Efficacy and Safety of Everolimus and Exemestane in Patients With Advanced Breast Cancer From Asia and Africa: Asian patients Subset Results From the Phase IIIB EVEREXES Study

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On behalf of the EVEREXES Investigators

Disclosures

Author name	Disclosure
Young-Hyuck Im	Nothing to disclose
Sung-Bae Kim	Nothing to disclose
Eun Sook Lee	Nothing to disclose
Raj Nagarkar	Nothing to disclose
Yuan-Ching Chang	Nothing to disclose
Wichit Arpornwirat	Nothing to disclose
Tuan Anh Le	Nothing to disclose
Hong Ling Xue	Novartis employee
Khemaies Slimane	Novartis employee
Ruchan Uslu	Nothing to disclose

Introduction

- In the pivotal BOLERO-2 trial, EVE + EXE improved PFS compared with EXE + placebo (investigators assessment: 7.8 months vs 3.2 months, respectively; [HR = 0.45; *P* < 0.0001], and central review 11 months vs 4.1 months, respectively; [HR = 0.38; *P* < 0.0001]) in patients with HR+/HER2− advanced breast cancer (ABC) progressing on prior nonsteroidal aromatase inhibitors (NSAIs)[1,2]
  - Safety profile of EVE + EXE was predictable and manageable with the most commonly reported adverse events (AEs) in the EVE + EXE arm being stomatitis, rash, and fatigue[2]
  - However, only a small proportion of the patients (20%) in the BOLERO-2 trial were recruited from Asia

EVE, everolimus; EXE, exmestane; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; HR+, hormone receptor-positive; PFS, progression-free survival

1. Baselga J, et al. N Engl J Med 2012;366(6):520-529, 2. Yardley DA, et al. Adv Ther 2013;30(10):870-884.

Rationale for EVEREXES Study

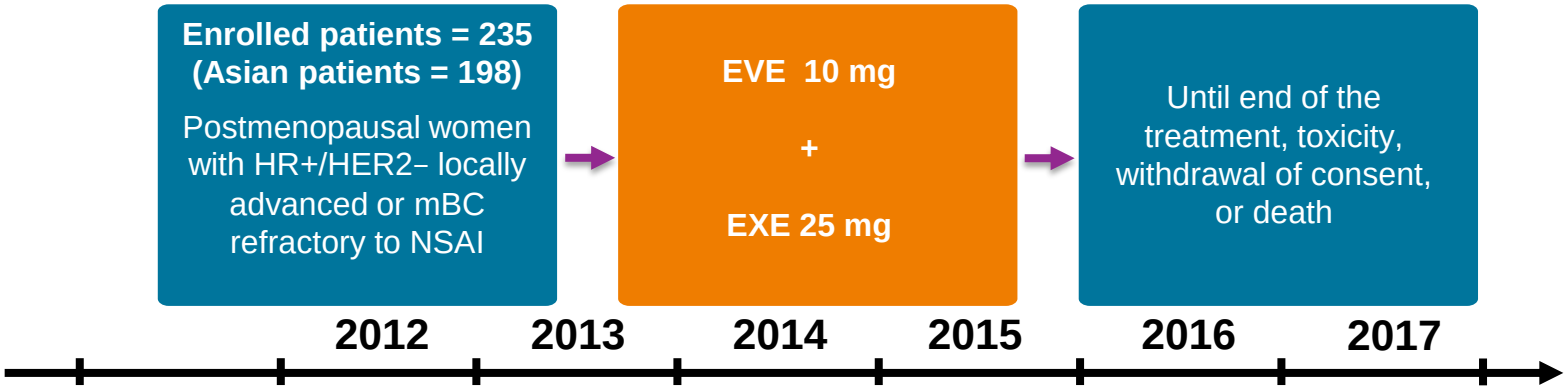
- Taking into consideration the possible influence of differences in culture and ethnicity on treatment effectiveness, it is important to evaluate the safety and efficacy profile of EVE + EXE in these patient population
- EVEREXES, a phase IIIB study, evaluated the safety and efficacy of EVE + EXE in patients from Asia and Africa
- First interim analysis data was presented at SABCS 2015[3]
- The results from the Asian subset of the EVEREXES study are presented here

