4EVER—Final Efficacy Analysis of the Phase IIIb, Multi-Center, Open-Label Study for Postmenopausal Women With Estrogen Receptor-Positive Locally Advanced or Metastatic Breast Cancer Treated With Everolimus in Combination With Exemestane

Poster P5-19-06

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Introduction

- The phase III BOLERO-2 trial demonstrated that everolimus (EVE) + exemestane (EXE) more than doubled median progression-free survival (PFS) compared with placebo (PBO) + EXE in postmenopausal women with hormone receptor positive (HR$^+$), human epidermal growth factor receptor 2–negative (HER2$^-$) advanced breast cancer (BC) progressing after nonsteroidal aromatase inhibitor (NSAI) therapy[1]
  - Final PFS by investigator review: 7.8 vs 3.2 months; HR = 0.45; 95% CI, 0.38-0.54; *P* < .0001
  - Final PFS by central review: 11.0 vs 4.1 months; HR = 0.38; 95% CI, 0.31-0.48; *P* < .0001
- In current recommendations of The German Working Group for Gynecological Oncology (AGO), EVE+EXE was assigned the highest recommendation grade of "+/+" (first-line when there is recurrence within 12 months of adjuvant therapy or second-line therapy)[2]
- The 4EVER trial further evaluated the efficacy, safety, and quality of life with EVE+EXE in a broader patient population than in BOLERO-2 with no limitations on:
  - Number of previous chemotherapy lines for advanced disease
  - Time of recurrence or progression after NSAI therapy
  - Previous EXE therapy
- Here we report the results of the planned analysis of the primary and secondary endpoints of the 4EVER trial

Objective

- To evaluate the efficacy and safety of EVE+EXE in postmenopausal women with HR$^+$, HER2$^-$ advanced BC after progressing or recurring during or after an NSAI with no limitations on the number of previous chemotherapy lines for advanced disease, the time of recurrence or progression after NSAI therapy, and previous EXE therapy

Methods

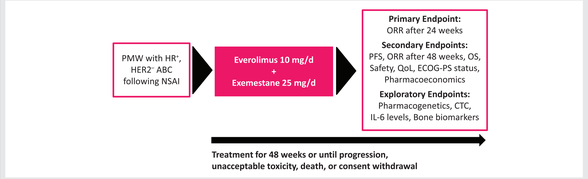
Study Design and Treatment

- Multi-center, open-label, single-arm, phase IIIB study examining EVE (10 mg daily) and EXE (25 mg daily; **Figure 1**)
- Postmenopausal women with HR$^+$, HER2$^-$ metastatic or locally advanced BC that recurred or progressed during or after an NSAI were enrolled
- Main inclusion criteria
  - Locally advanced or metastatic BC, not amenable to curative treatment by surgery or radiotherapy or any other nonsystemic treatment
  - Histological or cytological confirmation of HR$^+$ (ie, estrogen receptor positive and/or progesterone receptor-positive), HER2$^-$ BC
  - At least 1 lesion that can be accurately measured or bone lesions (lytic or mixed, lytic + sclerotic) in the absence of measurable disease
- Main exclusion criteria
  - Hormone receptor-negative or HER2-overexpressing disease
  - Symptomatic brain or other CNS metastases
  - Only non-measurable lesions (other than bone metastasis)
  - Known hypersensitivity or pretreatment to/with mTOR inhibitors
- Study treatment was for 48 weeks, or until progression, unacceptable toxicity, death or consent withdrawal
  - Further treatment after progression was at the investigator's discretion
- Tumor evaluations through computed tomography were performed for screening, after 24 weeks, and after 48 weeks or end of treatment
- Study visits were performed at baseline (Day 1), weeks 4, 12, 24, 36, and 48 or end of treatment
  - Each study visit included a physical exam, Eastern Cooperative Oncology Group performance status (ECOG PS) assessment, adverse event (AE) recording, blood analysis (ie, hematology, coagulation, biochemistry, lipid profile), urinalysis, and an electrocardiogram

Endpoints

- Primary endpoint was overall response rate (ORR ; complete response [CR] + partial response [PR]) per RECIST version X.X **[[AQ: PLEASE PROVIDE RECIST VERSION]]** after week 24
- Secondary endpoints include
  - Progression-free survival (PFS)
  - ORR after week 48
  - Overall survival (OS)
  - Safety assessed with the Common Terminology Criteria for Adverse Events, version 4.03
    - Incidence of AEs, serious adverse events (SAEs), changes from baseline in vital signs, ECOG-PS, and laboratory results (hematology, blood chemistry—if resulting in AE) were reported
- Exploratory endpoints include
  - Correlation of response to EVE+EXE with pharmacogenomics
  - Presence and molecular characteristics of circulating tumor cells
  - Correlation of anxiety and depression with IL-6 levels
  - Changes in serum biomarkers of bone metabolism

Figure 1. Study design.



