Health-Related Quality of Life of Patients With Advanced Breast Cancer Treated With Everolimus Plus Exemestane Versus Placebo Plus Exemestane in the Phase 3, Randomized, Controlled, BOLERO-2 Trial

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BACKGROUND: The randomized, controlled BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial demonstrated significantly improved progression-free survival with the use of everolimus plus exemestane (EVE + EXE) versus placebo plus exemestane (PBO + EXE) in patients with advanced breast cancer who developed disease progression after treatment with nonsteroidal aromatase inhibitors. This analysis investigated the treatment effects on health-related quality of life (HRQOL). **METHODS:** Using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire, HRQOL was assessed at baseline and every 6 weeks thereafter until disease progression and/or treatment discontinuation. The 30 items in 15 subscales of the QLQ-C30 include global health status wherein higher scores (range, 0-100) indicate better HRQOL. This analysis included a protocol-specified time to definitive deterioration (TDD) analysis at a 5% decrease in HRQOL versus baseline, with no subsequent increase above this threshold. The authors report additional sensitivity analyses using 10-point minimal important difference decreases in the global health status score versus baseline. Treatment arms were compared using the stratified log-rank test and Cox proportional hazards model adjusted for trial stratum (visceral metastases, previous hormone sensitivity), age, sex, race, baseline global health status score and Eastern Cooperative Oncology Group performance status, prognostic risk factors, and treatment history. **RESULTS:** Baseline global health status scores were found to be similar between treatment groups (64.7 vs 65.3). The median TDD in HRQOL was 8.3 months with EVE + EXE versus 5.8 months with PBO + EXE (hazard ratio, 0.74; $P = .0084$). At the 10-point minimal important difference, the median TDD with EVE + EXE was 11.7 months versus 8.4 months with PBO + EXE (hazard ratio, 0.80; $P = .1017$). **CONCLUSIONS:** In patients with advanced breast cancer who develop disease progression after treatment with nonsteroidal aromatase inhibitors, EVE + EXE was associated with a longer TDD in global HRQOL versus PBO + EXE. ***Cancer* 2013;119:1908–15.** © *2013 American Cancer Society.*

KEYWORDS: advanced breast cancer, everolimus, exemestane, health-related quality of life, hormone receptor-positive.

INTRODUCTION

Everolimus (EVE) is a mammalian target of rapamycin inhibitor with direct anticancer effects. In preclinical and clinical studies, EVE demonstrated that mammalian target of rapamycin inhibition can enhance the efficacy of endocrine therapy, including exemestane (EXE).[1-3] The phase 3 BOLERO-2 (Breast Cancer Trials of Oral Everolimus) trial was designed to evaluate the efficacy and safety of EVE + EXE versus placebo (PBO) + EXE in postmenopausal women with hormone

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receptor-positive advanced breast cancer who developed disease progression after treatment with nonsteroidal aromatase inhibitors (NSAIs; letrozole or anastrozole).[4] Data from an interim analysis at 7 months of follow-up demonstrated that EVE + EXE significantly improved the primary endpoint of progression-free survival (PFS) versus PBO + EXE (hazard ratio [HR], 0.43; $P < .001$) based on local investigator assessment.[4] Median durations of PFS were 6.9 months and 2.8 months, respectively. The PFS benefit was confirmed at 12.5 months and 18 months of median follow-up.[5,6] Adverse events were consistent with the safety profile of EVE.[6] The findings from this trial supported the recent approval in the United States and Europe of EVE + EXE for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer who developed disease progression while receiving treatment with NSAIs.[7,8]

Treatment-related toxicities combined with often painful and debilitating metastases resulting from disease progression can erode health-related quality of life (HRQOL).[9-12] Therefore, in addition to clinical benefit, providing palliation and maximizing HRQOL remain the key goals of treating patients with advanced breast cancer.[13] Studies of HRQOL can aid in treatment selection and provide information regarding the impact of disease progression on patients' lives.[14,15] Furthermore, evaluation of HRQOL concerns such as fatigue, pain, and anxiety, as well as the impact of disease on physical and social functioning, can augment the overall risk:benefit analysis, and HRQOL is now regarded as an important outcome in clinical cancer trials.[14,16,17] These outcomes are especially important in patients with hormone receptor-positive advanced breast cancer, in whom endocrine therapy options after disease progression with NSAI treatment (eg, fulvestrant and EXE) might provide limited therapeutic benefit, but have relatively low toxicity.[18] In the BOLERO-2 trial, time to HRQOL deterioration was a secondary objective because it was essential to determine the impact of EVE + EXE versus PBO + EXE on HRQOL. In the current study, we report the results of that HRQOL analysis.

