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Original Article

# Safety and Efficacy of Everolimus Plus Exemestane in Postmenopausal Women with Treatment-refractory Hormone Receptor-positive, Human Epidermal Growth Factor Receptor 2-negative Advanced Breast Cancer: Analysis from EVEREXES Taiwan Subset

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## Abstract

**Background:** This phase IIIb, open-label study enrolled patients from nine Asian and Middle Eastern countries to evaluate the safety and efficacy of the combination therapy in underrepresented patient populations from the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2). Here, we report the Taiwanese subset data. **Materials and Methods:** The primary objective was to evaluate the safety and tolerability of everolimus and exemestane (EVE + EXE); the secondary endpoints included progression-free survival (PFS), response rates, and clinical benefit rate. Postmenopausal patients who had metastatic, recurrent, or locally advanced hormone receptor-positive/human epidermal growth factor receptor 2-negative (HR+/HER2−) advanced breast cancer (ABC) refractory to nonsteroidal aromatase inhibitor (NSAI) and had received EVE + EXE were recruited. **Results:** From March 2013 to October 2014, 235 postmenopausal women were enrolled in EVEREXES. Taiwanese patients ($n$ = 22) had similar baseline characteristics compared with BOLERO-2 cohort; most (17/22) had discontinued due to disease progression. Only two patients dropped out due to unacceptable adverse events (AEs) despite worse stomatitis (any 77.3%; grade 3/4, 18.2%). Other common AEs included pneumonitis (45.5%), rash (27.3%), and hyperglycemia (9.1%). PFS and safety in EVEREXES compared favorably with BOLERO-2, especially among Taiwanese patients (median: 49 weeks; 95% confidence interval = 19.3–82.0). **Conclusion:** Although EVEREXES had a small Taiwanese population, the encouraging outcomes compared with BOLERO-2 showed that EVE + EXE is safe for Taiwanese patients with HR+ HER2− ABC who progressed on NSAIs. Large-scale verification is warranted.

**Keywords:** Asia, everolimus, exemestane, hormone receptor-positive human epidermal growth factor receptor 2-negative advanced breast cancer, Taiwan

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## Introduction

Breast cancer is one of the most common malignancies in women, with numbers rising yearly. The World Health Organization estimates a 46% rise in incidences of breast cancer by 2040 globally as well as in the Asian region.[1] Most mortalities of breast cancer are due to consequences arising from recurrence or metastasis, which eventually affects up to 30% of women treated for early-stage breast cancer. For metastatic disease, the median life expectancy after starting chemotherapy is only 2–3 years,[2] and treatment goals in this setting are usually palliative.

Endocrine therapy is one of the standard therapies for breast cancer, but 30%–50% of hormone receptor-positive (HR+) tumors do not respond to first-line anti-estrogen therapy,[3-5] and breast cancers recur in one-third of patients within 15 years after discontinuing tamoxifen.[6] Endocrine resistance has multifarious, complex, and interacting causes. Exemestane (EXE), a steroidal androstenedione analog, which is also indicated for treating disease progression following tamoxifen,[7] has been shown to be superior in prolonging survival following recurrence or progression on nonsteroidal aromatase inhibitors (NSAIs).[8,9] However, the clinical benefit rate (CBR) of EXE following NSAI is modest (<40%), and given that almost all HR+ advanced breast cancers (ABCs) eventually become refractory to endocrine therapy,[10] more effective alternatives are needed.

Everolimus (EVE), a selective inhibitor of the mechanistic target of rapamycin (mTOR), suppresses tumor cell proliferation[11,12] and has indications for treating diverse neoplasms.[13] mTOR is the downstream signal transducer of human epidermal growth factor receptor 2 (HER2) in the PI3K/AKT cascade, which plays a central role in tumorigenesis and is activated in endocrine-resistant breast cancer cell lines.[10,11] Efficacy of EVE in preclinical models[14] was affirmed by subsequent trials in estrogen receptor-positive (ER+) breast cancer, both as monotherapy[15] and with concomitant letrozole,[16] EXE,[17] and tamoxifen.[18]

Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) was a global, multicenter, randomized, double-blind, placebo-controlled, phase III study of EVE + EXE versus EXE monotherapy in 724 postmenopausal women with ER+/HER2-negative (HER2−) ABC that had recurred or progressed on NSAIs. The median progression-free survival (PFS) of women randomized to EVE + EXE was 7.8 months versus 3.2 months for EXE plus placebo (hazard ratio = 0.45; 95% confidence interval [CI] =0.38–0.54; $P < 0.0001$), with a significantly higher CBR (51.3% vs. 26.4%, $P < 0.0001$),[19] with generally mild or moderate and manageable adverse events (AEs). However, there are limited data on the safety and efficacy of EVE in the Asian population. Only 20% of the patients recruited in BOLERO-2 were Asian;[19] among all 143 Asian patients in BOLERO-2, 106 were Japanese and 5.1% were of Chinese descent.[20] *Post hoc* analysis showed that the median PFS for Asians was 8.5 months versus among non-Asians at 7.3 months.[20]

EVEREXES was conducted to evaluate the safety, tolerability, and efficacy of EVE in postmenopausal patients with ER+/HER2− breast cancer refractory to prior NSAI therapy. The final safety and efficacy outcomes from the EVEREXES trial were reported by Im *et al*.[21] Here, we report the results for the Taiwanese subset.

## Materials and Methods

### Patients

Postmenopausal women with HR+/HER2− locally advanced or metastatic breast cancer that recurred or progressed on/after NSAI therapy from 13 countries across Asia, the Middle East, and Africa were recruited in this international, multicenter, single-arm, prospective, open-label, phase IIIb study. The inclusion and exclusion criteria were previously reported by Im *et al*.[21]

This study was conducted in accordance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use-Good Clinical Practice guidelines and the ethical principles that are outlined in the Declaration of Helsinki 2008. The study protocol was reviewed and approved by the investigational center's ethics committee or institutional review boards. Written informed consent was obtained from each patient prior to any study-specific procedures being performed. This study is registered on ClinicalTrials.gov (NCT03176238).

### Treatment

Patients received EVE 10 mg/day and EXE 25 mg/day as long as CBR was observed until disease progression or unacceptable toxicity occurred. Severe and/or intolerable suspected AEs were managed by temporary dose reduction and/or interruption of EVE. If a dose reduction was required, the suggested dose was 50% lower than the daily dose previously administered. Dose reduction beyond two dose levels was not allowed, and patients were discontinued from the study in case of dose interruption for >28 days.

Study treatment was continued as long as clinical benefit was evident, with the end of the trial defined as the date of the last EVE dose before any of the following: treatment interruption >4 weeks; documented disease progression; unacceptable toxicity; death; concurrent illness or changes in a patient's condition precluding further EVE treatment; need for other anticancer therapy (except palliative radiotherapy for bone lesions); or withdrawal for any other reason. A safety follow-up visit was scheduled 30 days (±2 days) after the end of the trial. Any further AE during this period was logged; subsequent AEs suspected to be related to EVE were also documented.

### Outcome measures

The primary endpoints were safety and tolerability, assessed according to the Common Terminology Criteria for AEs, version 4.03.

The secondary efficacy endpoints were assessed by local investigators based on radiological assessments of tumor burden, defined according to RECIST 1.1,[22] and included overall response rate (ORR), defined as the total proportion of patients with best overall response of either complete response (CR) or partial response (PR); PFS, defined as the proportion of patients without documented progression or those dying from any cause during the study period; and CBR, defined as the proportion of patients with best overall response of CR, PR, or stable disease (SD) lasting ≥24 weeks (from first recorded response until first documented progression or death from cancer) during the study period.

### Data analysis and statistics

This was a descriptive study, with no hypothesis testing, that combined data from participating centers to accrue a proposed convenience sample of ≤400 subjects. Categorical variables were summarized by absolute and relative frequencies and continuous variables by descriptive statistics. Prespecified analyses included patients' baseline characteristics, exposure to EVE and EXE, treatment safety/tolerability, and efficacy assessments. CI was calculated using the Clopper–Pearson method and PFS using the Kaplan–Meier analysis. Best overall response (CR, PR, SD, progressive disease [PD], or unknown), ORR, and CBR were summarized for the whole study period using frequency tables together with their associated two-sided exact 95% CIs.

## Results

### Patient characteristics

From March 29, 2013, to October 31, 2014, 235 patients from 13 countries across Asia, the Middle East, and Africa were recruited, of which 22 patients were Taiwanese. The median age of the Taiwanese cohort was 61.3 years (range: 43.0–74.0 years), most patients were at Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 (72.7%). The baseline patient demographics and clinical characteristics are summarized in Table 1.