Abbreviations: ABC, advanced breast cancer; CTC, circulating tumor cell; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; HR$^+$, hormone receptor–positive; HER2$^-$, human epidermal growth factor receptor 2–negative; NSAI, nonsteroidal aromatase inhibitor; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PMW, postmenopausal women; QoL, quality of life.

Analysis Populations and Statistical Methods

- The ***Safety Set*** includes all patients who received at least 1 dose of study drug and had at least 1 postbaseline safety assessment
- The ***Full Analysis Set 1*** includes all patients who received at least 1 dose of study drug with the exception of 18 patients from centers with issues of Good Clinical Practice noncompliance
- ORR 95% CIs determined via Clopper-Pearson method
- PFS and OS were estimated via the Kaplan-Meier method

Results

Baseline Patient Demographics and Disease Characteristics

- Trial database lock occurred in June 2014
- A total of 299 patients (safety set) were enrolled from May 2012 to November 2012
- The full analysis set 1 included 281 patients (**Table 1**)
  - All efficacy analyses were performed on this group
  - All safety analyses were performed on the safety set
- Most recent prior therapy setting was metastatic for 78.6% of patients (n = 221) and adjuvant for 19.9% of patients (n = 56)
  - 16.0% of patients (n = 45) had 2 lines of prior therapy in the metastatic setting
  - 43.1% of patients (n = 121) had ≥3 lines of therapy in the metastatic setting
- The most common metastatic sites were liver (51.6%), lymph node (21.4%), lung (16.4%), and bone (13.2%)

Table 1. Baseline Patient Demographics and Disease Characteristics (Full Analysis Set 1)

Baseline Parameters	EVE+EXE (N = 281)
Patient Demographics	
Median age, years (range)[a]	67.0 (35-87)
Age Group, n (%)	
< 65 years	127 (45.2)
≥ 65 years	154 (54.8)
Race, n (%)	
Caucasian	279 (99.3)
Asian	2 (0.7)
Median weight, kg (range)[a]	68 (40-111)
ECOG-PS, n (%)[a,b]	
0	170 (60.9)
1	98 (35.1)
2	11 (3.9)
Missing	2 (0.7)
Disease Characteristics	
Disease status, n (%)	
Metastatic	270 (96.1)
Locally advanced	5 (1.8)
Metastatic + locally advanced	6 (2.1)
HR status, n (%)[c]	
ER$^+$ and/or PgR$^+$	280 (99.6)
ER$^-$, PgR$^-$[d]	1 (0.4)
HER2 status, n (%)[e,f]	
HER2$^-$	277 (98.6)
HER2$^{+/0}$	2 (0.7)
Unknown/Missing	2 (0.7)
Target lesion, n (%)[g]	
Liver	145 (51.6)
Lymph nodes	60 (21.4)
Lung	46 (16.4)
Bone	37 (13.2)
Prior Therapies	
Most recent prior therapy setting, n (%)	
Metastatic	221 (78.6)
Adjuvant	56 (19.9)
Neoadjuvant	1 (0.4)
Missing	3 (1.1)
Prior therapy in the metastatic setting, n (%)	
Chemo- or endocrine therapy	221 (78.6)
Chemotherapy	151 (53.7)
Endocrine therapy	204 (72.6)
Number of prior lines of therapy for metastatic disease, n (%)	
0	59 (21.0)
1	52 (18.5)
2	45 (16.0)
3	34 (12.1)
≥4	87 (31.0)
Unknown	4 (1.4)
NSAI as most recent therapy, n (%)	94 (33.5)
Prior exemestane, n (%)	89 (31.7)
Prior fulvestrant, n (%)	121 (43.1)

[a] At screening.
[b] No patient had an ECOG PS ≥ 3 at screening. However, 1 patient had an ECOG PS = 3 at baseline.
[c] Assessed in primary tumor in 71.6% of patients, in metastasis in 28.4% of patients.
[d] Major protocol deviations; patients were discontinued early.
[e] Assessed in primary tumor in 66.4% of patients, in metastasis in 33.6% of patients.
[f] For patients with HER2$^+$ disease, the primary tumor was HER2$^+$ but metastases were HER2$^-$. **[[AQ: ERIK, PLEASE CONFIRM.]]**
[g] Metastatic sites are not mutually exclusive (ie, a patient may have had metastases at more than 1 site listed). Only the 4 most frequent metastatic sites are shown here. Target lesions were not specified in 39 patients.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ER, estrogen receptor; EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; NSAI, nonsteroidal aromatase inhibitor; PgR, progesterone receptor.

