

Safety, Efficacy, and Patient Acceptability of Everolimus in the Treatment of Breast Cancer

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ABSTRACT: Everolimus combined with exemestane is an important treatment option for patients suffering from estrogen receptor-positive, human epidermal growth factor receptor 2-negative, advanced breast cancer (ABC) who have been previously treated with a nonsteroidal aromatase inhibitor (NSAI). After presentation of phase III registration trial BOLERO-2, several phase IIIb trials have been started to evaluate this regimen in a more real-world setting. Here, we review the efficacy and safety data published or presented at selected international meetings. These studies confirmed the outcome observed in the BOLERO-2 trial. Patient acceptance rate is also discussed by focusing on the permanent everolimus discontinuation rate in these trials. Factors influencing the safety profile are also reported, including the impact of age. The optimal sequence of combined therapy approaches associating targeted and endocrine therapy (ET) has yet to be determined as new treatment options such as cyclin-dependent kinase inhibitors become available. However, everolimus–exemestane remains an important treatment option with a major impact on progression-free survival (PFS) and an acceptable safety profile.

KEYWORDS: breast cancer, treatment, everolimus, safety, efficacy, progression-free survival

CITATION: Lousberg and Jerusalem. Safety, Efficacy, and Patient Acceptability of Everolimus in the Treatment of Breast Cancer. *Breast Cancer: Basic and Clinical Research* 2016;10:239–252 doi:10.4137/BCBCR.S12443.

TYPE: Review

RECEIVED: October 7, 2016. **RESUBMITTED:** November 21, 2016. **ACCEPTED FOR PUBLICATION:** November 23, 2016.

ACADEMIC EDITOR: Goberdhan P. Dimri, Editor in Chief

PEER REVIEW: Four peer reviewers contributed to the peer review report. Reviewers' reports totaled 524 words, excluding any confidential comments to the academic editor.

FUNDING: Authors disclose no external funding sources.

COMPETING INTERESTS: GJ received honoraria, played consulting/advisory role, and received research funding from Novartis, received honoraria, played consulting/advisory role, and received research funding from Roche, played consulting/advisory role in Pfizer, and received honoraria from Eli Lilly. LL discloses no potential conflicts of interest.

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Provenance: the authors were invited to submit this paper.

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Introduction

BOLERO-2 was a key phase III randomized trial.^{1,2} It used the mammalian target of rapamycin (mTOR) inhibitor, everolimus, in association with exemestane as a valid treatment option in postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, advanced breast cancer (ABC) progressing after a nonsteroidal aromatase inhibitor (NSAI).^{3,4} The progression-free survival (PFS) more than doubled in those metastatic patients if everolimus is combined with exemestane. However, all international guidelines indicate that this choice must consider the toxicities encountered with this treatment.^{3,4}

The safety profile of everolimus is a widely debated topic. Clinicians may fear this therapeutic option especially in light of the overall survival (OS) data in BOLERO-2. While the trial was not powered for this endpoint, there were no statistically significant differences.⁵ The goal of our review is to compare the most relevant and real-life data for efficacy and safety of everolimus in ABC. Indeed, patients in registration trials are usually younger with fewer comorbidities and comedications and enrolled at highly selected anticancer centers. Consequently, it is important that the result can be confirmed in a less selected patient population. We will also look for some factors influencing toxicities. With a good selection of patients and a careful management of adverse events (AEs),

this treatment is beneficial for patients suffering from metastatic disease and delays the use of chemotherapy (CT).

Recently, this drug combination and the advent of cyclin-dependent kinase inhibitors such as palbociclib have radically changed the treatment strategy of patients presenting ER-positive ABC. The current therapeutic approaches restore sensitivity to endocrine therapy (ET) and delay the use of CT except in patients presenting symptomatic visceral disease. Additional therapeutic weapons are under development in ongoing phase III registration trials. Thus, as more targeting agents become available, a good selection of patients and careful management of specific AE are of considerable interest. The optimal initial treatment modality and the best sequential use of targeted agents combined with ET are now important open questions. The efficacy, side effects, and costs have to be integrated when defining the optimal treatment sequence.

mTOR Inhibitors: Mechanism of Action

The phosphatidylinositol-3-kinase (PI3K)–protein kinase B (AKT)–mTOR signaling pathway is a key regulator of cell survival, proliferation, and angiogenesis. Preclinical data showed that there are effectors of the mTOR pathway including some protein kinases that phosphorylate different targets and control protein translocation. The subunit alpha of the ER is one of these targets. Thus, it facilitates crosstalk between the ER pathway and the PI3K–AKT–mTOR pathway.^{6,7}



The hyperactivation of the PI3K–AKT–mTOR pathway following, for example, loss of phosphatase and tensin homolog (PTEN) or phosphatidylinositol-3-kinase catalytic alpha polypeptide (PIK3CA)-activating mutations can lead to a ligand-independent activation of the ER signaling pathway. This could partly explain the resistance to ET in these cancers with hyperactivation of the PI3K–AKT–mTOR pathway. This is a rational use of an mTOR inhibitor in ET-resistant breast cancers (BCs).⁸

Everolimus: Pharmacological Data

Everolimus is a rapamycin analog that inhibits the mTORC1 cellular complex. This leads to pleomorphic and ubiquitous actions such as inhibition of cell proliferation, angiogenesis, protein synthesis, and metabolic dysregulation.⁹ Its peak plasma concentration is obtained between one and two hours after a single oral dose following oral daily administration. One week is necessary to reach the steady state. The plasma protein binding is about 74%. The metabolization is hepatic. The elimination half-life is from 18 to 35 hours, but this may be delayed in patients with hepatic failure.^{10,11}

Everolimus is a substrate for CYP3A4, CYP3A5, CYP2C8, and P-glycoprotein. Thus, many drug interactions can modify plasmatic concentrations of everolimus and affect its efficacy and toxicity.¹⁰ The patient's characteristics such as age, sex, or weight do not appear to affect the pharmacokinetic properties of everolimus.¹⁰

Everolimus: Efficacy Data in ABC

Some phase II studies have confirmed this hypothesis. The first one evaluated the safety and efficacy of oral everolimus alone in two different schedules in minimally pretreated patients with metastatic breast cancer (BC). This showed a clinical activity of the oral 10 mg daily therapy.⁹ The response rate was 12%.¹² The second was a neoadjuvant setting and explored whether sensitivity to letrozole was enhanced with everolimus.¹³ The response rate by clinical palpation in the everolimus arm was significantly higher than that with letrozole alone.¹³ The third study evaluated the efficacy and safety of everolimus in combination with tamoxifen in patients with metastatic BC resistant to aromatase inhibitors and suggested a better outcome with the combination versus tamoxifen alone.¹⁴ These preliminary results encouraged the realization of international multicenter phase III studies (Table 1).

