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Everolimus Plus Exemestane Versus Everolimus or Capecitabine Monotherapy in Breast Cancer: BOLERO-6

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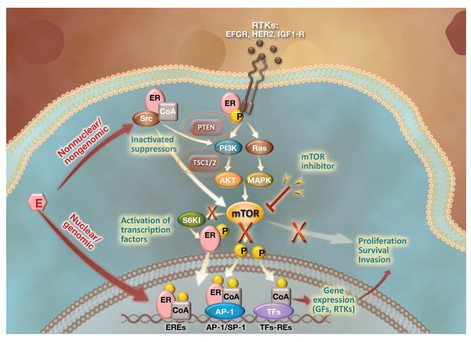
ABSTRACT

Aims: Everolimus (EVE), an oral inhibitor of mammalian target of rapamycin (mTOR), has clinical activity as monotherapy and in combination with endocrine therapy (Baselga, NEJM, 2012) for the treatment of hormone receptor-positive (HR^+) advanced breast cancer (BC). In BOLERO-2, the addition of EVE to exemestane (EXE) more than doubled median progression-free survival (PFS) compared with EXE alone in postmenopausal women with HR^+, $HER2^-$ advanced BC progressing after letrozole or anastrozole. Capecitabine, an oral 5-fluorouracil prodrug, is indicated as monotherapy for patients with locally advanced or metastatic BC after failure of taxanes and an anthracycline-containing regimen or for whom further anthracycline therapy is not indicated. Clinical activity of capecitabine monotherapy has been demonstrated in the first-line setting in patients with HR^+, $HER2^-$ metastatic BC. The objective of the BOLERO-6 study is to evaluate 2 concepts of EVE in HR^+, $HER2^-$ advanced BC progressing after letrozole or anastrozole: 1) PFS following EXE monotherapy compared with EVE + EXE, and 2) PFS following capecitabine monotherapy compared with EVE + EXE. **Methods:** BOLERO-6 is a 3-arm, randomized, open-label, multicenter phase 2 study in which 300 patients will be randomized in a 1:1:1 ratio to receive the combination of EVE (10 mg/day) + EXE (25 mg/day) versus EVE (10 mg/day) versus capecitabine (1,250 mg/m^2 twice daily for 14 days in 3-week cycles) until disease progression or intolerable toxicity. Patients will be stratified by the presence of visceral disease. The primary endpoint is PFS for EVE + EXE versus EVE alone based on local radiologic assessment. The key secondary endpoint is PFS for EVE + EXE versus capecitabine. Additional secondary endpoints include overall survival, objective response rate, clinical benefit rate, safety, time to deterioration in Eastern Cooperative Oncology Group performance status, time to deterioration in quality of life, and patient treatment satisfaction. Efficacy assessments will be evaluated every 6 weeks. **Results:** BOLERO-6 will open for enrollment in the first quarter of 2013, and estimated study completion is early 2015. **Conclusions:** This study will provide efficacy and safety information on EVE + EXE versus EVE or capecitabine monotherapy in patients with HR^+ $HER2^-$ advanced BC progressing after letrozole or anastrozole.

BACKGROUND

- Endocrine therapy (ET) with aromatase inhibitors (AIs) is the standard of care for post-menopausal women with hormone receptor-positive (HR^+) i.e., estrogen receptor-positive (ER^+) and/or progesterone receptor-positive (PgR^+) breast cancer (BC).[1-3]
  - Unfortunately, disease progression is observed in women with HR^+ advanced BC (ABC) while they are on ET.[1,2]
- Cross-talk between the ER signaling and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways plays an important role in the clinical sensitivity of BC to ET (**Figure 1**).[1-4] Thus, co-targeting both signaling pathways may help enhance the effectiveness of ET.[2,4]
- Everolimus (EVE) is a potent, orally bioavailable rapamycin derivative, that inhibits mTOR through allosteric binding to mTORC1.[3-5]
  - EVE has demonstrated clinical activity as monotherapy in previously treated patients with recurrent or advanced breast cancer (ABC):
    - In a phase 2 trial in women with histologically confirmed recurrent or ABC progressing on prior ET, EVE monotherapy has demonstrated potential anti-tumor activity.[6]
      - Four complete or partial responses (12%; 95% confidence interval [CI]: 3.4–28.2%) were observed with the 10 mg/day schedule (median duration: 13.1 and 3.7 mo, respectively).
      - Fifteen patients had a best response of stable disease (median duration: 4.9 mo).
  - Compared with ET alone, the combination of EVE and ET significantly improves treatment efficacy in BC, in neoadjuvant and advanced settings (**Table 1**)[4,5,7].