### Treatment

#### *Exposure to everolimus and exemestane*

The median follow-up duration in the EVEREXES Taiwan cohort was 16 months, with a median duration of dose exposure of 38.5 weeks. The median relative dose intensity (RDI) of EXE and EVE was 100% and 97%, respectively. Overall, 15/22 (68.2%) patients had dose reduction in EVE, primarily due to AEs (93.3%). All patients eventually discontinued treatment. A majority of the patients (17/22, 77.3%) discontinued due to disease progression, followed by 2 (9.1%) patients complaining of unacceptable AEs [Table 2].

#### *Safety*

Majority of the patients (21/22, 95.5%) had treatment-emergent AEs (TEAEs), with a large proportion of patients reporting stomatitis (grade 1, 63.6%; grade 2, 13.6%, grade 3/4, 18.2% [Table 3]).

A high number of patients experienced TEAEs of special interest associated with EVE (21/22, 95.5%), stomatitis (17, 77.3%), pneumonitis (10, 45.5%), and infections (3, 13.6%) affected >10% of patients [Table 4].

#### *Efficacy*

At the end of the study, there were no cases of CR reported. However, 4 patients had PR, 12 patients had SD, while 5 patients reported PD. The median PFS in the Taiwanese subset was 49 weeks (95% CI = 19.3–82.0), with a CBR of 63.6% [Table 5 and Figure 1].

## Discussion

The overall findings in EVEREXES were consistent with the safety profile and efficacy outcomes in BOLERO-2.[22] Moreover, due to the less restrictive inclusion criteria of EVEREXES, these results in Asian patients may be more representative of what can be practically achieved in real-world clinical practice. PFS of patients in Taiwan compared favorably with that from the BOLERO-2 cohort, supporting the rationale for using EVE + EXE combination therapy as an option for treating patients with HR+/HER− ABC.

Compared with BOLERO-2 treatment cohorts, a higher proportion of the Taiwanese subset in EVEREXES were fully

**Table 1: Baseline characteristics of EVEREXES Taiwanese patients**

| Characteristic | EVEREXES Taiwan (*n*=22), *n* (%) |
|---|---|
| Median age, years (range) | 61.3 (43.0–74.0) |
| ECOG performance status | |
| 0 | 16 (72.7) |
| 1 | 5 (22.7) |
| 2 | 1 (4.5) |
| Measurable disease | 21 (95.5) |
| Metastatic sites (%) | |
| Lung and/or liver | 72.7 |
| Bone | 54.5 |
| Bone only | 0 |
| Sensitive to prior endocrine therapy[a] | 12 (54.5) |
| NSAI as most recent treatment | 21 (95.5) |
| Prior tamoxifen | 8 (36.4) |
| Prior fulvestrant | 1 (4.5) |
| Any previous chemotherapy | 15 (68.2) |
| Prior chemotherapy for metastatic breast cancer | 6 (27.3) |
| Latest treatment setting (%) | |
| Adjuvant/neoadjuvant | 5 (22.7) |
| Advanced/metastatic disease | 17 (77.3) |
| Number of prior systemic therapies (in adjuvant or metastatic setting) | |
| 1 | 5 (22.7) |
| ≥2 | 17 (77.3) |

[a]Defined as at least 24 months of endocrine therapy before recurrence in the adjuvant setting or a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease. ECOG: Eastern Cooperative Oncology Group, NSAI: Nonsteroidal aromatase inhibitor

**Table 2: Drug exposure**

| | EVEREXES Taiwan (*n*=22) | |
|---|---|---|
| | Everolimus (*n*=22), *n* (%) | Exemestane (*n*=22), *n* (%) |
| Duration of drug exposure including interruptions (weeks) | | |
| Mean±SD | 44.7±34.10 | 44.7±34.13 |
| Median | 38.5 | 38.5 |
| RDI (%) | | |
| Mean±SD | 82.4±22.08 | 98.0±7.31 |
| Median | 97.0 | 100.0 |
| Patients with dose reduction, *n* (%) | 15 (68.2) | 15 (68.2) |
| Reason for dose reduction or interruption, *n* (%) | 15 | 5 |
| Per protocol | 0 (0.0) | 1 (20.0) |
| AE | 14 (93.3) | 2 (40.0) |
| Dosing error | 1 (6.7) | 2 (40.0) |
| Laboratory test abnormality | 0 | 0 |
| Scheduling conflict | 0 | 0 |
| Dispensing error | 0 | 0 |
| Primary reason for study treatment discontinuation, *n* (%) | 22 (100.0) | NA |
| Unacceptable AE | 2 (9.1) | NA |
| Abnormal laboratory value | 1 (4.5) | NA |
| Consent withdrawal | 1 (4.5) | NA |
| Disease progression | 17 (77.3) | NA |
| EVE dose interruption >4 weeks | 1 (4.5) | NA |