Everolimus: the BOLERO 2 trial. The key efficacy data on everolimus in ABC were reported in the BOLERO-2 trial.^{3–5} The study met its primary endpoint. It demonstrated a statistically significant benefit in PFS for the association of everolimus–exemestane versus placebo–exemestane for patients with ER-positive ABC who relapsed or progressed during or shortly after NSAI therapy. The median PFS was more than doubled with 3.2 months in the placebo group and 7.8 months in the everolimus group⁴ (hazard ratio (HR) = 0.45; 95% confidence interval (CI) = 0.38–0.54). The data on OS

were a secondary endpoint and did not meet statistical significance but with the addition of everolimus to exemestane, the OS increased by 4.4 months.⁵ However, this sample size was based on PFS, and the study was powered only with an eight-month OS improvement.⁵ These results are the cornerstone of international guidelines regarding everolimus in ABC.

Longer median PFS has been observed in the BOLERO-2 trial in both treatment arms in patients presenting better performance status, fewer sites of metastatic disease, no visceral disease (or bone-only disease), having received no prior CT, or no prior CT for advanced disease. This was also true in younger patients (under 65 years) and in patients receiving first-line therapy for advanced disease.²

Two other BOLERO trials have already been published in a different patient population with HER2-positive ABC. They hypothesized that the inhibition of mTOR could enhance trastuzumab sensitivity. BOLERO-1 evaluated the efficacy and safety of adding everolimus to trastuzumab and paclitaxel as first-line treatment for patients with HER2-positive ABC. It did not meet its primary endpoint, which was a gain in PFS.¹⁵ Interestingly, in the ER-negative subpopulation, the median PFS increased from 13.1 to 20.3 months (HR = 0.66; 95% CI = 0.48–0.91), but the protocol-specified significance threshold ($P = 0.0044$) was not crossed. BOLERO-3 evaluated the efficacy and safety of adding everolimus to trastuzumab and vinorelbine in patients with trastuzumab-resistant ABC who had previously received a taxane therapy.¹⁶ It met its primary endpoint with a gain in PFS of 1.22 months with everolimus (HR = 0.78; 95% CI = 0.65–0.95), but this benefit is not clinically meaningful.¹⁶ Based on these data, everolimus is not recommended in HER2-positive ABC. Nevertheless, an exploratory analysis combining biomarker data from BOLERO 1 and BOLERO 3 suggests that patients with HER2-positive ABC suffering from tumors presenting PIK3CA mutations, PTEN loss, or a hyperactive PI3K pathway could derive a PFS benefit from the addition of everolimus to trastuzumab and CT.¹⁷

There are two additional ongoing BOLERO trials in phase II. BOLERO-4 evaluates the safety and efficacy of adding everolimus to letrozole in the first-line setting of postmenopausal patients with ER-positive ABC.¹⁸ BOLERO-6 is assessing the efficacy and safety of everolimus and capecitabine monotherapies versus everolimus–exemestane combination in patients with ER-positive ABC.¹⁹

Everolimus: prospective observational studies. Some other studies have confirmed the BOLERO-2 efficacy data. These real-world studies represent a broader patient population than the BOLERO-2 trial with no limitations on the number of prior CT lines (except one study, EVEREXES, which is limited to one prior line), time of recurrence or progression after NSAI therapy, or prior exemestane therapy.

STEAUT was presented at the European Breast Cancer Conference in Amsterdam by Steger et al in March 2016.²⁰ This is an Austrian noninterventional study whose aim is to evaluate

Table 1. Outcome of key prospective clinical trials evaluating everolimus.

STUDY	TREATMENT	ENDPOINTS	RESULTS: MEDIAN PFS	SAFETY SERIOUS ADVERSE EVENTS	SAFETY ON-TREATMENT DEATHS DUE TO ADVERSE EVENTS	SAFETY DOSE MODIFICATIONS EVEROLIMUS/ PLACEBO	SAFETY DISCONTINUATION DUE TO ADVERSE EVENTS
BOLERO-1¹⁵ Phase 3, randomised (2:1), double-blind NCT00876395	A: EVEROLIMUS 10 mg/day + TRASTUZUMAB weekly + PACLITAXEL 80 mg/m ² weekly 3w/4 B: PLACEBO once a day + TRASTUZUMAB weekly + PACLITAXEL 80 mg/m ² weekly 3w/4	PRIMARY: PFS in the full population PFS in the HR-negative subpopulation (protocol amendment) SECONDARY: OS (full population and HR-negative) Proportion of patients with an OBJECTIVE RESPONSE Proportion of patients with a CLINICAL BENEFIT SAFETY	PFS full population: 14.95 months A vs 14.49 months B HR = 0.89 (95% CI = 0.73–1.08) P = 0.1166 PFS HR-negative subpopulation: 20.27 months A vs 13.08 months B HR = 0.66 (95% CI = 0.48–0.91) P = 0.0049 but not statistically significant (P < 0.0044 needed)	36% in the EVEROLIMUS group vs 15% in the PLACEBO group EVEROLIMUS – Pneumonitis 4% – Pneumonia 4% – Pyrexia 3%	4% (17 deaths) in the EVEROLIMUS group vs NONE in the PLACEBO group – Pneumonitis – Pulmonary embolism – Respiratory failure – Pulmonary oedema – Pneumonia – Cardiorespiratory arrest – Sepsis – Fall – Diabetes (metabolic acidosis) – Cerebrovascular accident	86% in the EVEROLIMUS group vs 74% in the PLACEBO group Median EVEROLIMUS Relative-Dose-Intensity = 0.54	Discontinuation of all three drugs: 12% in the EVEROLIMUS group vs 4% in the PLACEBO group Discontinuation of any of the three drugs: 50% in the EVEROLIMUS group vs 38% in the PLACEBO group
BOLERO-2² Phase 3, randomised (2:1), double-blind NCT00863655	A: EVEROLIMUS 10 mg/day + EXEMESTANE 25 mg/day B: PLACEBO once a day + EXEMESTANE 25 mg/day Until disease progression or unacceptable toxicity or withdrawal of consent.	PRIMARY: PFS SECONDARY: OS OVERALL RESPONSE RATE CLINICAL BENEFIT TIME TO DETERIORATION OF ECOG SAFETY QUALITY OF LIFE	PFS local assessment: 7.8 months A vs 3.2 months B HR = 0.45 (95% CI = 0.38–0.54) P < 0.0001 PFS central assessment: 11 months A vs 4.1 months B HR = 0.38 (95% CI = 0.31–0.48) P < 0.0001	1.7% (7 deaths) in the EVEROLIMUS group vs 0.4% (1 death) in the PLACEBO group EVEROLIMUS: – Sepsis – Staphylococcal sepsis – Pneumonia – Tumor hemorrhage – Cerebrovascular accident – Renal failure – Suicide EXEMESTANE: – Pneumonia	62.4% in the EVEROLIMUS group vs 5.5% in the PLACEBO group Median EVEROLIMUS Relative-Dose-Intensity = 0.86	Discontinuation of at least one drug: 26.3% in the EVEROLIMUS group vs 5% in the PLACEBO group	