Results (Continued)

Overall Response Rate

- The ORR (CR + PR) after 24 weeks of treatment (primary endpoint) was 8.9% [95% CI, 5.8%-12.9%) (**Table 2**)
- The disease control rate (CR + PR + SD) after 24 weeks of treatment was 33.5% [95% CI, 28.0%-39.3%]
- Approximately one third of patients (29.2%) had an unknown best overall response
  - Majority of these patients discontinued study treatment and left the study before 24 weeks of treatment and without postbaseline RECIST evaluation
- There was no difference in ORR in the subset of patients with prior EXE therapy (any setting); however, ORR was higher in patients without prior chemotherapy in the metastatic setting
  - ORR 8.9% [95% CI 5.3-13.9] without EXE therapy vs 8.8% [95% CI 3.9-16.6] with prior EXE therapy
  - ORR 11.5% [95% CI 6.6-18.3] without prior chemotherapy vs 6.6% [95% 3.2-11.8] with prior chemotherapy

Table 2. Overall Response Rate at 24 Weeks of Treatment (Full Analysis Set 1)

	EVE+EXE (N = 281)
Overall response rate (ORR), % [95% CI][a,b]	8.9 [5.8-12.9]
Disease control rate (DCR), % [95% CI][a,c]	33.5 [28.0-39.3]
Best overall response, %[d]	
Complete response (CR)	0.4
Partial response (PR)	8.5
Stable disease (SD)	24.6
Progressive disease (PD)	37.4
Unknown	29.2

[a] Clopper-Pearson CI.
[b] Proportion of patients with best overall response CR or PR (primary endpoint).
[c] Proportion of patients with best overall response CR or PR or SD.
[d] Based on local assessment, without required confirmation of response by repeated assessment.
Abbreviations: CI, confidence interval; CR, complete response; DCR, disease control rate; ORR, overall response rate; PD, progressive disease; PR, partial response.

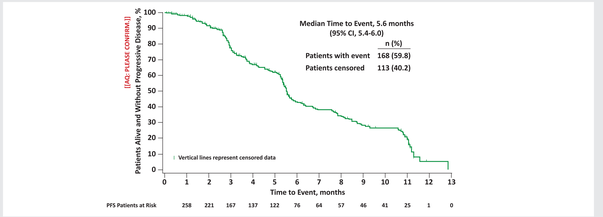
Progression-free Survival

- Median PFS was 5.6 months [95% CI, 5.4-6.0] (**Figure 2**)
  - Estimated (Kaplan-Meier) PFS rates were 50.0% after 24 weeks and 19.3% after 48 weeks
- There was no difference in median PFS in the subset of patients with prior EXE therapy (any setting); however, PFS was longer in patients with no prior chemotherapy in the metastatic setting
  - 5.5 months [95% CI, 5.3-6.3] without EXE therapy vs 5.6 months [95% CI, 4.2-6.9] with prior EXE therapy
  - 6.2 months [95% CI, 5.6-7.7] without prior chemotherapy vs 5.2 months [95% CI, 4.2-5.5] with prior chemotherapy

Overall Survival

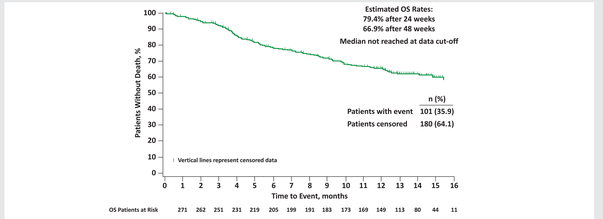
- Median OS duration could not be estimated due to the relatively short duration of the study (**Figure 3**)
  - Estimated (Kaplan-Meier) OS rates were 79.4% after 24 weeks and 66.9% after 48 weeks

Figure 2. Progression-free survival (full analysis set 1).



Abbreviation: CI, confidence interval.

Figure 3: Overall survival (full analysis set 1).



Abbreviation: OS, overall survival.

