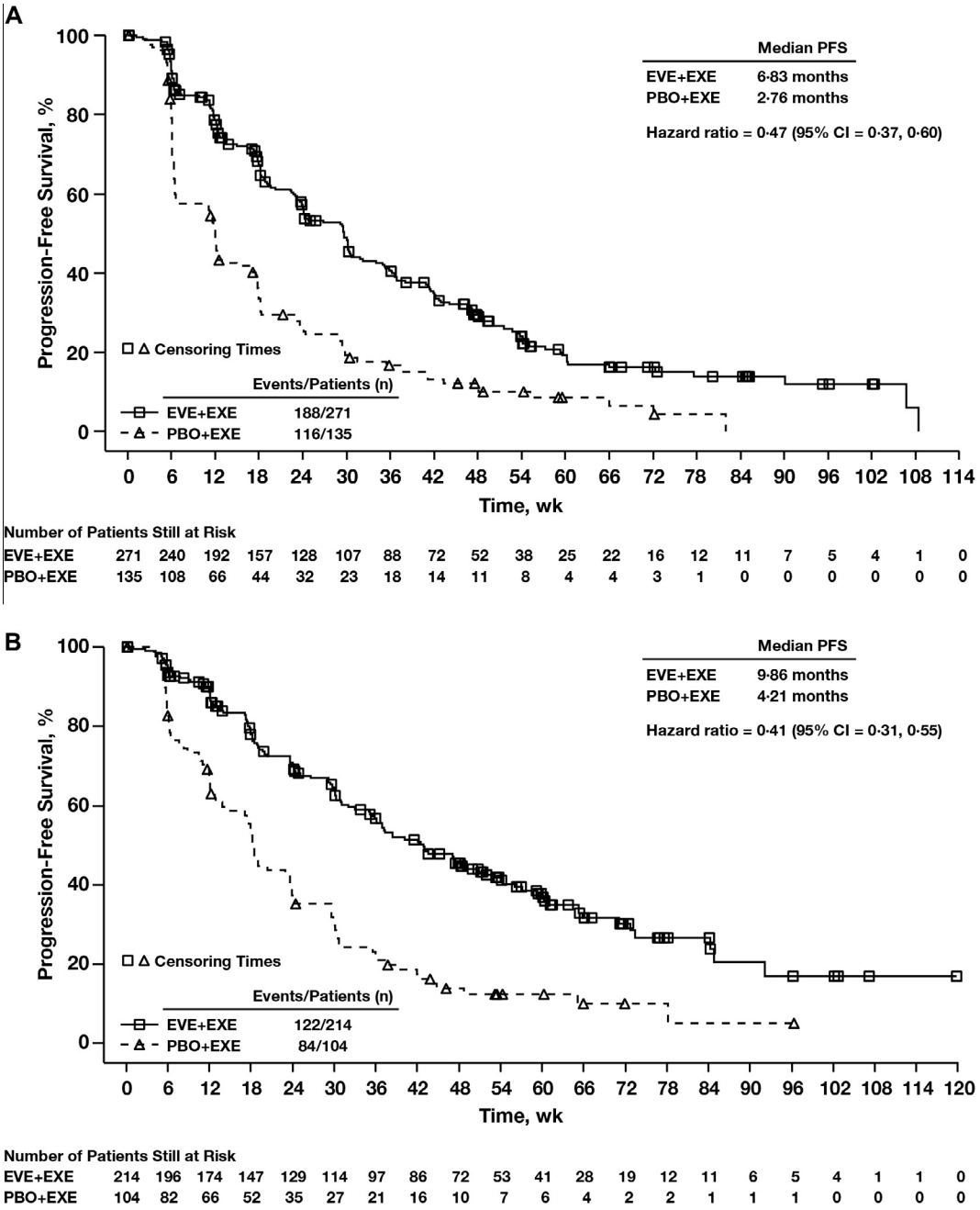

Fig. 2. Kaplan–Meier curve for PFS in patients (A) with and (B) without visceral involvement. *Abbreviations:* CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); PBO, placebo; PFS, progression free survival.

Table 2
Analysis of PFS by visceral disease and performance status at baseline.