(Continued)



Table 1. (Continued)

STUDY	TREATMENT	ENDPOINTS	RESULTS: MEDIAN PFS	SAFETY SERIOUS ADVERSE EVENTS	SAFETY ON-TREATMENT DEATHS DUE TO ADVERSE EVENTS	SAFETY DOSE MODIFICATIONS EVEROLIMUS/ PLACEBO	SAFETY DISCONTINUATION DUE TO ADVERSE EVENTS
BOLERO-3¹⁶ Phase 3, randomised (1:1), double-blind NCT01007942	A: EVEROLIMUS 5 mg/day + TRASTUZUMAB weekly + VINORELBINE 25 mg/m ² weekly in 3-week cycles B: PLACEBO once a day + TRASTUZUMAB weekly + VINORELBINE 25 mg/m ² weekly in 3-week cycles	PRIMARY: PFS locally-assessed SECONDARY: OS Proportion of patients with an OBJECTIVE RESPONSE Proportion of patients with a CLINICAL BENEFIT SAFETY TIME TO DETERIORATION OF ECOG QUALITY OF LIFE TIME TO OBJECTIVE RESPONSE DURATION OF OBJECTIVE RESPONSE PHARMACOKINETICS	PFS: 7 months A vs 5.78 months B HR = 0.78 (95% CI = 0.65–0.95) P = 0.0067	42% in the EVEROLIMUS group vs 20% in the PLACEBO group EVEROLIMUS – Febrile neutropenia 10% – Pyrexia 5% – Neutropenia 4% – Anemia 4% – Stomatitis 3%	2 deaths in each group EVEROLIMUS – Unknown – Acute Respiratory Distress Syndrome PLACEBO – Acute respiratory failure – Pneumonia	Dose interruptions of EVEROLIMUS vs PLACEBO : 83% vs 53% Dose reductions of EVEROLIMUS vs PLACEBO : 39% vs 13% Median EVEROLIMUS Relative-Dose-Intensity = 0.77	Discontinuation of all study treatments: 10% in the EVEROLIMUS group vs 5% in the PLACEBO group
569 patients HER2+ trastuzumab-resistant advanced breast cancer with previous taxane-therapy . Trastuzumab resistance = recurrence during or within 12 months of adjuvant treatment or progression during or within 4 weeks of treatment for advanced disease. No more than three previous lines of chemotherapy for advanced disease. Median follow-up: 20.2 months	EVEROLIMUS 10 mg/day + EXEMESTANE 25 mg/day Until disease progression or unacceptable toxicity or discontinuation form study due to other reasons or local reimbursement of Everolimus or death.	PRIMARY: SAFETY (frequency of AEs and serious AEs) SECONDARY: AES GRADES 3/4	NR	21.2% 8.5% EVEROLIMUS-RELATED – Dyspnea 2.4% – Non-infectious Pneumonitis 2.2% – Pyrexia 1.6% – Anemia 1.3% – Pleural effusion 1.2%	2.2% (46 deaths) AES EVEROLIMUS-RELATED leading to death in 4 patients : – 2 Non-Infectious Pneumonitis – General physical health deterioration – Cardio-respiratory arrest	Dose reductions EVEROLIMUS : 14.1% (10.3% medical decision) Dose interruptions EVEROLIMUS : 55.9% Median EVEROLIMUS Relative-Dose-Intensity = 0.98	17.1%
BALLET²⁶ Phase 3b, open label, single arm, expanded access trial EudraCT Number 2012-000073-23 2131 patients (safety analysis) ER+ , HER2- , advanced breast cancer recurring or progressing during or after prior non-steroidal aromatase inhibitors. NSAIs not necessarily the last treatment; no restriction on the number of prior lines of chemotherapy. Median follow-up: 4.6 months	EVEROLIMUS 10 mg/day + EXEMESTANE 25 mg/day Until disease progression or unacceptable toxicity or discontinuation form study due to other reasons or local reimbursement of Everolimus or death.	PRIMARY: SAFETY (frequency of AEs and serious AEs) SECONDARY: AES GRADES 3/4	NR	21.2% 8.5% EVEROLIMUS-RELATED – Dyspnea 2.4% – Non-infectious Pneumonitis 2.2% – Pyrexia 1.6% – Anemia 1.3% – Pleural effusion 1.2%	2.2% (46 deaths) AES EVEROLIMUS-RELATED leading to death in 4 patients : – 2 Non-Infectious Pneumonitis – General physical health deterioration – Cardio-respiratory arrest	Dose reductions EVEROLIMUS : 14.1% (10.3% medical decision) Dose interruptions EVEROLIMUS : 55.9% Median EVEROLIMUS Relative-Dose-Intensity = 0.98	17.1%



Table 1. (Continued)

