The role of everolimus in metastatic breast cancer and possibilities of moving forward—a narrative review

Gabor Rubovszky[1,2]^

[1]Department of Thoracic and Abdominal Tumors and Clinical Pharmacology and the National Tumor Biology Laboratory, National Institute of Oncology, Budapest, Hungary; [2]Department of Oncology, Semmelweis University, Budapest, Hungary
Correspondence to: Gabor Rubovszky, MD, PhD. Department of Thoracic and Abdominal Tumors and Clinical Pharmacology and the National Tumor Biology Laboratory, National Institute of Oncology, Ráth György Str. 7-9, 1122 Budapest, Hungary; Department of Oncology, Semmelweis University, Budapest, Hungary. Email: rubovszkyg@gmail.com.

Background and Objective: In hormone-receptor-positive (HR[+]) and human epidermal growth factor receptor 2-negative (HER2^{−}) metastatic breast cancer endocrine-based therapies are preferred over chemotherapy. One of the treatment options is the combination of everolimus with exemestane or other endocrine drug in later lines mainly based on progression-free survival (PFS) results of the phase 3 BOLERO-2 trial. Altogether, clinical trials did not prove an overall survival (OS) benefit and considerable side effects hampered its application in the day-by-day practice. In recent years CDK4/6-inhibitors became a first-choice combination partner to the endocrine treatment, everolimus still has a place within the treatment armamentarium. Although everolimus is a targeted drug, there is no accepted predictive biomarker and further patient selection is not possible. However, several directions can be defined how to optimally use everolimus. For update information on everolimus treatment in breast cancer I have performed a literature search.

Methods: I used the keywords "breast cancer" and "everolimus" and extended the search in PubMed from 01/01/2014 to 10/02/2023. I considered all phase 3 trials, the phase 1–2 trials with not repetitive information, studies with biomarker results and I also checked review articles to identify potential relevant other clinical trial reports. I also have made a search in clinicaltrials.gov for recently completed and ongoing trials.

Key Content and Findings: I summarized the search results in this concise and brief report focusing on main trial results and ongoing research with everolimus.

Conclusions: The most promising research directions seem to be further investigations for useable predictive biomarkers, for combinations with other targeted drugs (even in a triple combination) and for the feasibility of pharmacologically guided dosing method.

Keywords: Breast cancer; everolimus; targeted therapy

Introduction

The international recommendations are in favor of endocrine-based therapies in hormone-receptor-positive (HR[+]) and human epidermal growth factor receptor 2-negative (HER2^{−}) metastatic breast cancer (1). The unanimously accepted first-line treatment is the combination of an endocrine agent and a CDK4/6-inhibitor. After progression, there are several options, the most commonly used is fulvestrant with or without the PI3K-inhibitor alpelisib, but the combination of everolimus and endocrine therapy (especially exemestane) is also a good choice, usually in 3rd or later line. The BOLERO-2 registration trial showed

---

^ ORCID: 0000-0003-1723-5589.

that the combination of everolimus and exemestane resulted in higher response rates and longer median progression-free survival (mPFS) than the placebo-exemestane treatment, but the approximately 6 months difference in overall survival (OS) did not reach statistical significance (2,3). The lack of improvement in OS and in quality-of-life explains that it took a backseat to other therapeutic options and received only an European Society for Medical Oncology (ESMO) magnitude of clinical benefit category 2 (4). The high rate of grade 3/4 adverse events, the high percentage of patients discontinued everolimus in the combination-therapy group because of adverse events (19%) and the lack of predictive biomarker are also drawbacks of this combination. Despite of all these obstacles everolimus is a valuable alternative because there are only limited therapeutic options in metastatic HR+/HER2− breast cancer. Here I overview the main results of a literature search on everolimus treatment in breast cancer and delineate future perspectives. I present this article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups. com/article/view/10.21037/atm-23-1583/rc).

Methods

I have performed a literature search from 01.01.2014 to 10.02.2023 in PubMed with terms "breast cancer" and "everolimus", selecting clinical trials and randomized controlled trials (*Table 1* and Figure S1). It resulted in 83 hits. I considered all phase 3 trials, the phase 1–2 trials with not repetitive information, and studies with biomarker results. In a second search, I checked meta-analyses and systemic review articles from 2020 to 2023 using the same terms (seven hits) to identify other potential relevant clinical trial reports. I found 33 clinical trials (not counting subsequent publications of the same trial), and eight biomarker reports with these criteria and selected four meta-analysis or review articles. I did a search using the same terms in clinicaltrials.gov on 10.02.2023 and found 133 trials. I have selected recently completed and ongoing trials that have new information or trial design. I grouped the results according efficacy and safety data, and then results that dictate future research.