MATERIALS AND METHODS

Patients and Study Design

The study design for BOLERO-2 has been described previously.[4] The population comprised postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor-2 (HER2)–negative, metastatic or locally advanced breast cancer who developed disease progression despite prior treatment with anastrozole or letrozole. All patients provided informed consent.

In this multicenter, double-blind, randomized, placebo-controlled trial, all patients received EXE (at a dose of 25 mg/day) and were randomized 2:1 to treatment with EVE (at a dose of 10 mg/day) or matching PBO.[4] Randomization was stratified by the presence of visceral metastasis (yes vs no) and sensitivity to prior hormonal therapy (yes vs no).[4] Treatment continued until disease progression, the development of unacceptable toxicity, or withdrawal of patient consent.

The primary endpoint was PFS, as assessed by investigators. Overall survival, overall response rate, clinical benefit rate, time to deterioration of Eastern Cooperative Oncology Group (ECOG) performance status, safety, and HRQOL were secondary endpoints. This analysis includes HRQOL outcomes; the results of all other endpoints have been reported previously.[5,6]

HRQOL Assessment

HRQOL was evaluated at baseline and every 6 weeks thereafter until disease progression and/or discontinuation using version 3.0 of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). All questionnaires were completed at the study center before disease assessment. The questionnaire consists of 30 items arranged in 15 subscales, including a global health status/QOL scale; higher scores for this scale (range, 0-100) indicate better HRQOL.[19]

Statistical Analysis

All HRQOL analyses were performed on the full analysis set (N = 724). Partially completed questionnaires were included if the data were sufficient to calculate the global health status/QOL domain subscale score. A deterioration event was defined as a 5% decrease in HRQOL relative to baseline. Protocol-specified time to definitive deterioration (TDD) in the global health status score was defined as a 5% HRQOL decrease relative to baseline, with no subsequent increase above this threshold. The "5% decrease in HRQOL from baseline" criterion was selected based on previously established thresholds for minimal important differences (MID) in QOL from the perspective of the patient.[20] This criterion for TDD was less stringent than previously published MID values for global health status.[21-23] Generally established and accepted MID values for global health status range from 5 to 10 points. Therefore, a sensitivity analysis was performed to assess the larger, 10-point MID decrease in global health status score compared with baseline; this criterion has been

TABLE 1. ECOG Performance Status

Score	EVE+EXE, % (n = 485)	PBO+EXE, % (n = 239)
0	60	59
1	36	35
2	2	3

Abbreviations: ECOG, Eastern Cooperative Oncology Group; EVE, everolimus; EXE, exemestane; PBO, placebo.
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validated for EORTC QLQ-C30 in other studies.[21-23] TDD in global health status for each of the definitions was calculated using Kaplan-Meier estimates and was described using medians and 95% confidence intervals (95% CIs). TDD was compared between the treatment groups using a stratified log-rank test (strata were based on the presence of visceral metastases and sensitivity to hormonal therapy) with a 2-sided type I error rate of 0.05, and a multivariate Cox proportional hazards model adjusted for trial strata (the presence of visceral metastases and sensitivity to hormone therapy), age, sex, race, baseline score and ECOG performance status, prognostic risk factors, and treatment history. If a definitive deterioration event was observed after missing assessments, the event was backdated to the first of the missing assessments before the deterioration (ie, calculated as the last available assessment before the definitive deterioration plus 8 weeks). No other adjustments were made for missing data. Patients who had no definitive deterioration events were censored at the time of the last available assessment. All analyses were conducted using SAS statistical software for Windows (version 9.2; SAS Institute Inc, Cary, NC).

RESULTS

Patient Characteristics and Disposition

Between June 2009 and January 2011, 724 women across 189 centers in 24 countries were randomized to study treatments (485 in the EVE + EXE arm and 239 in the PBO + EXE arm).[4] The treatment arms were well balanced for patient and disease characteristics, including ECOG performance status score.[4] Notably, the majority of patients in both the EVE + EXE and PBO + EXE treatment arms had an ECOG performance status score of 0 (60% vs 59%, respectively) (Table 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.[6] The median duration of treatment exposure was 23.9 weeks for EVE and 29.5 weeks for EXE in the EVE + EXE arm and 13.4 weeks for PBO and 14.1 weeks for EXE in the PBO + EXE arm. Most patients in the EVE + EXE and PBO + EXE treatment arms discontinued treatment because of disease progression (62% vs 89%, respectively). Other reasons for discontinuation included adverse events (10% vs 3%, respectively) and consent withdrawal (9% vs 3%, respectively).