STUDY	TREATMENT	ENDPOINTS	RESULTS: MEDIAN PFS	SAFETY SERIOUS ADVERSE EVENTS	SAFETY ON-TREATMENT DEATHS DUE TO ADVERSE EVENTS	SAFETY DOSE MODIFICATIONS EVEROLIMUS/ PLACEBO	SAFETY DISCONTINUATION DUE TO ADVERSE EVENTS
BRAWO³⁰ Phase 4 (Non-intentional), Germany Second interim analysis	A: EVEROLIMUS 10 mg/day + EXEMESTANE 25 mg/day	PRIMARY: PFS Impact of PHYSICAL ACTIVITY on PFS	PFS FULL POPULATION: 8 months (95% CI = 6.7–9.1)	NR	NR	Dose interruptions FULL POPULATION: 34.4% Dose interruptions EVEROLIMUS 10 mg: 38.5% Dose interruptions EVEROLIMUS 5 mg: 7.6%	22.6%
500 patients ER+, HER2-, advanced breast cancer without symptomatic visceral metastasis undergoing treatment with Everolimus + Exemestane according to clinical routine	B: EVEROLIMUS 5 mg/day + EXEMESTANE 25 mg/day	SECONDARY: QoL Impact of PHYSICAL ACTIVITY on QoL STOMATITIS Management, prophylactic measures and treatment of stomatitis in clinical setting	PFS in first-line therapy: 10.1 months (95% CI = 6.7–17.6)			Dose reductions FULL POPULATION: 48.1% Dose reductions EVEROLIMUS 10 mg: 52.2% Dose reductions EVEROLIMUS 5 mg: 21.2%	
	C: EVEROLIMUS 5 mg/day + 10 mg/day + EXEMESTANE 25 mg/day.	SEQUENCE of therapies				Median EVEROLIMUS Relative-Dose-Intensity FULL POPULATION = 0.88 Median EVEROLIMUS Relative-Dose-Intensity EVEROLIMUS 10 mg = 0.935 Median EVEROLIMUS Relative-Dose-Intensity EVEROLIMUS 5 mg = 0.5	



efficacy and safety in patients treated with everolimus and exemestane according to clinical routine. Its enrollment is still ongoing. The analysis was recently presented on 134 patients. The median PFS is 9.23 months (95% CI = 6.83–10.03), which is consistent with the results obtained in BOLERO-2. A subgroup analysis was made according to everolimus dosing. Interestingly, PFS was lower for patients with 5 mg (4.97 months; 95% CI = 3.13–10.03) compared to 9.83 months with 10 mg (95% CI = 6.43–10.3). Patients receiving the 5 mg starting dose did have less favorable prognostic factors (more visceral metastases, worse eastern cooperative oncology group (ECOG) performance status, and more prior therapies). Only the 10 mg starting dose was prospectively evaluated, and this is the registered starting dose of everolimus.

The planned interim analysis of EVEREXES was presented at San Antonio Breast Cancer Symposium by Im et al in December 2015.²¹ It is a phase IIIb study of safety as primary endpoint and efficacy as secondary endpoint with enrollment of a poorly represented population in BOLERO-2—concerning patients from Asia Pacific, Africa, and Middle East. The analysis was made on 227 patients. The median PFS is 9.45 months (95% CI = 7.4–9.9), which is also consistent with BOLERO-2.

The final efficacy analysis of 4EVER was also presented at the San Antonio Breast Cancer Symposium by Tesch et al in December 2015.²² This is a German phase IIIb study that aims to evaluate the efficacy and safety in a broader patient population than BOLERO-2. This analysis was made on 281 patients. The efficacy was lower than BOLERO-2 with a median PFS of 5.6 months (95% CI = 5.4–6). This can be partially explained by the patient population, which was more advanced and heavily pretreated. A subgroup analysis showed a better efficacy of the everolimus–exemestane combination without prior CT (PFS 6.2 months; 95% CI = 5.6–7.7) compared to that with prior CT (PFS 5.2 months; 95% CI = 4.2–5.5).

Finally, the second interim analysis of BRAWO was presented at European Society of Medical Oncology by Fasching et al in September 2014.²³ It is a German noninterventional study. One of the primary endpoints was to extend the understanding of the efficacy of the combination treatment. This second interim analysis was made on 500 patients. The 8-month median PFS was also consistent with BOLERO-2 (95% CI = 6.7–9.1). The PFS was higher at 10.1 months in a subgroup analysis where the combination was used in the first-line setting (95% CI = 6.7–17.6).

All these data confirm the considerable benefit in PFS obtained with the everolimus–exemestane combination. Combined with the safety data, we show that better selection of patients and careful management of AE would be beneficial to the majority of patients.

Everolimus: Safety Data in ABC

The safety profile of everolimus is clearly worse than the placebo. The frequency of AE is always higher in the everolimus

group with more serious adverse events (SAEs), more dose interruptions or modifications, more discontinuations of treatment due to AE, and more on-treatment deaths. An important question is if this toxicity could be considered tolerable and manageable. A detailed analysis of the safety data is necessary for each patient to determine individually the risk/benefit ratio of this treatment and the patient acceptance rate.

AEs are globally similar between all the trials published or presented until today (Tables 1–3). Most AEs are mild to moderate (grade 1/2). The most frequent AEs are stomatitis, diarrhea, rash, fatigue, nausea, decreased appetite, weight loss, cough, dyspnea, and anemia. The metabolic AEs—hyperlipidemia and hyperglycemia—are of particular interest because they may worsen cardiovascular comorbidities of postmenopausal women. Noninfectious pneumonitis (NIP) is less frequent, but can be life threatening. The most frequent grade 3/4 AEs are stomatitis, fatigue, diarrhea, hyperglycemia, dyspnea, NIP, and anemia.

BOLERO-1. We emphasize two safety data issues. The first one is the relative dose intensity (RDI) of everolimus, which is clearly less than that in the other trials (everolimus RDI BOLERO-1 = 0.54). According to Hurvitz et al,¹⁵ the dose adjustments were more frequent because of the toxicity encountered from the combination with CT. The second one is the higher frequency of on-treatment deaths perhaps because of the limited experience with everolimus when used with paclitaxel and trastuzumab. Of note, there was a higher frequency of on-treatment deaths in regions with limited experience with everolimus; in some cases, the protocol-defined AE management guidelines were not followed.¹⁵ This indicates a key point of everolimus treatment monitoring—careful management in experienced centers is required.