Figure 1. Cross-talk Between ER Signaling and PI3K/AKT/mTOR Pathway Supports the Use of mTOR Inhibition For Enhancing Sensitivity to ET



EFGR, Epidermal growth factor receptor; ER, Endocrine receptor; ET, Endocrine therapy; MAPK, Mitogen-activated protein kinase; TSC1/2, Tuberous sclerosis complex.
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Table 1. EVE and ET Combination Therapy For BC Treatment in Neoadjuvant and Metastatic Settings

Phase of Trial	Treatment Groups	Patient Characteristics	Key Results
Phase 2[5]	EVE + LET versus LET alone	• Previously untreated post-menopausal women • ER^+ BC in neoadjuvant setting	• ORR EVE + LET: 68.1% (95% CI: 60.3–75.9) LET: 59.1% (95% CI: 50.7–67.5) [p=0.062]
Phase 2 (TAMRAD)[4]	EVE + TAM versus TAM alone	• Post-menopausal women • HR^+, $HER2^-$ mBC progressing on prior AI therapy	• CBR EVE + TAM: 61% (95% CI: 47.0–74.0) vs TAM: 42% (95% CI: 29.0–56.0) [p=0.045] • Median TTP EVE + TAM: 8.6 mo (95% CI: 5.9–13.9) vs TAM: 4.5 mo (95% CI: 3.6–8.7) [p=0.002] • Risk of progression ↓ 46% (HR=0.54; 95% CI: 0.36–0.81) with EVE + TAM vs TAM • Risk of death ↓ 55% (HR=0.45; 95% CI: 0.24–0.81) with EVE + TAM vs TAM
Phase 3 (BOLERO-2)[7]	EVE + EXE versus EXE alone	• Post-menopausal women • HR^+ ABC progressing on NSAIs, LET or ANA	• Median PFS [local and central assessments] EVE + EXE: 7.8 mo and 11.0 mo vs EXE: 3.2 mo and 4.1 mo (HR=0.45; 95% CI: 0.38–0.54; and HR=0.38; 95% CI: 0.31–0.48) [p<0.0001 for both]

ABC, Advanced breast cancer; AI, Aromatase inhibitor; ANA, Anastrozole; BC, Breast cancer; CBR, Clinical benefit rate; CI, Confidence interval; ER^+, Estrogen receptor-positive; EVE, Everolimus; EXE, Exemestane; $HER2^-$, Human epidermal growth factor receptor-2-negative; HR^+, Hormone receptor-positive; HR, Hazard ratio; LET, Letrozole; mBC, Metastatic breast cancer; NSAIs, Non-steroidal aromatase inhibitors; ORR, Overall response rate; PFS, Progression-free survival; TAM, Tamoxifen; TTP, Time to progression

- EXE, an orally-active, potent, selective, third-generation steroidal aromatase inactivator, is a treatment of choice in patients with HR^+ ABC progressing on/after prior non-steroidal aromatase inhibitors (NSAIs) therapy.[8] Hence, it is considered to be an appropriate candidate for combination strategy.
- Capecitabine is an orally administered fluoropyrimidine carbamate approved for treating mBC resistant to prior treatment with paclitaxel and/or anthracyclines (**Table 2**).[9,10]

Table 2. Clinical Outcomes in Phase 2 Trials of Capecitabine Monotherapy

Phase of Trial	Treatment Groups	Patient Characteristics	Key Results
Phase 2[9]	Capecitabine monotherapy	• Histologically confirmed BC recurring during or following a taxane containing chemotherapeutic regimen	• ORR 15% (95% CI: 10.0–23.0%) • Median TTP 3.5 mo (95% CI: 2.8–4.1) • Median OS 10.1 mo (95% CI: 8.2–11.5)
Phase 2[10]	Capecitabine monotherapy	• Histologically confirmed locally advanced or mBC recurring during or following a taxane- or anthracycline containing chemotherapeutic regimen	• Median TTP 4.9 mo (95% CI: 4.0–6.4) • Median OS 15.2 mo (95% CI: 13.5–19.6)

BC, Breast cancer; CBR, Clinical benefit rate; mBC, Metastatic breast cancer; ORR, Overall response rate; OS, Overall survival; TTP, Time to progression

Study Rationale

- Combination therapies have been a key strategy for treating patients with recurrent or progressive ABC.[11]
- In the pivotal BOLERO-2 phase 3 trial, the combination of EVE and EXE prolonged PFS, compared with EXE alone, in patients with HR^+ ABC progressing on/after letrozole (LET) or anastrozole (ANA).[7]
- The **Sixth B**reast cancer trials of **O**ra**L** **E**ve**RO**limus (BOLERO-6) study will evaluate the safety and effectiveness of the combination of EVE and EXE compared with EVE or capecitabine monotherapy in patients with ABC recurring or progressing on/after prior NSAI therapy.