EVE, everolimus; EXE, exemestane

3. Im Y-H, et al. SABCS 2015:Abstract # P4-13-09 [poster]

EVEREXES Study Design and Objectives

- International, multicenter, open label, single arm study



Study Objectives

- *Primary objective*
  - Safety and tolerability
- *Secondary objectives*
  - To evaluate the efficacy of EVE + EXE (ORR, PFS, CBR)
  - Changes from baseline in ECOG performance status
  - To provide early access to EVE + EXE for patients eligible for this treatment in Asian and other Eastern countries
- *Exploratory objective* – Changes from baseline in bone turnover markers

CBR, clinical benefit rate; ECOG, eastern cooperative oncology group; EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; mBC, metastaic breast cancer; NSAI, non-steroidal aromatase inhibitor; ORR, overall response rate; PFS, progression-free survival

Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Postmenopausal women with metastatic, recurrent or locally advanced BC, refractory to NSAIs
- Histological or cytological confirmed HR+ /HER2− BC
- Patients with at least one measurable lesion(s) or bone lesions (lytic or mixed) in the absence of measurable disease
- Adequate bone marrow, coagulation, liver and renal function

Exclusion Criteria

- Patients overexpressing HER2 by local laboratory testing
- Patients with only non-measurable lesions other than bone metastasis
- Patients with more than one prior chemotherapy line for ABC
- Previous treatment with mTOR inhibitors
- Known hypersensitivity to mTOR inhibitors
- History of brain or other CNS metastases, including leptomeningeal metastasis

ABC, advanced breast cancer; BC, breast cancer; CNS, central nervous system; CYP3A, cytochrome P4503A4; ECOG, eastern cooperative oncology group; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; mTOR, mammalian target of rapamycin; NSAI, non-steroidal aromatase inhibitor

Statistical Plan

- No hypothesis testing was performed in this study, which is descriptive in purpose
- Data summarized with respect to demographic and baseline characteristics, efficacy observations and measurements, and safety observations and measurements

Patient Disposition Asian Patients Population (By Country)

Country	Screened (N)	Screen failures (N)	Enrolled (N)	Evaluable for analysis (N)
India	20	6	14	9
Indonesia	15	7	8	8
Jordan	15	8	7	7
Malaysia	14	4	10	10
South Korea	90	10	80	80
Taiwan	24	2	22	22
Thailand	22	6	16	16
Turkey	56	21	35	34
Vietnam	7	1	6	5
Total	263	65	198	191

Results: Baseline Characteristics (Asian Subset, 191 Evaluable Patients)

Characteristic	Patients (n = 191)
Age, median (range), years	58 (32–87)
ECOG performance status, n (%)	
0	69 (36.1)
1	114 (59.7)
≥ 2	8 (4.2)
Measurable disease, n (%)	143 (74.9)
Metastatic site, n (%)	
Lung and/or liver	106 (55.5)
Bone	127 (66.5)
Bone only	40 (20.9)
Sensitivity to previous endocrine therapy, n (%)	86 (45.0)
ANA or LET as most recent treatment for advanced disease, n (%)	136 (71.2)
Previous tamoxifen, n (%)	74 (38.7)
Previous fulvestrant, n (%)	7 (3.7)
Purpose of most recent treatment	
Adjuvant therapy	56 (29.3)
Therapy for advanced/metastatic disease	135 (70.7)

ANA, anastrozole; ECOG, eastern cooperative oncology group; LET, letrozole

Results: Exposure to EVE and EXE

Therapy	Asian subset (n = 191)	Full population (N = 227)
Median follow-up time, months (95% CI)	11.71 (9.27–12.68)	11.64 (9.27–12.13)
Median relative dose intensity (%)		
EVE	92.4	92.6
EXE	100	100
Mean daily dose level, including interruptions (mg/days)		
EVE	9.2 (range, 2–10)	9.2 (range, 2–10)
EXE	25.0 (range, 5–25)	25.0 (range, 5–25)
Median duration of exposure (weeks)		
EVE	22.0	21.1
EXE	21.4	21.1