BOLERO-2. AEs were seen in all patients in the everolimus–exemestane arm and in 91% of patients in the placebo–exemestane arm.² In this trial, it is important to consider treatment duration in the two arms. Indeed, in the everolimus–exemestane arm, the median duration of exposure to everolimus was 23.9 weeks and the median exposure to exemestane was 29.5 weeks. This is longer than median exposure to exemestane in the placebo–exemestane arm (14.07 weeks).² This nearly doubled treatment duration and may partially contribute to the higher incidences of AE, dose modifications, and treatment discontinuation among everolimus-treated patients. The majority of the AEs were resolved using protocol-defined management strategies. Stomatitis, NIP, and thrombocytopenia were the most common AEs leading to dose modifications in the everolimus–exemestane arm. The two most common AEs leading to treatment discontinuation in this arm were NIP and stomatitis.^{2,24}

More than one-third of stomatitis events was reported in the first two weeks. A total of 97% of patients with grade 3 stomatitis experienced resolution to grade ≤ 1 following dose interruption/reduction.^{2,24} The time course for pneumonitis differed from stomatitis with few early events and an increased



Table 2. Adverse events, all grades. Key prospective clinical trials evaluating everolimus.

ADVERSE EVENTS (ALL GRADES)	BOLERO-1 EVEROLIMUS GROUP ¹⁵	BOLERO-2 EVEROLIMUS GROUP ²	BOLERO-3 EVEROLIMUS GROUP ¹⁶	BALLET ⁶	STEPAUT ²⁰	EVEREXES ²¹	4EVER ²²	BRAWO ³⁰
STOMATITIS	67%	59%	62%	52.8%	46%	60.4%	49.2%	39.8%
RASH	41%	39%	25%	16.5%	27.33%	27.8%	22.7%	7.6%
NAUSEA— DECREASED APPETITE	56% NAUSEA: 33% DECREASED APPETITE: 23%	62% NAUSEA: 31% DECREASED APPETITE: 31%	68% NAUSEA: 36% DECREASED APPETITE: 32%	28% NAUSEA: 12% DECREASED APPETITE: 16%	20.67%	NR	51.5% NAUSEA: 26.1% DECREASED APPETITE: 25.4%	22.4% NAUSEA: 12% DECREASED APPETITE: 10.4%
DIARRHEA	56%	34%	38%	16.8%	16%	NR	26.4%	13.2%
WEIGHT LOSS	20%	28%	30%	10.2%	13.33%	15.4%	15.1%	6.8%
FATIGUE	35%	37%	44%	14%	16%	17.2%	36.1%	15.6%
PYREXIA	39%	16%	39%	14%	NR	NR	10%	5%
DYSPNEA—COUGH	66% DYSPNEA: 25% COUGH: 41%	48% DYSPNEA: 22% COUGH: 26%	49% DYSPNEA: 19% COUGH: 30%	22.2% DYSPNEA: 10.3% COUGH: 11.9%	23.33%	NR	42.4% DYSPNEA: 24.7% COUGH: 17.7%	21.8% DYSPNEA: 13% COUGH: 8.8%
PNEUMONITIS— INTERSTITIAL LUNG DISEASE	21%	16%	10%	9.5%	9.33%	14%	7.8%	NR
PERIPHERAL OEDEMA	33%	21%	15%	12.2%	12%	NR	16.7%	9.8%
HYPERGLYCEMIA	13%	14%	9%	12.4%	6%	24.7%	NR	NR
INCREASED ALAT	21%	12%	13%	NR	NR	NR	NR	NR
INCREASED ASAT	16%	14%	13%	NR	NR	NR	NR	NR
INCREASED GGT	4%	10%	11%	NR	NR	NR	NR	NR
ANEMIA	30%	21%	49%	14.4%	5.33%	NR	17.7%	6%
NEUTROPENIA	38%	NR	82%	NR	NR	NR	NR	NR

Table 3. Adverse events, grade 3 or 4. Key prospective clinical trials evaluating everolimus.

ADVERSE EVENTS GRADE 3/4	BOLERO-1 EVEROLIMUS GROUP ¹⁵	BOLERO-2 EVEROLIMUS GROUP ²	BOLERO-3 EVEROLIMUS GROUP ¹⁶	BALLET ²⁶	STEPAUT ²⁰	EVEREXES ²¹	4EVER ²²	BRAWO ³⁰
STOMATITIS	13%	8%	13%	9.4%	3.33%	10.6%	8.3%	3.6%
RASH	<1%	1%	0%	0.9%	0%	0%	1%	0%
NAUSEA— DECREASED APPETITE	<2% NAUSEA: <1% DECREASED APPETITE: 1%	2% NAUSEA: 1% DECREASED APPETITE: 1%	4% NAUSEA: 3% DECREASED APPETITE: 1%	1.7% NAUSEA: 0.6% DECREASED APPETITE: 1.1%	2.67%	NR	6% NAUSEA: 3% DECREASED APPETITE: 3%	2.8% NAUSEA: 2% DECREASED APPETITE: 0.8%
DIARRHEA	9%	2%	4%	1.2%	1.34%	NR	2%	0.8%
WEIGHT LOSS	1%	1%	<1%	0.1%	3.34%	0.9%	0.6%	0.4%
FATIGUE	5%	5%	13%	1.2%	0%	2.2%	3.3%	2.2%
PYREXIA	1%	<1%	3%	0.4%	NR	NR	0.7%	0.8%
DYSPNEA—COUGH	<5% DYSPNEA: 4% COUGH: <1%	<7% DYSPNEA: 6% COUGH: <1%	<3% DYSPNEA: 2% COUGH: <1%	2.4% DYSPNEA: 2% COUGH: 0.4%	0.67%	NR	5.4% DYSPNEA: 4.7% COUGH: 0.7%	7.4% DYSPNEA: 3.4% COUGH: 4%
PNEUMONITIS— INTERSTITIAL LUNG DISEASE	7%	3%	2%	1.9%	0.67%	1.3%	2.3%	NR
PERIPHERAL OEDEMA	<1%	1%	0%	0.6%	0%	NR	1%	0.4%
HYPERGLYCEMIA	6%	5%	2%	2.9%	0%	7%	NR	NR
INCREASED ALAT	6%	3%	4%	NR	NR	NR	NR	NR
INCREASED ASAT	4%	3%	3%	NR	NR	NR	NR	NR
INCREASED GGT	2%	7%	7%	NR	NR	NR	NR	NR
ANEMIA	9%	7%	19%	0%	0.67%	NR	4.3%	0.8%
NEUTROPENIA	25%	NR	73%	NR	NR	NR	NR	NR



number of events over time without seeing a plateau. A total of 80% of patients with grade 3 pneumonitis experienced resolution to grade ≤ 1 following dose interruption/reduction.^{2,24}