AE: Adverse event, EVE: Everolimus, RDI: Relative dose density, NA: Not available, SD: Standard deviation

**Table 3: Common treatment-emergent adverse events by Common Terminology Criteria for Adverse Events grade (>5%)**

| CTCAE grade | Grade 1, *n* (%) | Grade 2, *n* (%) | Grade 3 or 4, *n* (%) |
|---|---|---|---|
| Number of patients with at least one TEAE suspected due to study drug | 21 (95.5) | 17 (77.3) | 9 (40.9) |
| Stomatitis | 14 (63.6) | 3 (13.6) | 4 (18.2) |
| Hyperglycemia | 3 (13.6) | 5 (22.7) | 0 |
| Blood cholesterol increased | 3 (13.6) | 0 | 0 |
| Aspartate aminotransferase increased | 2 (9.1) | 2 (9.1) | 2 (9.1) |
| Alanine aminotransferase increased | 2 (9.1) | 0 | 2 (9.1) |
| Pneumonitis | 2 (9.1) | 2 (9.1) | 0 |
| Pruritus | 2 (9.1) | 1 (4.5) | 1 (4.5) |
| Rash | 2 (9.1) | 2 (9.1) | 0 |
| Hypertriglyceridemia | 2 (9.1) | 1 (4.5) | 0 |
| Dermatitis | 2 (9.1) | 0 | 0 |
| Rash maculopapular | 2 (9.1) | 0 | 0 |
| Interstitial lung disease | 1 (4.5) | 2 (9.1) | 0 |
| Blood creatinine increased | 0 | 2 (9.1) | 2 (9.1) |

CTCAE: Common Terminology Criteria for Adverse Events, TEAE: Treatment-emergent adverse event

active (ECOG PS score 0). The study population also had comparatively less bone involvement than their BOLERO-2 counterparts, with one-quarter the prevalence of bone-only metastases; hence, a higher proportion had measurable disease. In comparison, proportionally fewer Taiwanese patients in EVEREXES were sensitive to prior endocrine therapy; higher proportions of patients from Taiwan had NSAI as the latest treatment for advanced disease, and prior chemotherapies for metastatic disease were twice more than as in BOLERO-2.

The median RDI of EXE was 100% in all cohorts and was slightly higher for EVE for the Taiwanese subset in EVEREXES than in BOLERO-2 (97.0% vs. 86.0%). Taiwanese patients also showed a higher median exposure duration to EVE (including interruptions) than those in BOLERO-2 (38.5 weeks vs. 23.9 weeks).[19]

Consistent with a higher incidence of stomatitis among Asian versus non-Asian patients in BOLERO-2 (80% vs. 54%),[20] patients in EVEREXES Asia were also worse affected by stomatitis (any grade, 62.8% vs. 59.1%),[22] and this was also reflected in the Taiwanese population. However, studies have shown that the incidences of stomatitis did not impact PFS.[23] As shown from real-world data from Austria, patients treated with EVE 10 mg versus 5 mg had superior PFS;[24] therefore, the

**Table 4: Treatment-emergent adverse event of special interest associated with everolimus (*n*=22)**

| Type | Number of AEs, *n* (%) Any grade |
|---|---|
| Stomatitis | 17 (77.3) |
| Pneumonitis | 10 (45.5) |
| Skin rash | 6 (27.3) |
| Hyperlipidemia | 4 (18.2) |
| Infections | 3 (13.6) |
| Hyperglycemia | 2 (9.1) |
| Increased creatinine/renal failure/proteinuria | 2 (9.1) |