Efficacy and Safety

Data from a preplanned analysis at a median follow-up of 18 months demonstrated that EVE + EXE more than doubled PFS versus PBO + EXE.[6] However, EVE + EXE was associated with a higher incidence of adverse events than PBO + EXE, with the most common grade 3 or 4 adverse events (graded using the NCI CTCAE version 3.0) being stomatitis, hyperglycemia, and fatigue.[6]

Questionnaire Completion Rates

At baseline, questionnaires were completed by 455 patients (93.8%) in the EVE + EXE arm and 224 patients (93.7%) in the PBO + EXE arm. Data are presented through 48 weeks only, given a substantial decrease in subsequent data availability in both treatment arms. Questionnaire compliance was > 80% through week 48 and was not found to be markedly different between the treatment arms (Fig. 1a). Questionnaire completion rates decreased from baseline to week 48 (Fig. 1b), mainly because of disease progression and subsequent removal from the study. Compared with baseline, completion rates from weeks 12 through 48 were higher in the EVE + EXE arm versus the PBO + EXE arm (Fig. 1b).

TDD in Global Health Status

Baseline global health status scores were similar between the EVE + EXE and PBO + EXE arms (64.7 vs 65.3, respectively; difference, −0.7 [95% CI, −4.3 to 3.0]).

At a median follow-up of 18 months, the cumulative percentages of patients with a definitive deterioration in global health status treated with EVE + EXE versus PBO + EXE were comparable for both TDD definitions (Table 2). At a 5% change from baseline, 49% of patients in the EVE + EXE arm versus 44% of patients in the PBO + EXE arm had a definitive deterioration event, and death occurred in 3% of patients in each treatment arm. At a 10-point MID, definitive deterioration rates were 39% in the EVE + EXE arm versus 30% in the PBO + EXE arm, and death rates were 3% and 5%, respectively.

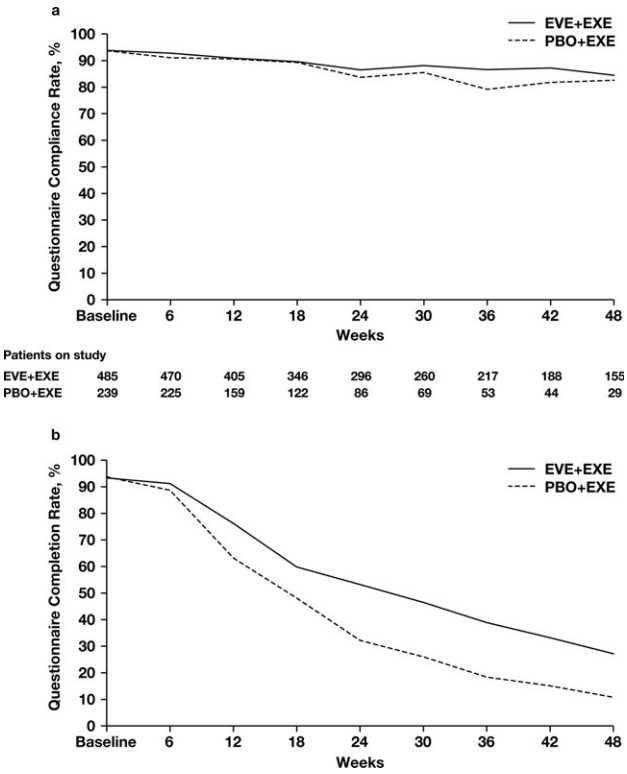

Figure 1. The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status questionnaire results for (a) compliance and (b) completion rates at baseline and follow-up visits are shown. (a) Percentage compliance rates were calculated based on the number of on-study patients in each treatment arm at every visit. (b) Percentage completion rates were calculated based on the intent-to-treat population in each treatment arm. EVE indicates everolimus; EXE, exemestane; PBO, placebo.