OBJECTIVE

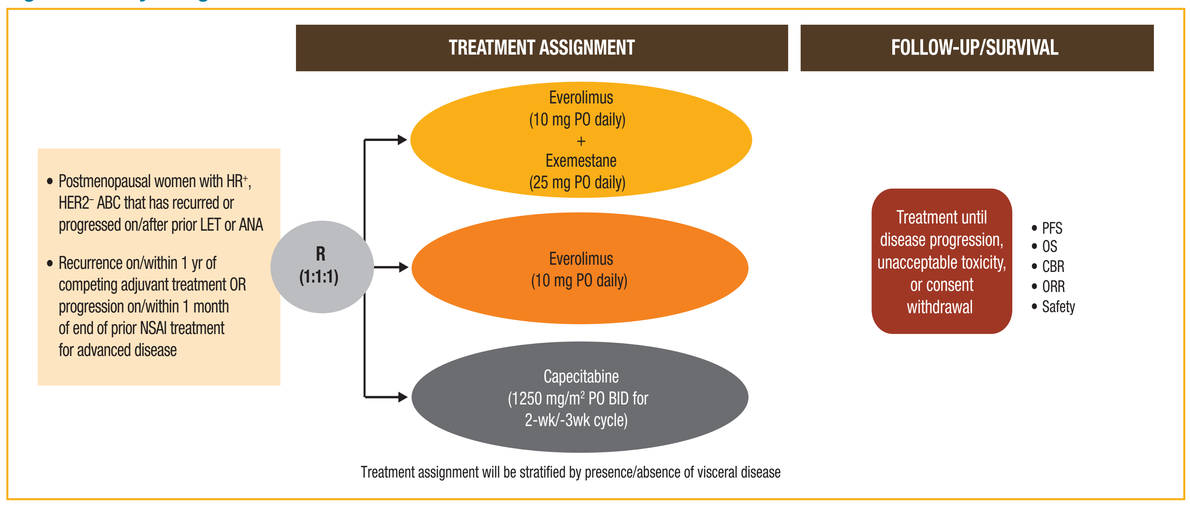
- The primary objective of the BOLERO-6 study is to compare the PFS for the combination of EVE and EXE with that for EVE monotherapy in post-menopausal women with HR^+, human epidermal growth factor receptor-2-negative ($HER2^-$) ABC, progressing on/after prior LET or ANA.

METHODS

Study Design

- Multicenter, open-label, randomized, three-arm, phase 2 study (ClinicalTrials.gov identifier: NCT 01783444).
- A total of 300 post-menopausal women with HR^+, $HER2^-$ ABC that has recurred or progressed on/after prior LET or ANA, are to be enrolled starting Q1 2013.
- Patients will be randomized to receive the combination of EVE (10 mg/d) and EXE (25 mg/d) or EVE monotherapy (10 mg/d), or capecitabine monotherapy (1250 mg/m^2 twice daily for a 2-week/3-week cycle) until disease progression, or unacceptable toxicity.
- Patients will be stratified by presence/absence of visceral disease (**Figure 2**).

Figure 2. Study Design



ANA, Anastrozole; BID, Twice daily; CBR, Clinical benefit rate; HR, Hormone receptor; HER2, Human epidermal growth factor receptor 2; LET, Letrozole; NSAI, Nonsteroidal aromatase inhibitor; ORR, Overall response rate; OS, Overall survival; PFS, Progression-free survival; PO, Per oral

Patients

Table 3. BOLERO-6 Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
• Post-menopausal women • Metastatic or locally advanced unresectable BC, not amenable to curative treatment by surgery or radiotherapy • Histological or cytological confirmation of HR^+, $HER2^-$ BC • Radiological/objective evidence of recurrence while on or within 1 year of the end of adjuvant treatment with an NSAI, or progression while on or within 1 month of the end of prior treatment with an NSAI for ABC • ≥1 measurable lesion at baseline per RECIST v1.0 • Adequate bone marrow, liver, and renal function • Serum creatinine ≤ 1.5 × ULN, fasting serum cholesterol ≤ 300 mg/dL (7.75 mmol/L), fasting triglyceride ≤ 2.5 x ULN • ECOG performance status ≤ 2	• ≥1 line of prior chemotherapy for ABC • Presence of only non-measurable lesions other than bone metastasis • Previous treatment with EXE, mTOR/PI3K/AKT inhibitors • HER2 overexpression confirmed by most recent local laboratory testing (IHC 3+ staining or in situ hybridization^{++}) • Chemotherapy with fluoropyrimidine containing regimen within 24 wk before randomization • Hypersensitivity to mTOR inhibitors • Known sensitivity to study drugs • Concurrent hormone replacement therapy • Chronic treatment with immunosuppressants • Current or history of CNS metastases