	Everolimus + exemestane			Placebo + exemestane			Hazard ratio (95% CI)
	Pts	Events	Median PFS (months)	Pts	Events	Median PFS (months)	
Patients with visceral disease at baseline	271	188 (69.4%)	6.83	135	116 (85.9%)	2.76	0.47 (0.37–0.60)
ECOG PS 0	167	114 (68.3%)	6.83	84	70 (83.3%)	2.79	0.54 (0.40–0.73)
ECOG PS $\geqslant$1	100	71 (71.0%)	6.77	48	43 (89.6%)	1.45	0.35 (0.23–0.52)

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; pts, patients.

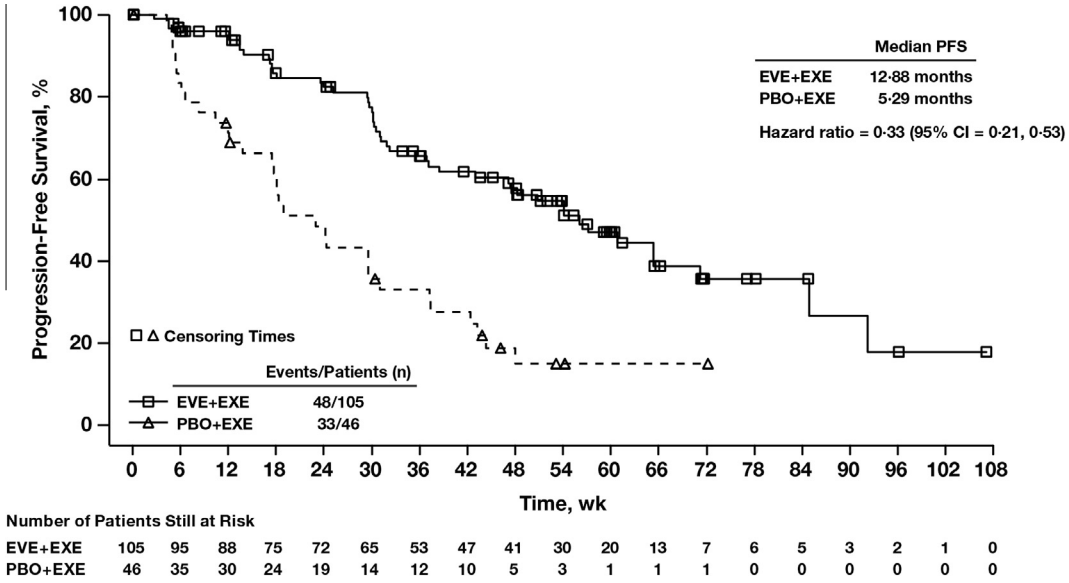

Fig. 3. Kaplan–Meier curve for PFS in patients with bone-only metastases. *Abbreviations:* CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); PBO, placebo; PFS, progression free survival.

PFS compared with PBO + EXE (6.8 versus 1.5 months; hazard ratio 0.35; 95% CI 0.23–0.52; $p < 0.05$) (Table 2). Improvement in PFS with EVE + EXE was also observed in patients who had bone-only lesions at baseline (12.88 versus 5.29 months; $N = 105$ for EVE + EXE; $N = 46$ for PBO + EXE; hazard ratio 0.33; 95% CI 0.21–0.53; $p < 0.05$) (Fig. 3).

Consistent with the longer PFS seen in EVE + EXE treated patients; clinical benefit rate (CBR) was also significantly higher among patients who received EVE + EXE irrespective of visceral involvement (Table 3). Clinical benefit rate was highest among patients without visceral disease at baseline treated with EVE + EXE (59.8%; 95% CI 52.9%–66.4% versus 31.7%; 95% CI 22.9%–41.6% for PBO + EXE). Patients with visceral disease treated with EVE + EXE had a similar CBR independent of ECOG PS (ECOG PS 0, 43.7%; ECOG PS $\geqslant$1, 44%). An increase in CBR was also observed among patients with visceral metastases at baseline and ECOG PS $\geqslant$1 treated with EVE + EXE (44%) compared with PBO + EXE (8.3%) (Table 3). Additionally, the time to 5% deterioration in global health status was consistently longer with EVE + EXE versus PBO + EXE in patients with (7.82 versus 4.40 months; hazard ratio 0.74; 97.5% CI 0.52–1.05) or without (8.38 versus 7.03 months; hazard ratio 0.73; 97.5% CI 0.49–1.08) baseline visceral metastases (Fig. 4).

