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ORIGINAL RESEARCH

Everolimus Plus Exemestane in Postmenopausal Patients with HR$^+$ Breast Cancer: BOLERO-2 Final Progression-Free Survival Analysis

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ABSTRACT

Introduction: Effective treatments for hormone-receptor-positive (HR$^+$) breast cancer (BC) following relapse/progression on nonsteroidal aromatase inhibitor (NSAI) therapy are needed. Initial Breast Cancer Trials of OraL EveROlimus-2 (BOLERO-2) trial data demonstrated that everolimus and exemestane significantly prolonged progression-free survival (PFS) versus placebo plus exemestane alone in this patient population.

Methods: BOLERO-2 is a phase 3, double-blind, randomized, international trial comparing everolimus (10 mg/day) plus exemestane (25 mg/day) versus placebo plus exemestane in postmenopausal women with HR$^+$ advanced BC with recurrence/progression during or after

Portions of the data have been presented previously: Piccart-Gebhart MJ, Noguchi S, Pritchard KI, Burris HA, Rugo HS, Gnant M, et al. Everolimus for postmenopausal women with advanced breast cancer: Updated results of the BOLERO-2 phase III trial [abstract]. Presented at the 48th Annual Meeting of the American Society of Clinical Oncology; June 1–5, 2012; Chicago, IL. Abstract 559.

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NSAIs. The primary endpoint was PFS by local investigator review, and was confirmed by independent central radiology review. Overall survival, response rate, and clinical benefit rate were secondary endpoints.

Results: Final study results with median 18-month follow-up show that median PFS remained significantly longer with everolimus plus exemestane versus placebo plus exemestane [investigator review: 7.8 versus 3.2 months, respectively; hazard ratio = 0.45 (95% confidence interval 0.38–0.54); log-rank $P < 0.0001$; central review: 11.0 versus 4.1 months, respectively; hazard ratio = 0.38 (95% confidence interval 0.31–0.48); log-rank $P < 0.0001$] in the overall population and in all prospectively defined subgroups, including patients with visceral metastases, patients with recurrence during or within 12 months of completion of adjuvant therapy, and irrespective of age. The incidence and severity of adverse events were consistent with those reported at the interim analysis and in other everolimus trials.

Conclusion: The addition of everolimus to exemestane markedly prolonged PFS in patients with HR^+ advanced BC with disease recurrence/progression following prior NSAIs. These results further support the use of everolimus plus exemestane in this patient population. ClinicalTrials.gov #NCT00863655.

Keywords: Advanced breast cancer; Everolimus; Exemestane; Hormone receptor positive; Nonsteroidal aromatase inhibitors; Oncology; Postmenopausal; Progression-free survival

INTRODUCTION

The majority of women with breast cancer (BC; approximately 70% worldwide) have hormone-receptor-positive (HR^+) tumors [1]. Almost all of these women will receive endocrine therapy as a standard part of their treatment for early and/or advanced-stage disease [2–4]. Currently, third-generation nonsteroidal aromatase inhibitors (NSAIs: anastrozole and letrozole) and steroidal exemestane (EXE) represent the preferred front-line therapy for postmenopausal women with HR^+ advanced BC [4]. However, progressive disease ultimately develops in virtually all patients, either as early failure to respond to endocrine therapy (de

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novo resistance) or as relapse/progression after initial response (acquired resistance) [5].

A significant proportion of tumors in BC patients retain their sensitivity to endocrine-directed approaches even after disease progression on prior endocrine therapy, and may respond to another endocrine agent [6, 7]. In view of the favorable safety profile of endocrine-directed agents, extending the benefit of endocrine therapy at relapse/progression is an important clinical consideration. In particular, the low toxicity of endocrine agents compared with chemotherapy represents a major advantage in a population of patients with a high incidence of comorbidities. However, sequential lines of single-agent endocrine therapy are associated with modest clinical benefit [6, 7]. Accordingly, combination endocrine therapies [8–10] and co-targeting of downstream elements of the molecular pathways associated with BC progression and the development of endocrine resistance [e.g., histone deacetylase or mammalian target of rapamycin (mTOR)] have been investigated [11, 12].

Preclinical and clinical evidence shows that everolimus (EVE), a rapamycin derivative, has direct anticancer effects, and that mTOR inhibition can enhance the efficacy of endocrine therapy in breast tumors [13–15]. The strategy of dual inhibition with endocrine therapy and an mTOR inhibitor was investigated in the **B**reast Cancer Trials of **O**ra**L** **Eve**ro**l**imus-**2** (BOLERO-2) trial [16]. Data from the protocol-defined interim analysis at 7.6-month median follow-up of this randomized, placebo-controlled, phase 3 trial demonstrated that EVE+EXE significantly improved progression-free survival (PFS) compared with placebo (PBO) + EXE [hazard ratio (HR) 0.43; $P < 0.001$ based on local investigator assessment; HR 0.36; $P < 0.001$ based on the independent central radiology assessment] [16]. This led to the recent regulatory approval in the United States and Europe of EVE in combination with EXE for the treatment of postmenopausal women with HR^+, human epidermal growth factor receptor 2-negative ($HER2^-$) advanced BC recurring or progressing after prior NSAIs [9]. The final analysis of PFS, other efficacy endpoints, and updated safety are reported here.

METHODS

Details of patient selection criteria and the clinical protocol of this study have been previously reported [16].

Patients

Enrolled patients were adult postmenopausal women with HR^+ metastatic/locally advanced BC not amenable to surgery or radiotherapy and progressing after anastrozole or letrozole (defined as disease recurrence during or within 12 months of end of adjuvant treatment or progression during or within 1 month of end of treatment for advanced disease). Patients whose tumors showed HER2 overexpression (immunohistochemistry 3+) or gene amplification (in situ hybridization positive) or who had received prior therapy with EXE or mTOR inhibitors were excluded.