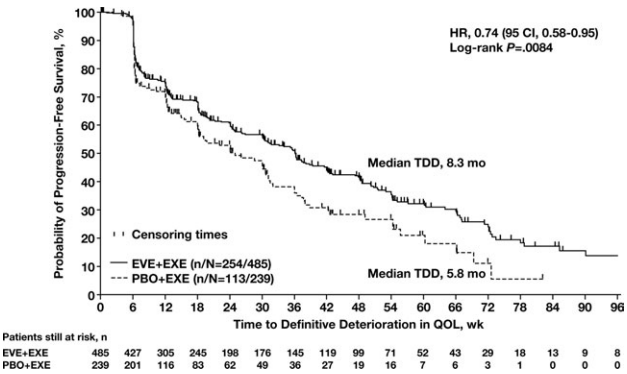

Figure 2. Time to definitive deterioration (TDD) for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status is shown, indicating a 5% change from baseline. HR indicates hazard ratio; 95% CI, 95% confidence interval; EVE, everolimus; EXE, exemestane; PBO, placebo; QOL, quality of life.

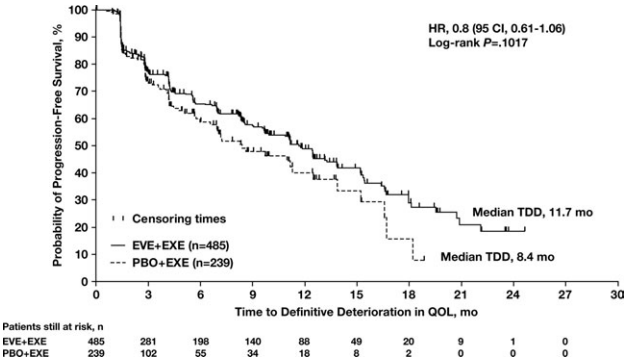

Figure 3. Time to definitive deterioration (TDD) for European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status is shown, with a minimal important difference of 10. HR indicates hazard ratio; 95% CI, 95% confidence interval; EVE, everolimus; EXE, exemestane; PBO, placebo; QOL, quality of life.

At 5% change from baseline, EVE + EXE was associated with longer TDD in global health status versus PBO + EXE. The median TDD was 8.3 months (95% CI, 7.0 months-9.7 months) in the EVE + EXE arm versus 5.8 months (95% CI, 4.2 months-7.2 months) in the PBO + EXE arm (Fig. 2). This translated into a 26% reduction in the risk of definitive deterioration with EVE + EXE (HR, 0.74; 95% CI, 0.58-0.95 [$P = .0084$ by the log-rank test]). Using the 10-point MID, the median TDD remained longer in the EVE + EXE arm versus the PBO + EXE arm (11.7 months [95% CI, 9.7 months-13.3 months] vs 8.4 months [95% CI, 6.6 months-12.5 months], respectively) (HR, 0.8; 95% CI, 0.61-1.06 [$P = .1017$ by the log-rank test]) (Fig. 3). The P value for TDD using a 5% change from baseline was found to be more significant than the P value for TDD using a 10-point MID (.0084 vs .1017, respectively), although the magnitudes of effect in terms of HR and difference in TDD were similar. This may be because of the number of patients for whom censoring was greater based on the 10-point MID criteria for TDD.

Regardless of the definition used (a 5% change from baseline or a 10-point MID), no statistically significant differences were observed with regard to the TDD of global health status for the majority of the prospectively defined patient-related and disease-related variables (Fig. 4); 1 exception was baseline ECOG performance status: in the overall trial, patients with a baseline ECOG performance status of 1 or 2 were found to have an increased risk of deterioration in global health status versus patients with a baseline performance status of 0.

In addition, TDD of global health status was analyzed for subsets defined by baseline ECOG performance