Approximately half of all hyperglycemia/new-onset diabetes mellitus events occurred within the first six weeks.^{2,24} More than one-third of fatigue events occurred within six weeks of treatment initiation. In all, 72% of patients with grade 3/4 fatigue in the experimental arm experienced resolution to grade ≤ 1 following dose interruption/reduction.^{2,24} Thus, the majority of *class-effect* AEs, except pneumonitis, had a relatively short time to onset with an *incidence plateau* thereafter.²⁴

Grade 3/4 AEs were experienced by 41% of patients. They mostly resolved to grade ≤ 1 fairly rapidly following dose interruption/modification. Consequently, close follow-up in the first weeks of everolimus/exemestane treatment is indicated. Management recommendations for everolimus-related AEs (comprising dose interruptions/reductions) were included in the trial and facilitated continued treatment in most cases. The duration of dose interruptions/reductions was relatively short, and most patients who resumed the full dose (10 mg everolimus) did so within two weeks to maintain dose intensity.²⁴ Of note, 34% of patients in the everolimus–exemestane arm experienced a one-level dose reduction at 5 mg of everolimus daily.²⁴

Moreover, BOLERO-2 included a health-related quality of life (HRQOL) analysis using the EORTC QLQ-C30 as a secondary endpoint. This is one of the most common, well-developed, and validated instruments for measuring HRQOL in oncology trials.^{2,25} The EORTC QLQ-C30 global health status scores were analyzed based on two definitions of time to definitive deterioration (TDD): a protocol-specified 5% change from baseline and a minimal important difference (MID) of a 10-point change from baseline. With the 5% change from baseline, the TDD of global health status was prolonged in patients who received everolimus–exemestane (8.3 months) versus those receiving placebo–exemestane (5.8 months).²⁵ Using the 10-point MID assessment, the difference in TDD between the two arms was similar with more profound benefits noted in patients with a baseline ECOG performance status of 1 or 2 and those aged < 65 years.²⁵ Thus, in light of these results, we can conclude that the patients in the experimental arm had a better quality of life than those in the placebo arm. This is particularly evident in younger patients and those with a reduced ECOG performance status at baseline.

BOLERO-3. The safety data in BOLERO-3 are of limited interest in our review. Indeed, everolimus was administered at 5 mg daily.¹⁶ The actual recommended starting dose is 10 mg daily. Moreover, in combination with vinorelbine, the trial reports a high incidence of hematological AEs, especially leukopenia.¹⁶ This does not allow a good safety analysis of everolimus with regard to the current approved regimen in BC.

BALLET. BALLET is a European phase IIIb, expanded-access multicenter trial that evaluated the safety of

everolimus plus exemestane in a patient population similar to BOLERO-2.

BALLET is very interesting because it represents the largest ever reported safety dataset on a general patient population. It also includes the largest safety dataset in an elderly subgroup (see below).

BALLET studied a more heavily pretreated patient population than BOLERO-2. The median follow-up was shorter in BALLET with 4.6 versus 17.7 months in BOLERO-2. Nevertheless, safety data in BALLET are quite similar to those in BOLERO-2.²⁶ There are some differences. First, the incidence of stomatitis and NIP was lower in the BALLET trial. This may be attributed to the shorter median follow-up and the fact that some patients dropped out of the study but continued everolimus under reimbursement.²⁶ Thus, the long-term safety profile could not be evaluated in these patients. Another difference was the median everolimus treatment duration. It was shorter in BALLET than in BOLERO-2 (16 vs. 23.9 weeks). In addition, the median RDI of everolimus was higher in the BALLET trial. This may be attributable to an improvement in treatment optimization with a lower rate of discontinuation due to AEs (17.1% in BALLET vs. 26.3% in BOLERO-2).²⁶

Everolimus and Safety: Sequence Therapies in ABC

One can compare the administration of everolimus–exemestane in the first-line setting with later lines of therapy.

BALLET. Median treatment duration is longer in patients who received the treatment as a first-line therapy (4.4 vs. 3.7 months in the full population).²⁶

Also, the incidence of everolimus-related AEs appear to be lower in the first-line setting versus later lines with less stomatitis (45.6% vs. 51.4%), rash (11.4% vs. 15.1%), asthenia (10.9% vs. 15.1%), and diarrhea (9.1% vs. 10.7%).²⁶ Grade 3/4 stomatitis (7.7% vs. 9.4%), diarrhea (0.5% vs. 0.9%), rash (0.5% vs. 1%), and NIP (0.9% vs. 1.9%) were also reported less frequently in the first-line setting versus later lines.²⁶

4EVER. There was no difference in the objective response rate (ORR) in the subset of patients with prior exemestane therapy.²² However, ORR was higher in patients without prior CT in the metastatic setting (11.5% without prior CT vs. 6.6% with prior CT).²² Similarly, there was no difference in median PFS in the subset of patients with prior exemestane therapy.²² However, PFS was longer in patients with no prior CT in the metastatic setting (6.2 months without prior CT vs. 5.2 months with prior CT).²²

BRAWO. The median PFS observed in the first 500 patients was 8.0 months, which is inferior to the 10.1 months median PFS observed in the subset of patients who received the combination everolimus–exemestane as first-line therapy for advanced disease.²³

First- or second-line-treated patients were less likely to experience any AE than those receiving everolimus–exemestane in later-line setting.²³



Together, these data support the use of combination everolimus–exemestane as an early therapy for ABC.

Interestingly, a recent Italian retrospective trial was published. It was conducted to evaluate the safety in an unselected population of 181 patients and the possible association of toxicities with previous treatments.²⁷ Eligible patients were women with ABC ER-positive, HER2-negative, whose disease was refractory to previous inhibitor aromatase therapy. Prior CT regimens and anticancer endocrine therapies for advanced disease were allowed. The multivariate analysis did not show any association between the numbers of previous treatments neither the toxicity nor the response.²⁷ Of note, an association was found between the previous anthracycline exposure and a toxicity equal to or greater than grade 2.²⁷ The authors interpret this result as a possible selection bias (patients heavily pretreated).

Everolimus and Safety: Selection of Patients in ABC

Older people are underrepresented in clinical trials, but they constitute a significant proportion of BC patients. BC incidence rates in women aged 65 years or older are nearly two to three times greater than in younger women.²⁸ They have more comorbidities than younger people, and clinicians can undertreat them. However, is any starting dose modification according to age justified?

BOLERO-2. In BOLERO-2, 164 of the 724 patients (22.7%) were aged 70 years or older.