AEs: Adverse events

**Table 5: Best overall response (*n*=22)**

| Overall study period | EVEREXES Taiwan, *n* (%) 95% CI |
|---|---|
| Best ORR | |
| CR | 0 |
| PR | 4 (18.2) |
| SD | 12 (54.5) |
| PD | 5 (22.7) |
| ORR (CR + PR) | 4 (18.2) |
| CBR (CBR: CR + PR + [SD ≥24 weeks]) | 14 (63.6) |

CBR: Clinical benefit rate, CR: Complete response, PR: Partial response, ORR: Overall response rate, PD: Progressive disease, CI: Confidence interval, SD: Stable disease

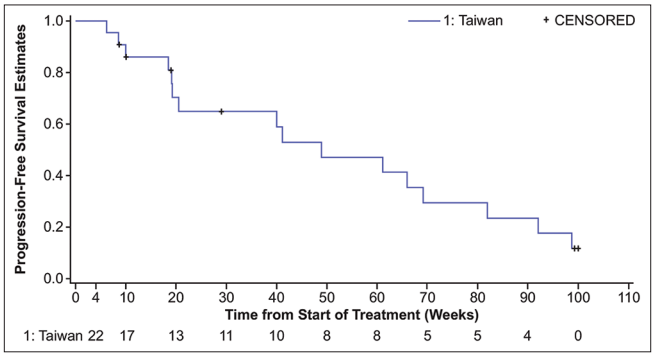


**Figure 1:** Progression-free survival

use of prophylactic steroid mouthwash which has been shown to decrease the incidences of stomatitis would enable patients to be maintained on the full dose, thereby enhancing treatment efficacy.[25] Taiwanese patients who reported stomatitis in this trial were treated with steroid mouthwash to manage their symptoms and they maintained close to 100% median RDI of EVE. This confirms that good stomatitis management can make an important contribution to prolonging survival, as well as improving patients' quality of life.

Patients in EVEREXES Asia and its Taiwanese subset had nearly twice the incidence of hyperglycemia observed in BOLERO-2;[20,21] however, no Taiwanese patients had a grade 3/4 episode, indicating that, like stomatitis, hyperglycemia was adequately managed.

Proportionally fewer patients from Taiwan discontinued treatment due to unacceptable AEs despite the high incidence of hyperglycemia and any grade stomatitis. Dose reduction or interruption due to AEs was similar to BOLERO-2 (9.1% vs. 9.1%), and a comparatively higher dose intensity indicated that patients in Taiwan were better able to tolerate EVE + EXE at the per-protocol dosage. There was no grade ≥3 rash reported in the Taiwanese cohort.

Despite their potentially unfavorable visceral tumor burden, efficacy outcomes of EVE + EXE in Taiwanese patients were comparable to the BOLERO-2 cohorts (ORR: 18.2% vs. 12.6%; CR: 0% vs. 0.6%; PR: 18.2% vs. 12.0%).[19] The results reaffirm the choice of EVE + EXE in HR + HER2-ABC.

These studies do, however, predate the use of cyclin-dependent kinase 4/6 (CDK 4/6) inhibitors, which are recently considered the standard of care for ABC in combination with backbone endocrine therapy in the first- or second-line setting. MONALEESA-3/7 and MONARCH-2 have shown that CDK4/6 inhibitors greatly improve PFS and overall survival over ET monotherapy.[26-28]

Despite these advancements, tumors initially responding to endocrine therapy, including CDK4/6 inhibitor combination, would eventually develop resistance due to the aberrant signaling in the phosphatidylinositol 3-kinase/protein kinase B (AKT)/mTOR complex 1 (PI3K/AKT/mTORC1) pathway.[29] It is only logical to combine inhibitors of this pathway with endocrine therapy.

In patients with *PIK3CA* mutation which causes constitutive PI3K activation, alpelisib + fulvestrant is an option of treatment after progression from endocrine-based therapy.[30] In the BOLERO-2 study, *PIK3CA* mutation did not affect PFS benefit with EVE; however, patients with exon-9 mutations exhibited greater PFS improvement compared to those with exon-20 mutation, which highlights the need for mutation testing.[31] In case alpelisib is unavailable, mTOR inhibitors such as EVE can also be considered the next step in therapy for patients who have progressed on NSAI therapy.[30] In clinical practice, EVE in combination with fulvestrant may also be an option for patients who do not respond to EXE;[32] however, more studies would be required to understand the optimal choice of companion drug.

