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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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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.
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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,