The baseline performance status in this subgroup of patients was slightly worse, and these patients had more comorbidities and comedications than younger patients, resulting in an imbalance between age subgroups.^{2,29} The mean duration of everolimus exposure was 23.2 weeks in the elderly versus 33.8 weeks in the younger subgroup.²⁹ The median dose intensity of everolimus was 7.2 mg daily in elderly patients and 8.9 mg daily in the younger ones.²⁹ Dose modifications (reductions/interruptions) were similar between the two age subgroups (66.8% in younger and 66.9% in older patients). However, a greater proportion of older patients discontinued everolimus–exemestane treatment because of AE than younger patients.²⁹

The relative gain in PFS was similar in older and younger patients with a HR of 0.45 and 0.44, respectively (median PFS of 6.77 vs. 1.51 months in older patients; median PFS of 8.11 vs. 4.01 months in younger patients).²⁹ There was a lower incidence of stomatitis, rash, hypercholesterolemia, and liver enzyme increases in the elderly subsets receiving everolimus–exemestane than in younger subsets.²⁹ In contrast, the incidences of decreased appetite, dyspnea, anemia, asthenia, and increased creatinine levels were higher in elderly patients receiving everolimus–exemestane than in younger cohorts.²⁹ The most frequent grade 3/4 AEs were similar in the two age subgroups. With the exception of stomatitis, rash, and diarrhea, their incidence was somewhat higher in the elderly.²⁹

The time to deterioration in performance status was similar between treatment arms in elderly patients. The reduction in performance status due to AE may be balanced by preservation of performance status as a result of longer disease control.²⁹ After adjustment for treatment exposure, the incidence of on-treatment deaths due to AE was similar between the two treatment arms in younger patients but was higher in the everolimus–exemestane arm (7.7% vs. 0%) in the elderly.²⁹ This may be attributable to preexisting comorbidities that were imbalanced between the two treatment arms in the elderly population (more vascular disorders, cerebrovascular accidents, anemia, and psychiatric disorders in the everolimus–exemestane arm at baseline).²⁹

BALLET. The safety dataset in the elderly subgroup of BALLET is the largest ever reported with this regimen in this age group. Of the 2133 patients, there were 563 elderly patients (aged 70 years or older). This represents 26.4% of all patients in this trial.²⁶ Everolimus was slightly more toxic in the elderly.

In the elderly, the median treatment duration was shorter (3.2 vs. 3.7 months in the full population); the median RDI was slightly lower (0.95 vs. 1 in nonelderly); and dose reductions (37.7% vs. 26.7%), interruptions (60.5% vs. 54.2%), and discontinuations (18.9% vs. 10.6%) due to AEs were higher than that in the younger subgroup.²⁶ In the elderly subset, 95.2% of patients experienced at least one AE (vs. 94.7% in the full population). The most common AEs across all grades were stomatitis (55.5% vs. 51.9% in nonelderly), asthenia (28.5% vs. 20.7% in nonelderly), and decreased appetite (22.4% vs. 13.7% in nonelderly).²⁶

The most frequent grade 3/4 AEs were stomatitis (12.3% vs. 8.3% non-elderly), asthenia (5.7% vs. 2.9% nonelderly), and hyperglycemia (4.6% vs. 2.3% in nonelderly). NIP was also slightly higher in elderly with 11.2% versus 8.9% in nonelderly patients.²⁶ Treatment-related SAEs were reported in 10.3% of the elderly versus 7.8% of nonelderly patients.²⁶ On-treatment deaths were also higher in the elderly: 6.9% vs. 5.7% in the full population.²⁶

BRAWO. Subgroup analyses of the second interim analysis and longer median PFS durations were also seen in the following patient subgroups: Ki-67 expression \leq 20%, bone-only metastases, first-line therapy with longer recurrence-free interval, and no prior CT.³⁰

The third interim analysis was presented at European Society of Medical Oncology (ESMO) in 2015 and focused on the correlation of patient characteristics and treatment duration.³¹ Age, ECOG performance status, body mass index (BMI), and Charlson comorbidity index correlated significantly with the duration of treatment. Patients who were younger, who had a better ECOG performance status, with no comorbidities, and/or who had a higher BMI were found to be on treatment with everolimus–exemestane for a longer duration.³¹

A subgroup analysis of elderly patients (>70 years) was also presented.³² A higher proportion of elderly patients in



BRAWO had severe comorbidities versus nonelderly patients. Fewer elderly patients (46.4%) received prior CT compared to nonelderly patients (59.8%). The conclusion was that the everolimus–exemestane treatment had a manageable safety profile in the elderly patients and was consistent with that reported previously in BOLERO-2 and BALLET.³² Lower patient age (<74 years) was significantly associated with a longer duration of treatment.³²

Everolimus and Safety: Impact of Dose in ABC

The correlation between dose, toxicity, and outcome has been reported in STEPAUT and BRAWO.

STEPAUT. In STEPAUT, 40% of patients conserved a 10 mg dose of everolimus during treatment; 28% conserved a 5 mg dose, and 7% had dose escalation from 5 to 10 mg.²⁰ The 10-mg group had the longest median PFS of 9.83 months, while the 5-mg group had a median PFS of 4.97 months; the dose-escalation group had a median PFS of 6.83 months.²⁰ The difference between the 10-mg group and the 5-mg group was not statistically significant. In terms of toxicity, the frequency of AE was highest in the 10-mg group in comparison with the 5-mg group (33.3% vs. 23.07%). The frequency of SAE was also the highest in the 10-mg group (25.64% vs. 10.25% in the 5-mg group and 5.13% in the dose-escalation group).²⁰

BRAWO. In BRAWO, 80.7% of patients received a 10-mg daily dose. Only 18.7% of patients started with a 5-mg dose. Patients with 5 mg received a median dose intensity of 50%, while those with 10 mg received a median dose intensity of 93.5%.²³ There were no data on efficacy in the 5-mg group. A statistically significant correlation was demonstrated between everolimus starting dose and the occurrence of stomatitis within eight weeks—most of these were grades 1 and 2.³³

The longer median PFS and manageable safety in patients receiving everolimus 10 mg versus 5 mg supports 10 mg. The only dosing used here was the recommended starting and maintenance dose in routine clinical practice. This confirms prior data about the optimal 10 mg daily dosing of everolimus with an acceptable tolerance.^{12,34,35}

Everolimus and Safety: AEs Management in ABC

Incidence and severity of class-effect AEs observed in BC were comparable with phase III studies of everolimus monotherapy in renal cell carcinoma^{36,37} and pancreatic neuroendocrine tumor.³⁸ There were no new or unexpected safety signals identified. Thus, the addition of exemestane to everolimus did not significantly affect its safety profile.³⁴ However, rates of treatment discontinuation, and dose modifications are slightly higher in BOLERO-2 than in other phase III trials with everolimus monotherapy.³⁴ This might be because clinicians were not familiar with this treatment in BC. AE may also be amplified in patients who received only prior ET with a more favorable toxicity profile.³⁴ In addition, alternative treatment

options for other indications might also increase the acceptance rate of AE.