3.3. Safety

Similar to the safety profile observed in the overall population,[14] in this subgroup analysis patients treated with EVE + EXE had a higher incidence of treatment-emergent AEs compared with those treated with PBO + EXE. In general, the incidence of AEs among treatment groups was similar irrespective of the presence of visceral metastases at baseline, and there was no indication of increased risk of specific AEs (e.g. metabolic abnormalities or elevated levels of liver enzymes) in patients with visceral metastases (Table 4). The most common treatment-emergent AEs among patients with visceral disease at baseline receiving EVE + EXE were stomatitis, rash, fatigue, decreased appetite and diarrhoea. The type and frequency of these AEs are consistent with those observed in the overall study population receiving EVE + EXE.[14]

4. Discussion

The present study is a subgroup analysis from the BOLERO-2 trial that provides support for the efficacy and safety of combined treatment with EVE and EXE to enhance sensitivity to ET in postmenopausal women with visceral metastases from HR^+ ABC and progression during/after NSAI treatment. The combination of EVE + EXE prolonged PFS by 4 months in patients with visceral metastases (6.8 versus 2.8 months). This PFS improvement was confirmed by independent central assessment and is consistent with that observed in the overall population in the BOLERO-2 trial.[22] A superior CBR (~44%) was also observed among these patients for the combination arm versus the EXE-only arm irrespective of their ECOG PS. The majority of patients (69% in the overall population; 84% in patients with visceral metastases at baseline) in the BOLERO-2 trial had metastases at two or more sites and, although such patients may receive chemotherapy in clinical practice, these results show that they can indeed gain substantial benefit from the combination of

Table 3
Analysis of clinical benefit rate by visceral disease and performance status at baseline.

	Everolimus + exemestane			Placebo + exemestane		
	n/*N*	%	95% CI	*n*/*N*	%	95% CI
No visceral disease at baseline	128/214	59.8	(52.9–66.4)	33/104	31.7	(22.9–41.6)
Visceral disease at baseline	121/271	44.6	(38.6–50.8)	30/135	22.2	(15.5–30.2)
ECOG PS 0	73/167	43.7	(36.1–51.6)	23/84	27.4	(18.2–38.2)
ECOG PS ⩾1	44/100	44.0	(34.1–54.3)	4/48	8.3	(2.3–20.0)

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status.