## Limitations

EVEREXES was subject to limitations of having a nonrandomized open-label design. Comparisons between patient cohorts in EVEREXES and BOLERO-2 are entirely subjective, and must therefore be interpreted with caution, especially given the relatively smaller number of Taiwanese patients. It is possible that results from Taiwan may reflect a selection bias toward patients with strong hormone receptor expression. Nevertheless, overall similarities of inclusion criteria and characteristics of their patient cohorts between the EVEREXES Asia and BOLERO-2 support the validity of making comparisons between them. Moreover, the great

geographic and cultural diversity of the Asian populations included justifies examining data from individual participating countries, Further studies with a larger number of Taiwanese patients are warranted to validate our data.

## Conclusion

The safety and tolerability profile of EVE + EXE in Taiwanese populations were consistent with results as reported in BOLERO-2. AEs were typical for EVE and were mostly mild to moderate and manageable. Adequate prophylactic management of stomatitis may contribute to better tolerability of high-dose treatment and thereby enhance efficacy. Efficacy in EVEREXES also compared favorably with BOLERO-2, with patients meeting these inclusion criteria deriving no less PFS benefit from EVE + EXE than the global clinical trial population. The encouraging treatment outcomes in Taiwanese warrant further investigation in large-scale controlled studies and suggest a new strategy of initiating EVE + EXE immediately after failure of previous NSAIs and CDK4/6 inhibitors instead of chemotherapy. Overall, the results from EVEREXES Taiwan seem to support the rationale for combining EVE 10 mg/day plus EXE 25 mg/day for postmenopausal Taiwanese women with HR+/HER2− ABC refractory to NSAIs. However, owing to the small sample size, these data should be interpreted carefully.

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### Conflicts of interest

There are no conflicts of interest.