Most AEs can be managed without treatment discontinuation. It is possible to maximize treatment exposure and obtain the best clinical benefit for patients.³⁴ On active monitoring, good patient education and a prompt identification of specific AEs can reduce their rate and severity and optimize everolimus dose intensity. Clinicians should also consider some everolimus-specific concerns in BC patients including their particular comorbidities. They are often postmenopausal women with diabetes, metabolic syndrome, vascular comorbidities, etc. Task-specific guidelines to manage AEs have been published to help clinicians.^{34,39–45}

Only a few data are available to confirm the effectiveness of this proactive management.

In BRAWO, we already mentioned that the overall safety profile of everolimus–exemestane was consistent with that reported previously in BOLERO-2. The incidence of stomatitis in BRAWO (39.5%) was lower than that reported in BOLERO-2 (59.0%).³³ The incidence of grade 3 stomatitis events was also lower in BRAWO (2.3%) versus BOLERO-2 (8%).³³ The majority of these stomatitis events in BRAWO occurred within the first eight weeks, consistent with what has been reported previously.³³ The majority of the patients in BRAWO received prophylactic recommendations and therapeutic interventions for stomatitis management, which could potentially explain the lower incidence of stomatitis in BRAWO.³³

Recently, a poster at the 2016 American Society of Clinical Oncology congress by Rugo et al demonstrated that the systematic use of an alcohol-free, steroid-based mouthwash significantly minimized or prevented the incidence of all grade, especially grade ≥ 2 , stomatitis.⁴⁶ This is the SWISH study (dexamethasone mouthwash for everolimus-related stomatitis prevention in HR+, HER2– metastatic breast cancer (MBC) everolimus and exemestane treatment). It was a multicenter, single-arm, phase II prevention trial. The incidence of grade ≥ 2 stomatitis at eight weeks was 2.4% compared with 33% in BOLERO-2.⁴⁶ The incidence of all-grade stomatitis at eight weeks was 21.2%—a marked reduced incidence rate versus BOLERO-2 (67%).⁴⁶

Because the majority of class-effect AEs, except pneumonitis, had a relative short time to onset, the authors in BALLET recommend close follow-up in the first months with a first visit two weeks after starting everolimus.²⁶

Everolimus and Safety: Relationship Between AEs and Efficacy

Recently, a meta-analysis was published with data from seven randomized, double-blind, phase III clinical trials of everolimus to determine the clinical impact of stomatitis on efficacy and safety.⁴⁷ Data were pooled from BOLERO-2 and BOLERO-3 (BC), RECORD-1 (renal cell carcinoma), RADIANT-2 (carcinoid tumors), RADIANT-3 (pancreatic



neuroendocrine tumors), and EXIST-1/2 (tuberous sclerosis complex studies). Data from solid tumor trials and tuberous sclerosis complex (TSC) trials were analyzed separately.⁴⁷

The rate of stomatitis was 67% in the solid tumor trials and 70% in the TSC trials. Most stomatitis events were grade 1/2.⁴⁷ In the solid tumor trials, 89% of first stomatitis episodes were observed within eight weeks.⁴⁷ Patients with stomatitis occurring within eight weeks of everolimus initiation had longer PFS than everolimus-treated patients without stomatitis in BOLERO-2 (8.5 vs. 6.9 months; HR = 0.78) and RADIANT-3 (13.9 vs. 8.3 months, HR = 0.7). A similar trend was observed in RECORD-1 (HR = 0.90) and RADIANT-2 (HR = 0.87), but not in BOLERO-3 (HR = 1.01). The authors concluded that stomatitis did not adversely affect PFS. This supports the administration of everolimus in accordance with standard management guidelines.⁴⁷

As mentioned earlier, the recent Italian retrospective trial in an unselected population of 181 patients was also conducted to evaluate a possible association between toxicity and response. No association between toxicity and response was found.²⁷

Conclusion

Despite its toxicity profile, the addition of everolimus to exemestane is quite beneficial to patients with ER-positive, HER2-negative, ABC who progressed on prior NSAI therapy.

Most AEs are grade 1 or 2 and resolve without the need for treatment interruption. Moreover, the quality of life is better with everolimus than with placebo.

The physician's delicate aim when treating patients with everolimus is to obtain a good balance between adequate management of AE and the optimization of treatment exposure. This is only feasible with a good knowledge of the treatment, a careful selection of patients (especially the older ones and those with comorbidities), a detailed and time-consuming but primordial patient's education, and proactive monitoring following AE management guidelines.

The role of everolimus needs to be reevaluated in light of cyclin-dependent kinase inhibitors such as palbociclib with their own new safety profile. More than ever, clinicians must perfectly manage this molecule because it represents another weapon to circumvent endocrine resistance in ER-positive, HER2-negative, ABC.

The optimal sequence of combined ET with targeted therapy in particular in regard to the cyclin-dependent kinase inhibitors has yet to be determined. Cost, side effect profile, and disease aggressiveness at time of progression after each regimen should be considered when defining the specific treatment for each patient. Another important question is if all patients suffering from ER-positive, HER2-negative, ABC need upfront combined therapy approaches or if some subgroups remain candidates for endocrine monotherapy. Regardless, the current regimen combining everolimus and exemestane is an important treatment option after failure

of NSAI therapy. Unfortunately, we cannot select a clinical subgroup of patients who benefit most because the treatment effect of adding everolimus is similar in terms of relative improvement across all subgroups. In addition, research on biomarkers was not successful. The situation is similar for cyclin-dependent kinase inhibitors.

Author Contributions

Wrote the first draft of the manuscript: LL. Developed the structure and arguments for the paper: LL and GJ. Made critical revisions: GJ. Both the authors reviewed and approved the final manuscript.

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