Written informed consent was obtained from all patients before enrollment. The institutional review board at each participating center approved the study, which was conducted in accordance with the principles of Good Clinical Practice, the provisions of the Declaration of Helsinki of 1975, as revised in 2000 and 2008, and other applicable local regulations. A steering committee supervised

study conduct. An independent data and safety monitoring committee performed semiannual safety reviews and reviewed the interim efficacy results.

Study Design

BOLERO-2 was a multicenter, double-blind, randomized, placebo-controlled, international phase 3 study. Patients were randomly allocated in a 2:1 ratio to receive EVE 10 mg/day or matching PBO in a blinded manner; all patients received open-label EXE 25 mg/day ($N = 724$). Patients were stratified according to the presence of visceral metastasis (yes vs no) and sensitivity to previous hormonal therapy (yes vs no), as previously described [16]. The primary endpoint for this study was PFS as assessed by local investigator [based on Response Evaluation Criteria In Solid Tumors (RECIST) 1.0] and confirmed by central review. Secondary endpoints included overall response rate (complete response or partial response); clinical benefit rate (CBR; defined as complete response + partial response + stable disease for at least 24 weeks); overall survival (OS); quality of life (QOL), changes in bone marker levels, and patient safety.

Study Assessments

Tumor assessments were based on computed tomography (CT) scans or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis at baseline and every 6 weeks until disease progression. Patients who discontinued one or both study treatments for any reason other than progression were followed with the same assessment schedule until progression. A bone scan or skeletal survey using radiography, CT scanning, or MRI was required within 6 weeks before randomization. Abnormalities observed on bone scans were assessed using the same method every 6 weeks. After discontinuation of treatment, patients who progressed were followed every 3 months for survival.

Hematologic parameters, biochemical measures, and vital signs were assessed at baseline and at each visit, and the lipid profile was assessed every 6 weeks. Adverse events (AEs) were monitored continuously throughout the study and graded according to Common Terminology Criteria for Adverse Events, version 3.0 [17].

Statistical Analysis

The primary efficacy analysis of PFS by local investigator assessment required 528 PFS events to achieve 90% power to detect an HR of 0.74 (26% risk reduction) using a log-rank test and 2-look Lan-DeMets group [18] sequential design with O'Brien–Fleming-type boundary at a one-sided cumulative 2.5% significance level; one interim analysis was conducted after observing 60% of events (previously reported) [16]. Based on the magnitude and stability of the EVE treatment effect over time, as well as lower-than-expected event rates, final analysis after slightly fewer events than planned (i.e., 510 events) was considered appropriate.

RESULTS

A total of 724 patients were randomized between June 2009 and January 2011 to receive EVE+EXE ($n = 485$) or PBO+EXE ($n = 239$). Baseline characteristics were similar between treatment groups (Table 1) [16]. At baseline, 77% of patients had bone lesions (21% had bone-only lesions), and of the approximately 59% with visceral disease, 84% had involvement at 2 or more sites.

Table 1 Patient demographic, baseline disease, and treatment characteristics

Characteristic	EVE+EXE (n = 485), %	PBO+EXE (n = 239), %
Median age, years (range)	62 (34–93)	61 (28–90)
Race		
White	74	78
Asian	20	19
Black	3	1
Other	3	2
ECOG performance status 0	60	59
Visceral disease	58	59
Measurable disease[a]	70	68
Metastatic site		
Lung	30	33
Liver	33	30
Bone	77	77
Prior therapy		
Setting of most recent treatment		
Adjuvant	21	16
Advanced/ metastatic disease	79	84
LET or ANA as most recent treatment	74	75
Tamoxifen	47	50
Fulvestrant	17	16
Chemotherapy (any setting)	69	65
Chemotherapy for metastatic BC	26	26
Radiotherapy	70	69
Number of prior therapies[b]		
1 or 2	46	47
≥3	54	53

From Baselga et al. [16]. Copyright © 2012 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society. Any minor differences between this table and the original report by Baselga et al. [16] are a consequence of the investigator's data correction at the subsequent analysis

ANA anastrozole, *BC* breast cancer, *ECOG* Eastern Cooperative Oncology Group, *EVE* everolimus, *EXE* exemestane, *LET* letrozole, *PBO* placebo

[a] All other patients had ≥1 mainly lytic bone lesion

[b] Prior therapies include those used in the adjuvant setting or to treat advanced disease

Approximately 48% of patients had been previously treated with tamoxifen (TAM), and approximately 17% had previously received fulvestrant (both in addition to the NSAI required per inclusion criteria). Approximately 80% of patients received prior therapy for metastatic disease, including chemotherapy (26%), whereas 20% of patients received study treatment as their first therapy for metastatic disease.

At the cutoff date for the final PFS analysis, December 15, 2011, 510 PFS events had accrued based on local assessment and 320 per central radiology review. The median duration of follow-up at data cutoff was 17.7 months (range 10.9–28.6 months). Eighty-one patients (16.7%) in the EVE+EXE arm and 10 patients (4.2%) in the PBO+EXE arm continued to receive study treatment.

In the EVE+EXE arm, median duration of exposure to EVE was 23.9 weeks (range 1.0–123.3 weeks) and median exposure to EXE was 29.5 weeks (range 1.0–123.3 weeks). In the PBO+EXE arm, median exposure to EXE was 14.07 weeks (range 1.0–101.0 weeks). The

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