EVE, everolimus; EXE, exemestane

Results: Treatment Discontinuation

Reasons for treatment discontinuation	Asian subset (n = 191) n (%)	Full population (N = 227) n (%)
Discontinuation	139 (72.8)	167 (73.6)
Disease progression	96 (69.1)	113 (67.7)
Unacceptable AEs	11 (7.9)	18 (10.8)
Patient switched to commercial drug	10 (7.2)	11 (6.6)
Consent withdrawal	9 (6.5)	10 (6.0)
EVE dose interruption of >4 weeks	7 (5.0)	7 (4.2)
Lost to follow-up	1 (0.7)	1 (0.6)
Death	1 (0.7)	2 (1.2)
General or specific changes in the patient's condition which render the patient unacceptable for further EVE treatment at the discretion of the investigator	1 (0.7)	1 (0.6)
Need for any other types of anticancer therapy, except for palliative radiotherapy for bone lesions	1 (0.7)	1 (0.6)
Intercurrent illness that prevent further administration of EVE treatment	1 (0.7)	2 (1.2)

AEs, adverse events; EVE, everolimus

Results: Adverse Events

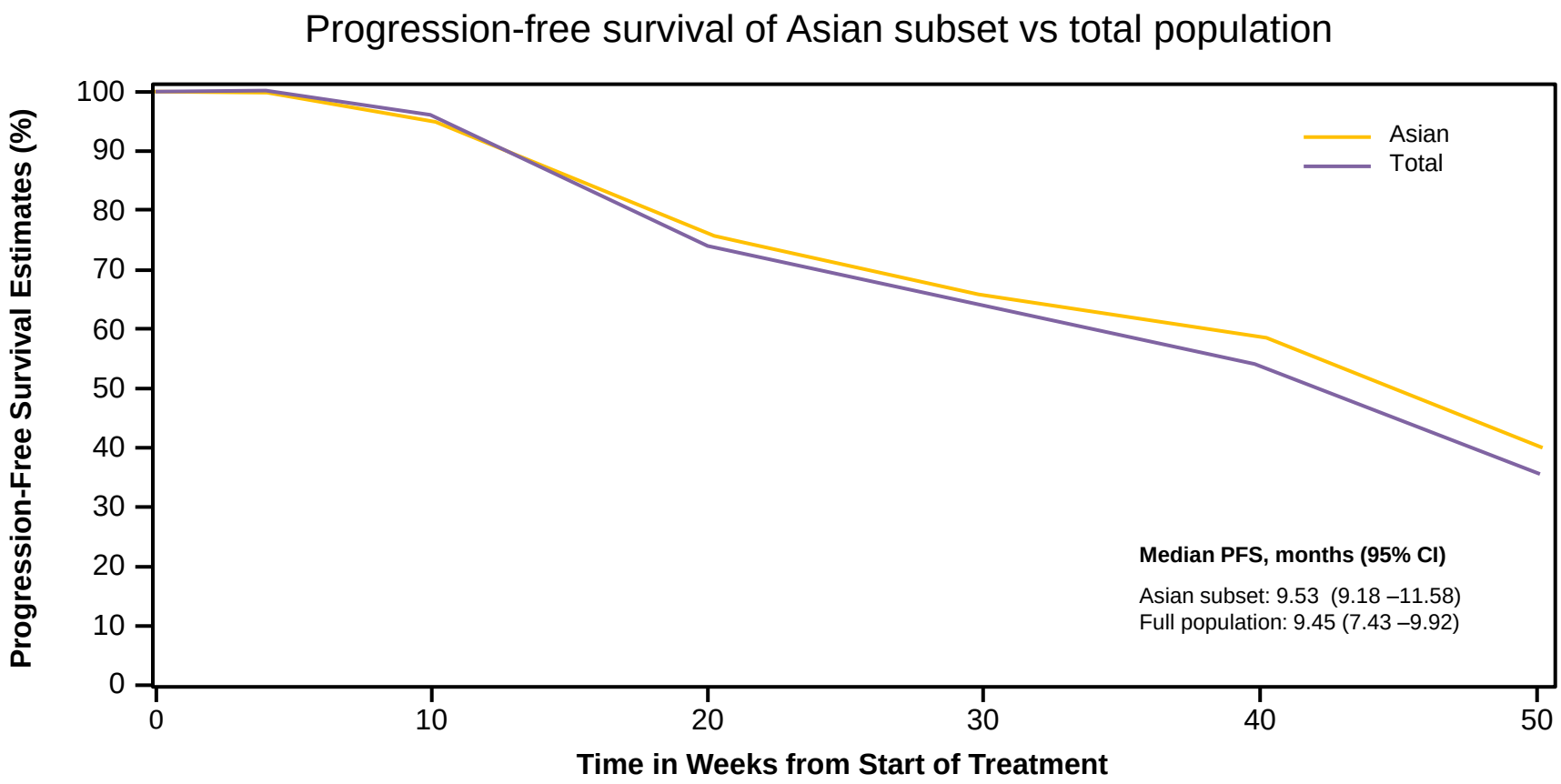
Adverse event	Asian subset (n = 191) n (%)			Full population (N = 227) n (%)		
	Any	Grade 3	Grade 4	Any	Grade 3	Grade 4
Stomatitis*	122 (63.9)	22 (11.5)	0	137 (60.4)	24 (10.6)	0
Rash	50 (26.2)	0	0	63 (27.8)	0 (0.0)	0
Hyperglycemia*	49 (25.7)	12 (6.3)	0	56 (24.7)	16 (7.0)	0
Weight decreased	30 (15.7)	2 (1)	0	35 (15.4)	2 (0.9)	0
Fatigue*	27 (14.1)	3 (1.6)	0	39 (17.2)	5 (2.2)	0
Pneumonitis*	24 (12.6)	2 (1)	1 (0.5)	32 (14.1)	2 (0.9)	1 (0.4)
Infection (including pneumonia)	11 (5.8)	1 (0.5)	1 (0.5)	12 (5.3)	1 (0.4)	1 (0.4)
Hypertension	8 (4.2)	1 (0.5)	0	9 (4.0)	1 (0.4)	0
Hypophosphatemia	7 (3.7)	3 (1.6)	0	7 (3.1)	3 (1.3)	0
Hyperlipidemia	5 (2.6)	1 (0.5)	0	5 (2.2)	1 (0.4)	0
Congestive cardiac failure	1 (0.5)	0	0	1 (0.4)	0 (0.0)	0