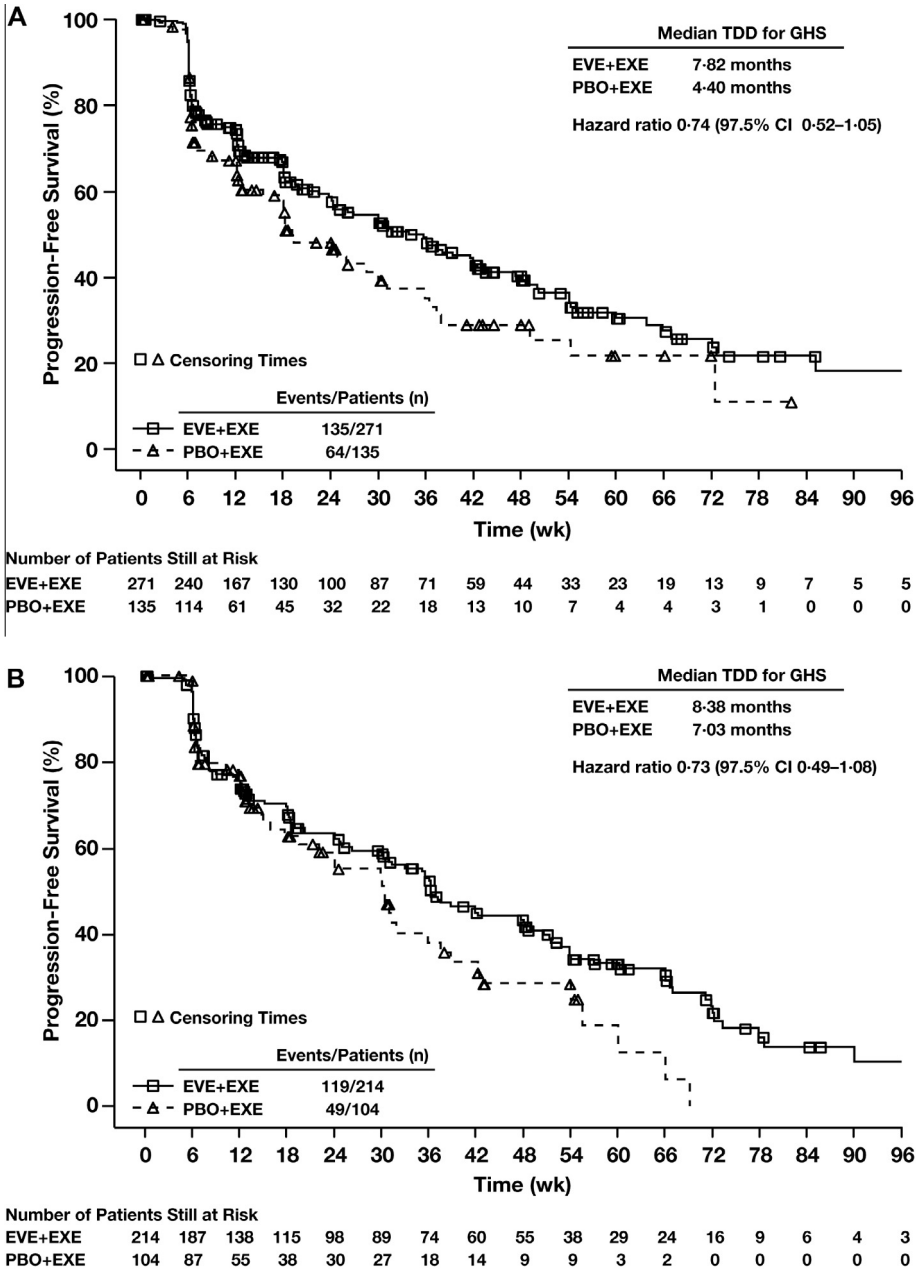

Fig. 4. Kaplan–Meier curve for time to 5% deterioration in global health status in patients (A) with and (B) without visceral involvement. *Abbreviations:* CI, confidence interval; EVE, everolimus (10 mg/day); EXE, exemestane (25 mg/day); GHS, global health status; PBO, placebo; TDD, time to definitive deterioration.

Table 4
Any-grade adverse events[a] with ⩾20% incidence.[b]

Adverse event	Everolimus + exemestane		Placebo + exemestane	
	Visceral ($N = 269$) (%)	Non-visceral ($N = 213$) (%)	Visceral ($N = 135$) (%)	Non-visceral ($N = 103$) (%)
Stomatitis	59	59	13	10
Rash	40	39	4	10
Fatigue	40	36	29	25
Decreased appetite	36	24	15	11
Diarrhoea	34	34	16	22
Nausea	33	27	29	28
Weight decreased	30	25	7	8
Cough	27	24	13	11
Dysgeusia	24	19	6	6
Headache	20	25	15	15
Hyperglycaemia	16	12	2	2
AST increased	15	12	5	6
Pneumonitis	14	19	0	0
ALT increased	12	13	4	5
Interstitial lung disease	2	6	0	0
Hyperlipidaemia	1	1	1	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase.
Note: Percentages are rounded to the closest whole number.
[a] Adverse event incidences are reported for the safety population.
[b] Metabolic abnormalities and pulmonary adverse events are reported even if the incidence was <20% because these are class effects with mammalian target of rapamycin inhibitors.

EVE + EXE.[14] In the BOLERO-2 trial, the efficacy of EVE + EXE was maintained in patients who had visceral disease per stratification criteria. Therefore, this combination offers a viable alternative treatment approach with less toxicity compared with most cytotoxic chemotherapy agents.