Results (Continued)

Adverse Events (Table 3)

- Overall, the safety results of this study were consistent with the established safety profile of EVE+EXE
  - Any grade stomatitis (49.2%), fatigue (36.1%), diarrhea (26.4%), nausea (26.1%), and decreased appetite (25.4%) were the most commonly reported AEs
- There was no indication of any new signals or unexpected safety risk of EVE in this study population

Table 3. Adverse Events Incidence ≥ 10% by Preferred Term

	Safety Set (N = 299)				
Adverse Event, n (%)	**Any Grade**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Any adverse event[a]	295 (98.7)	30 (10.0)	88 (29.4)	137 (45.8)	39 (13.0)
Stomatitis	147 (49.2)	70 (23.4)	52 (17.4)	24 (8.0)	1 (0.3)
Fatigue	108 (36.1)	66 (22.1)	32 (10.7)	9 (3.0)	1 (0.3)
Diarrhea	79 (26.4)	42 (14.0)	31 (10.4)	6 (2.0)	0
Nausea	78 (26.1)	47 (15.7)	22 (7.4)	8 (2.7)	1 (0.3)
Decreased appetite	76 (25.4)	44 (14.7)	23 (7.7)	9 (3.0)	0
Dyspnea	74 (24.7)	40 (13.4)	20 (6.7)	11 (3.7)	3 (1.0)
Rash	68 (22.7)	48 (16.1)	17 (5.7)	3 (1.0)	0
Dysgeusia	55 (18.4)	45 (15.1)	8 (2.7)	2 (0.7)	0
Anemia	53 (17.7)	12 (4.0)	28 (9.4)	11 (3.7)	2 (0.7)
Cough	53 (17.7)	36 (12.0)	15 (5.0)	2 (0.7)	0
Peripheral edema	50 (16.7)	34 (11.4)	13 (4.3)	3 (1.0)	0
Weight decreased	45 (15.1)	30 (10.0)	13 (4.3)	1 (0.3)	1 (0.3)
Vomiting	43 (14.4)	22 (7.4)	11 (3.7)	9 (3.0)	1 (0.3)
Epistaxis	43 (14.4)	36 (12.0)	7 (2.3)	0	0
Headache	37 (12.4)	30 (10.0)	6 (2.0)	0	0
General physical health deterioration	36 (12.0)	6 (2.0)	10 (3.3)	16 (5.4)	4 (1.3)
Arthralgia	32 (10.7)	22 (7.4)	9 (3.0)	1 (0.3)	0
Pyrexia	30 (10.0)	20 (6.7)	7 (2.3)	2 (0.7)	0
Pneumonitis[b]	22 (7.8)	5 (1.7)	10 (3.3)	6 (2.0)	1 (0.3)

[a] Patient numbers for individual AEs or AEs by grade need not add up to the total number of patients with all grades of any AE.
[b] Adverse event of interest included despite incidence rate < 10%.

Discussion

- The 4EVER trial further evaluated the efficacy and safety of EVE+EXE in a broader patient population than in BOLERO-2. In 4EVER there were no limitations on:
  - Number of previous chemotherapy lines for advanced disease
  - Time of recurrence or progression after NSAI therapy
  - Previous EXE therapy
- The efficacy of EVE+EXE in patients with HR$^+$, HER2$^-$ locally advanced or metastatic BC after an NSAI presented here are lower than in the BOLERO-2[1] and the BRAWO[3,4] studies
  - ORR and PFS in the 4EVER trial (8.9% ORR, 5.6 mo median PFS) were lower than observed in BOLERO-2 (12.6% ORR, 7.8 mo median PFS; both by local assessment),[1] or BRAWO (19.4% ORR, 8.0 mo median PFS)[3,4], likely because the 4EVER trial had a more advanced and heavily pretreated patient population
  - Together, data from the 4EVER and BRAWO[3,4] trials support improved ORR and PFS when EVE+EXE is used as earlier therapy for advanced disease
- Safety results presented here confirm the known safety profile of EVE
  - The similarity in AE profiles between 4EVER and BOLERO-2 is reassuring, given the more heavily pretreated patient population in 4EVER

Acknowledgements

The results are presented on behalf of all participating sites of the 4EVER study. We thank the patients for their participation, as well as the staff at each site—all of whom significantly contributed to the success of the study. Medical editorial and graphics assistance for this poster presentation was supported by Novartis Pharmaceuticals Corporation.

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Presented at the 2014 San Antonio Breast Cancer Symposium (SABCS); December 9-13, 2014; San Antonio, Texas, USA.