*AE of clinical importance

- The majority of the AEs were mild to moderate intensity
  - No new AEs were reported
- Most common grade 3 or 4 AE (incidence ≥ 5.0%) was stomatitis and hyperglycemia

AE, adverse event

Results: Efficacy (1/2)



- The median PFS of the Asian subset of the EVEREXES was similar to the full population

CI, confidence interval; PFS, progression free survival

Results: Efficacy (2/2)

Response rate (week 50), n (%)	Asian subset (n = 191)		Full population (N = 227)	
	EVE + EXE	95% CI	EVE + EXE	95% CI
ORR	33 (17.3)	12.2–23.4	36 (15.9)	11.4–21.3
Complete response	1 (0.5)	0.0–2.9	1 (0.4)	0.0–2.4
Partial response	32 (16.8)	11.8–22.8	35 (15.4)	11.0–20.8
Stable disease	156 (81.7)	75.4–86.9	189 (83.3)	77.8–87.9
CBR	81 (42.4)	35.3–49.8	90 (39.6)	33.2–46.3

CBR, clinical benefit rate; CI, confidence interval; EVE, everolimus; EXE, exemestane; ORR, overall response rate

Conclusions

- EVEREXES provided access to patients until disease progression or commercial availability of EVE in the participating Asian countries
- Median PFS (9.53 months) with EVE + EXE for the Asian subset of EVEREXES study was similar to the overall population (9.45 months)
- The incidence of AEs leading to treatment discontinuation in the Asian subset were lower compared to the overall population
  - The most common AEs (any grade) were stomatitis, rash, and hyperglycemia
  - Most frequent grade 3 or 4 AEs were stomatitis and hyperglycemia
- Treatment discontinuation was observed in 139 (72.8%) patients, with 11 (7.9%) patients discontinuing treatment due to unacceptable AEs
- Overall, the results from the EVEREXES study support the use of EVE (at a start dose of 10 mg) in combination with EXE as the first dual blockage strategy (targeted therapy + endocrine therapy) for Asian patients with HR+, HER2− ABC progressing on NSAIs

Acknowledgment: We would like to thank all patients who participated in the study and their families

ABC, advanced breast cancer; AEs, adverse events; EVE, everolimus; EXE, exemestane; HER2, human epidermal growth factor receptor 2; HR+, hormone receptor-positive; NSAI, non-steroidal aromatase inhibitor; PFS, progression-free survival