Alterations in signalling via the serine threonine kinase mTOR are common in cancer and, thus, mTOR is being actively pursued as a therapeutic target. Previous reports indicate that blocking the PI3K/Akt/mTOR pathway serves as a novel approach to restore or enhance sensitivity to ET.[23] In the TAMRAD study, EVE added to tamoxifen delayed time to disease progression (8.6 versus 4.5 months for tamoxifen alone) and improved OS (median not reached versus 24 months, $p = 0.002$) in patients with HR^+, $HER2^-$, metastatic breast cancer.[24] However, the patient population was too small to perform subset analysis on the 53% of patients with visceral disease.[24] The results from the current subset analysis therefore add to the growing evidence supporting the addition of an mTOR inhibitor to ET as a means to enhance endocrine sensitivity in patients with visceral disease. Overall, this analysis demonstrates that EVE, an mTOR inhibitor, given at a dose of 10 mg/day in combination with the steroidal AI EXE at 25 mg/day, is a valuable treatment option for postmenopausal women with visceral metastases from ABC who have progressed on prior NSAI treatment, have few symptoms and retain a reasonably good performance status.

Visceral metastases in patients with ABC are associated with poor prognosis. In routine clinical practice, these patients are likely to receive chemotherapy, especially after failure of prior NSAI therapy. Although chemotherapy may be necessary when rapid symptom control is needed (i.e. patients with highly symptomatic visceral disease and/or a high disease burden in vital organs), many patients with visceral metastases have lower disease burden and may benefit from ET.[18,19] By extending the number of treatment options available in such cases, it may be possible to postpone cytotoxic chemotherapy and thereby delay the burden of treatment-related myelosuppression and other AEs.[18] The analyses presented herein add to the body of evidence supporting delaying chemotherapy for HR^+ disease in the advanced setting.

Although AEs in the present analysis were more frequent with EVE + EXE versus EXE alone, they were generally manageable and occurred irrespective of visceral involvement. The AEs observed with EVE in this study (e.g. stomatitis, rash, fatigue, decreased appetite, diarrhoea and hyperglycaemia) are consistent with those observed with EVE monotherapy in other tumour types (e.g. renal cell carcinoma) and are manageable with established strategies including dose adjustments.[9,25] Furthermore, quality of life as measured by time to 5% deterioration in global health status was maintained in patients receiving EVE.

A limitation of this study is that patients with extensive visceral disease were initially explicitly excluded. However, the protocol was amended such that appreciation of massive visceral involvement in the lung or liver was left to investigator discretion. Although not the intention of the amendment, some patients with extensive visceral disease may have entered the study.

Although a subset of women with visceral metastases will continue to require chemotherapy for rapid clinically significant symptom control, the combination of

EVE + EXE offers an important alternative for the large proportion of patients whose visceral metastases are not immediately life-threatening. The convenience of this all-oral combination, together with favourable tolerability, adds to the armamentarium against HR^+ ABC progressing after NSAI therapy.

4.1. Panel: research in context

4.1.1. Prespecified exploratory subgroup analysis

A subgroup analysis of the BOLERO-2 phase 3 study was conducted to evaluate the efficacy and safety of EVE + EXE versus PBO + EXE in a prospectively defined subgroup of patients with visceral metastases. In BOLERO-2, postmenopausal women with HR^+, $HER2^-$ ABC who had recurred or progressed during/after anastrozole or letrozole were enrolled in the study. Patients were randomised (at a 2:1 ratio in favour of EVE + EXE group) to oral EVE (10 mg/day) or matching PBO, both plus EXE (25 mg/day). The present analyses were based on stratification by the presence of visceral metastases (yes versus no) at randomisation. Visceral metastases included pulmonary, hepatic, pleural, pleural effusions, peritoneal and ascites involvement. Any other sites of metastasis (e.g. bone, lymph nodes and skin) were considered non-visceral. Patients with visceral metastases, irrespective of the presence of any other metastatic sites (e.g. bone), were categorised as visceral. All other patients without visceral metastases were categorised as non-visceral.

4.1.2. Interpretation

Adding EVE to EXE markedly extended PFS by more than 4 months among patients with HR^+, $HER2^-$ ABC regardless of the presence of visceral metastases. Although a subset of women with visceral metastases will continue to require chemotherapy for rapid clinically significant symptom control, the combination of EVE + EXE offers an important alternative for the large proportion of patients whose visceral metastases are not immediately life-threatening. The convenience of this all-oral combination, together with favourable tolerability, adds to the armamentarium against HR^+ ABC progressing after NSAI therapy.