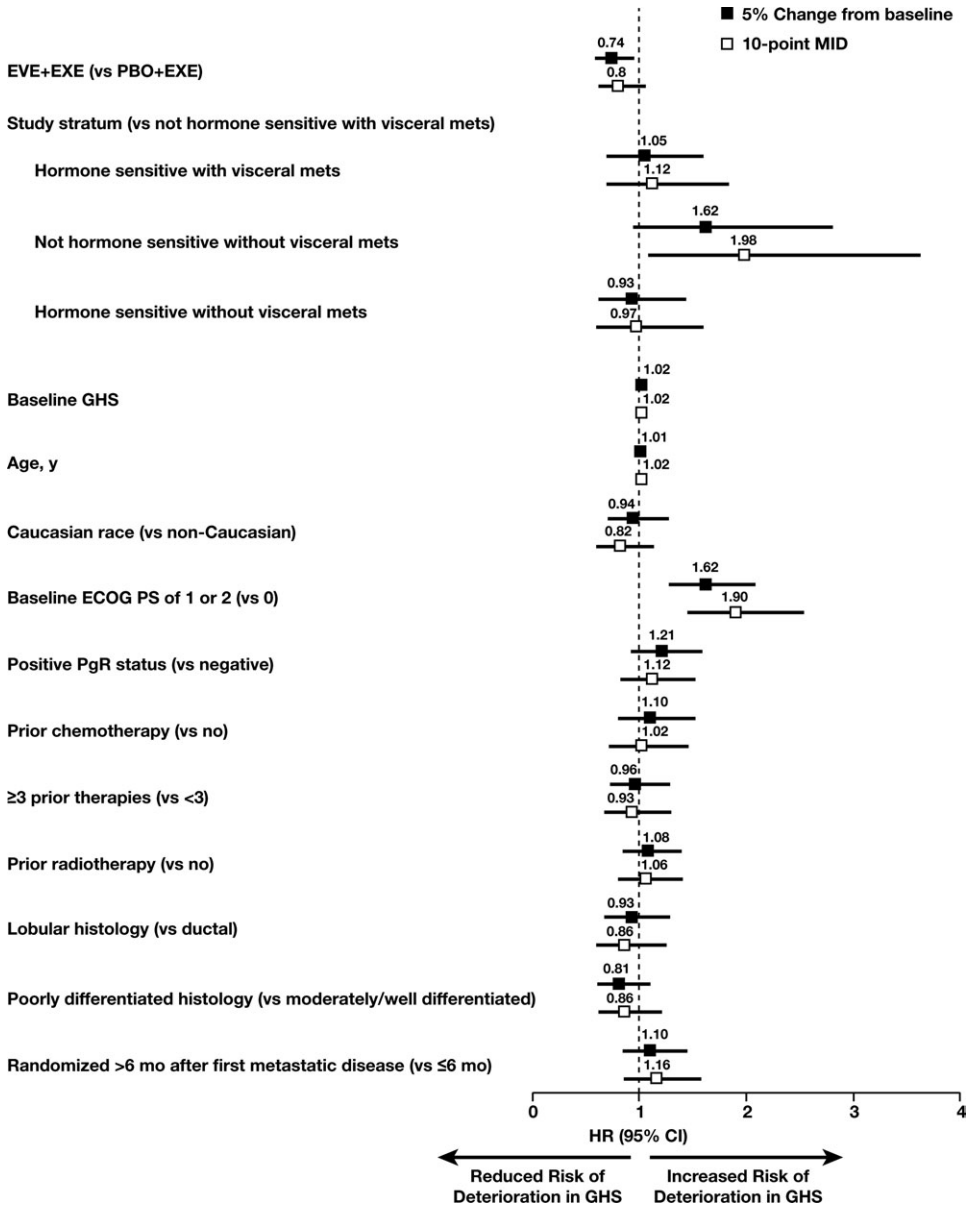

Figure 4. Risk of definitive deterioration in European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) global health status (GHS) by subgroups is shown, based on a 5% change from baseline and a 10-point minimal important difference (MID). Only patients with a valid baseline score were included, and only extended model data were reported. The hazard ratios (HRs) represent multiplicative increases in the risk of definitive deterioration per 1-unit increase in age or GHS. EVE, everolimus; EXE, exemestane; PBO, placebo; mets, metastases; ECOG PS, Eastern Cooperative Oncology Group performance status; PgR, progesterone receptor; 95% CI, 95% confidence interval.

status (0 vs 1-2) and age (< 65 years vs ≥ 65 years). Kaplan-Meier estimates indicated a longer median TDD for EVE + EXE versus PBO + EXE by both definitions in patients with an ECOG performance status of 1 or 2 (5% change from baseline: 8.2 months vs 4.1 months [$P = .0076$]; 10-point MID: 9.7 months vs 6.0 months [$P = .0342$]) and in patients aged < 65 years (5% change from baseline: 9.6 months vs 5.6 months [$P = .0130$]; 10-point MID: 12.5 months vs 9.7 months [$P = .0353$]). Cox proportional hazards models adjusted for study strata (the presence of visceral metastases and sensitivity to hormone therapy) also demonstrated a longer median TDD for EVE + EXE versus PBO + EXE in patients with an ECOG performance status of 1 or 2 (5% change from baseline: HR, 0.58 [95% CI, 0.41-0.84]; 10-point MID: HR, 0.61 [95% CI, 0.41-0.91]) and in those aged

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