## References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, *et al*. Global cancer observatory. In: Cancer Tomorrow. Lyons, France: International Agency for Research on Cancer; 2020. Available from: https://gco.iarc.fr/tomorrow.[Last accessed on 2020 Jun 12].
2. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005;10 Suppl 3:20-9.
3. Ciocca DR, Fanelli MA. Estrogen receptors and cell proliferation in breast cancer. Trends Endocrinol Metab 1997;8:313-21.
4. Lumachi F, Brunello A, Maruzzo M, Basso U, Basso SM. Treatment of estrogen receptor-positive breast cancer. Curr Med Chem 2013;20:596-604.
5. Osborne CK, Schiff R. Mechanisms of endocrine resistance in breast cancer. Annu Rev Med 2011;62:233-47.
6. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 2005;365:1687-717.
7. Coombes RC, Kilburn LS, Snowdon CF, Paridaens R, Coleman RE, Jones SE, *et al.* Survival and safety of exemestane versus tamoxifen after 2-3 years' tamoxifen treatment (intergroup exemestane study): A randomised controlled trial. Lancet 2007;369:559-70.
8. Gennatas C, Michalaki V, Carvounis E, Psychogios J, Poulakaki N, Katsiamis G, *et al.* Third-line hormonal treatment with exemestane in postmenopausal patients with advanced breast cancer progressing on letrozole or anastrozole. A phase II trial conducted by the hellenic group of oncology (HELGO). Tumori 2006;92:13-7.
9. Lønning PE, Bajetta E, Murray R, Tubiana-Hulin M, Eisenberg PD, Mickiewicz E, *et al.* Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial. J Clin Oncol 2000;18:2234-44.
10. Zhao M, Ramaswamy B. Mechanisms and therapeutic advances in the management of endocrine-resistant breast cancer. World J Clin Oncol 2014;5:248-62.
11. Lane HA, Wood JM, McSheehy PM, Allegrini PR, Boulay A, Brueggen J, *et al.* mTOR inhibitor RAD001 (everolimus) has antiangiogenic/vascular properties distinct from a VEGFR tyrosine kinase inhibitor. Clin Cancer Res 2009;15:1612-22.
12. Mabuchi S, Altomare DA, Connolly DC, Klein-Szanto A, Litwin S, Hoelzle MK, *et al.* RAD001 (everolimus) delays tumor onset and progression in a transgenic mouse model of ovarian cancer. Cancer Res 2007;67:2408-13.
13. AFINITOR® [package insert]. East Hanover (NJ): Novartis Pharmaceuticals Corp; 2022.
14. Boulay A, Rudloff J, Ye J, Zumstein-Mecker S, O'Reilly T, Evans DB, *et al.* Dual inhibition of mTOR and estrogen receptor signaling *in vitro* induces cell death in models of breast cancer. Clin Cancer Res 2005;11:5319-28.
15. Ellard SL, Clemons M, Gelmon KA, Norris B, Kennecke H, Chia S, *et al.* Randomized phase II study comparing two schedules of everolimus in patients with recurrent/metastatic breast cancer: NCIC clinical trials group IND.163. J Clin Oncol 2009;27:4536-41.
16. Baselga J, Semiglazov V, van Dam P, Manikhas A, Bellet M, Mayordomo J, *et al.* Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 2009;27:2630-7.
17. Baselga J, Campone M, Piccart M, Burris HA 3rd, Rugo HS, Sahmoud T, *et al.* Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.
18. Bachelot T, Bourgier C, Cropet C, Ray-Coquard I, Ferrero JM, Freyer G, *et al.* Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: A GINECO study. J Clin Oncol 2012;30:2718-24.
19. Yardley DA, Noguchi S, Pritchard KI, Burris HA 3rd, Baselga J, Gnant M, *et al.* Everolimus plus exemestane in postmenopausal patients with HR(+) breast cancer: BOLERO-2 final progression-free survival analysis. Adv Ther 2013;30:870-84.
20. Noguchi S, Masuda N, Iwata H, Mukai H, Horiguchi J, Puttawibul P, *et al.* Efficacy of everolimus with exemestane versus exemestane alone in Asian patients with HER2-negative, hormone-receptor-positive breast cancer in BOLERO-2. Breast Cancer 2014;21:703-14.
21. Im YH, Karabulut B, Lee KS, Park BW, Adhav A, Cinkir HY, *et al.* Safety and efficacy of everolimus (EVE) plus exemestane (EXE) in postmenopausal women with locally advanced or metastatic breast cancer: Final results from EVEREXES. Breast Cancer Res Treat 2021;188:77-89.
22. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, *et al.* New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
23. Rugo HS, Hortobagyi GN, Yao J, Pavel M, Ravaud A, Franz D, *et al.* Meta-analysis of stomatitis in clinical studies of everolimus: Incidence and relationship with efficacy. Ann Oncol 2016;27:519-25.
24. Steger GG, Egle D, Bartsch R, Pfeiler G, Petru E, Greil R, *et al.* Efficacy and safety of everolimus plus exemestane in patients with HR+, HER2- advanced breast cancer progressing on/after prior endocrine therapy in routine clinical practice: Primary results from the non-interventional study, STEPAUT. Breast 2020;50:64-70.

25. Jones VE, McIntyre KJ, Paul D, Wilks ST, Ondreyco SM, Sedlacek S, *et al.* Evaluation of miracle mouthwash plus hydrocortisone versus prednisolone mouth rinses as prophylaxis for everolimus-associated stomatitis: A randomized phase II study. Oncologist 2019;24:1153-8.
26. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, *et al.* Overall survival with ribociclib plus fulvestrant in advanced breast cancer. N Engl J Med 2020;382:514-24.
27. Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA, *et al.* Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018;36:2465-72.
28. Sledge GW Jr., Toi M, Neven P, Sohn J, Inoue K, Pivot X, *et al.* MONARCH 2: Abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35:2875-84.
29. Miller TW, Hennessy BT, González-Angulo AM, Fox EM, Mills GB, Chen H, *et al.* Hyperactivation of phosphatidylinositol-3 kinase promotes escape from hormone dependence in estrogen receptor-positive human breast cancer. J Clin Invest 2010;120:2406-13.
30. Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, André F, *et al*. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31:1623-49.
31. Hortobagyi GN, Chen D, Piccart M, Rugo HS, Burris HA 3rd, Pritchard KI, *et al*. Correlative analysis of genetic alterations and everolimus benefit in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: Results from BOLERO-2. J Clin Oncol 2016;34:419-26.
32. Kornblum N, Zhao F, Manola J, Klein P, Ramaswamy B, Brufsky A, *et al.* Randomized phase II trial of fulvestrant plus everolimus or placebo in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer resistant to aromatase inhibitor therapy: Results of PrE0102. J Clin Oncol 2018;36:1556-63.