Authors' contributions

Responsible for the conception and design of the study: MG, HSR, KIP, GNH, JB, TT, TS and MP. *Contributed to the collection and assembly of data:* MC, BP, MS, KIP, LP, LH, BM, FA, AH, ME-H, TT and TS. *Responsible for writing the manuscript:* MC, TB, MG, BP, SN, KIP, LP, HB, BM, GNH, JB, AP, ME-H and TT. *Responsible for data analysis and interpretation:* MC, MG, HSR, BP, SN, KIP, LP, HB, LH, BM, GNH, JB, AP, AH, ME-H, TT, TS and MP. *Responsible for provision of study material or patients:* MC, TB, DI, HSR, BP, MS, KIP, LP, HB, LH, BM, GNH, FA, JB, AH, ME-H, TT, TS and MP.

Conflict of interest statement

- M. Campone is a consultant to and has received honoraria from Novartis.
- T. Bachelot is a consultant to and has received honoraria and research funding from Novartis.
- M. Gnant has received research support from GlaxoSmithKline, sanofi-aventis, Novartis and Roche; is a consultant to Merrion and Novartis; and has received honoraria (speaking, advisory boards, etc.) and travel support from Amgen, Pfizer, Novartis, GlaxoSmithKline, Bayer, Sandoz, AstraZeneca and Genomic Health.
- I. Deleu has nothing to disclose.
- H.S. Rugo has received grant support from Pfizer, Novartis and Merck, and has received travel support from Novartis.
- B. Pistilli has received honoraria from Novartis.
- S. Noguchi has received grant support and honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai, GlaxoSmithKline, Novartis, Pfizer, sanofi-aventis, Taiho and Takeda.
- M. Shtivelband has nothing to disclose.
- K.I. Pritchard is a consultant with sanofi-aventis, AstraZeneca, Roche, Pfizer, Novartis, Abraxis, Amgen and GlaxoSmithKline; has received research funding either directly through per-case funding for studies or indirectly through the National Cancer Institute of Canada Clinical Trials Group; contracted with pharmaceutical companies including AstraZeneca, Bristol-Myers Squibb, sanofi-aventis, Amgen, Pfizer, Novartis, GlaxoSmithKline and Ortho Biotech; has received honoraria or been part of speaker's bureaus from sanofi-aventis, AstraZeneca, Pfizer, Roche, Novartis, GlaxoSmithKline and Amgen; has given paid expert testimony for sanofi-aventis, AstraZeneca and GlaxoSmithKline; and has been a member on an Advisory Committee for sanofi-aventis, AstraZeneca, Roche, Pfizer, Novartis, GlaxoSmithKline and Amgen.
- L. Provencher is a consultant for Novartis and Roche; has received honoraria from Roche, Novartis and Amgen; has received research funding from Pfizer and Roche; has received research funding either directly or through per-case funding for studies or indirectly through the National Cancer Institute of Canada Clinical Trials Group and the NSABP; and has received travel support from Novartis, GlaxoSmithKline and Roche.
- H. Burris has nothing to disclose.
- L. Hart has nothing to disclose.

- B. Melichar has received honoraria (speaking, advisory boards, etc.) and travel support from Amgen, Pfizer, Novartis, GSK and Roche.
- G.N. Hortobagyi is a member of the Scientific Advisory Board of Allergan; is a consultant to Allergan, Novartis, Genentech and sanofi-aventis; has received grant support from Novartis; and has received travel expense reimbursement from Novartis, Genentech and sanofi-aventis.
- F. Arena has received research funding from Arena Oncology Associates, PC.
- J. Baselga is a consultant to Novartis, Roche, Merck, sanofi-aventis, Verastem, Bayer, Chugai, Exelixis, Onyx and Constellation.
- A. Panneerselvam is an employee of Novartis with stock/stock options.
- A. Héniquez is an employee of Novartis.
- M. El-Hashimy is an employee of Novartis with stock/stock options.
- T. Taran is an employee of Novartis with stock/stock options.
- T. Sahmoud is an employee of Novartis with stock.
- M. Piccart is a board member for PharmaMar; is a consultant to Bristol-Myers Squibb, Merck, Boehringer, Roche, Verastem and Bayer; has received grant support from Pfizer, Novartis, Merck, Boehringer, Bristol-Myers Squibb, GlaxoSmithKline, Roche and sanofi-aventis; and has received honoraria from Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Boehringer, Roche, Amgen, sanofi-aventis and AstraZeneca.

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