ABC, Advanced breast cancer; CNS, Central nervous system ECOG, Eastern cooperative oncology group; mTOR, Mammalian target of rapamycin; RECIST, Response Evaluation Criteria In Solid Tumors

Study Endpoints

Table 4. BOLERO-6 Endpoints

Primary	Secondary
• PFS (EVE + EXE vs. EVE) – Time from randomization to first documented disease progression (RECIST v1.0) or death from any cause, assessed by the local investigator	• PFS (EVE + EXE vs. Capecitabine) – Time from randomization to first documented disease progression (RECIST v1.0) or death from any cause, assessed by the local investigator • EVE + EXE vs. EVE; and EVE + EXE vs. Capecitabine • OS – Time from randomization to death from any cause • ORR – Best complete or partial response according to RECIST v1.0, assessed by the local investigator • CBR – Complete or partial response or stable disease according to (RECIST v1.0), with duration ≥ 24wk • Safety • Change in QoL score using the EORTC QLQ-C30 questionnaire along with the BR23 module • Treatment satisfaction using the TSQM v1.4

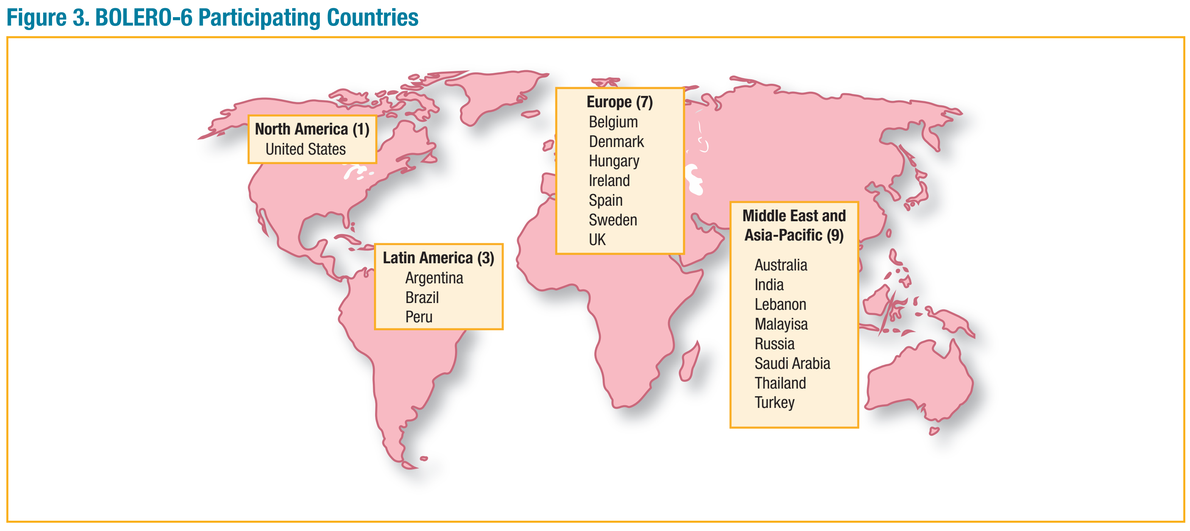
CBR, Clinical benefit rate; EVE, Everolimus; EXE, Exemestane; EORTC, European Organization for Research and Treatment of Cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; QoL, Quality of life; RECIST, Response Evaluation Criteria In Solid Tumors; TSQM, Treatment satisfaction questionnaire for medication

- Safety assessments will include monitoring and recording of all adverse events and abnormal laboratory values.
- Exploratory endpoints will include biomarker analysis including mutation analyses of pathways involving *PIK3CA/PI3K*, *AKT*, *PTEN*, *TSC1/2*, *RAS*, and *RAF*, and the evaluation of potential biomarkers that may predict sensitivity to EVE therapy.

Statistical Analysis

- PFS distribution will be estimated using the Kaplan-Meier method; hazard ratios (HRs) and 90% CIs will be estimated using a stratified Cox regression model.
- Start of enrollment: Q1 2013; enrollment period: 18 months (**Figure 3**).
- Estimated study completion period: Q1 2015.

Figure 3. BOLERO-6 Participating Countries



SUMMARY

- **The data from this trial will provide insight into the safety and efficacy of the combination of EVE and EXE versus EVE or capecitabine monotherapy in women with ER^+, $HER2^-$ ABC progressing on/after prior LET or ANA.**

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