Discussion

Efficacy

Everolimus registered in Europe for the treatment of advanced (irresectable or metastatic) HR+/HER2− breast cancer, renal cell cancer and neuroendocrine tumor of pancreatic, gastrointestinal or lung origin (5). In advanced breast cancer the BOLERO (Breast Cancer Trials of Oral Everolimus) studies provided essential results (*Table 2*). The everolimus exemestane combination was more effective than exemestane or everolimus monotherapy, although an OS benefit could not be detected. It is probable that this combination is also effective after CDK4/6-inhibitor therapy based on small retrospective trials (11). A meta-analysis including the results of eight studies also showed advantages of the combination in disease control rate and risk of progression, but not in OS (12). However, it is questionable whether the everolimus exemestane combination or the commencement of chemotherapy is more preferable. In the BOLERO-6 study capecitabin was at least as effective as the everolimus combination. In the German IMPROVE cross-over, phase 4 trial the capecitabine bevacizumab and everolimus exemestane combinations were compared (13). The cross-over occurred upon progression. As the primary end point (patients' preference for either regimen assessed 12 weeks after cross-over), most of the 77 patients preferred starting with the capecitabin combination (61.5% *vs.* 15.4%), although patients' quality-of-life and satisfaction were similar in the two arms. The median PFS also favored the chemotherapy arm (11.1 *vs.* 3.5 months, P=0.0008).

The studies where everolimus was combined with chemotherapy or with trastuzumab, did not detect clinically meaningful efficacy of everolimus (6,7). Although, in the BOLERO-1 trial the mPFS was longer with the combination of weekly paclitaxel plus trastuzumab and everolimus (compared with placebo) in HR-negative tumors (hazard ratio: 0.66, P=0.0049) it did not cross-protocol specified significance threshold and should be verified in further investigation. The lack of everolimus efficacy in this trial among HR+ tumors may highlight the importance of simultaneous blockade of all relevant "driver" pathways. Everolimus or placebo was added to first-line paclitaxel plus bevacizumab combination in 133 HER2− breast cancer patients in a phase 2 trial. All efficacy endpoints were similar in the two arms (14). In the phase 2 VicTORia study with 133 participants, everolimus didn't improved the efficacy of second-line vinorelbine (mPFS: 4 months in both arms) (15). Interestingly, everolimus did not ameliorate significantly the efficacy of maintenance exemestane therapy after the first-line chemotherapy in the phase 3 MAIN-A trial (16). In the small NECTAR trial 24 triple-negative breast

Table 1 The search strategy

Items	Specification
Date of search	10.02.2023
Databases and other sources searched	PubMed, clinicaltrials.gov
Search terms used	"Breast cancer" and "everolimus"
Timeframe	01.01.2014 to 10.02.2023
Inclusion criteria	All phase 3 trials, phase 1–2 trials with not repetitive information, and studies with biomarker results (PubMed search)
	Meta-analyses and systemic review articles from 2020 to 2023 using the same terms (PubMed search)
	Active trials or trials with results not yet published; in metastatic breast cancer (clinicaltrials.gov search)
	Article in English
Exclusion criteria	Retrospective research
	Early breast cancer trials (neoadjuvant, adjuvant)
	Report of the same study with repetitive information (the more informative selected)
	Article not in English
Selection process	The literature review was performed by a single person

cancer patients, who had residual tumor after neoadjuvant chemotherapy were treated with everolimus and cisplatin. Five patients achieved a major response, which is encouraging but warrants further investigation (17).

Side effects

Everolimus may be associated with severe side effects. The more pronounced side effects are stomatitis, anemia, fatigue, hyperglycemia and pneumonitis (*Table 3*). Approximately 20% of patients discontinue everolimus due to adverse effects (2,18). Several trials were conducted to gather more information on the safety of everolimus (4EVER, BALLET, EVA, BRAVO, STEPOUT) with concordant results (19-23). In the largest BALLET trial, adverse events of clinical interest (non-infectious pneumonia, stomatitis, asthenia, and weight loss) occurred at very similar rates as in the BOLERO-2 trial, regardless of prior treatment, metabolic disease, or the presence of visceral metastases (18). However, supportive and preventive treatment may improve adherence to everolimus therapy. The lowest rate of stomatitis was reported in the BRAWO trial, where 87% of patients received treatment to prevent stomatitis (22). In the randomized, phase 3 ORAL-BC study investigating the role of active preventive

measures, the frequency and severity of mucositis, as well as the rate of dose reduction and treatment discontinuation, were reduced with the use of steroid mouthwash, although this was not associated with improved survival (24,25). Another method was investigated in the randomized, phase 2 DESIREE trial. The 160 participating patients were randomly assigned to a dose-escalation arm (increasing the dose of everolimus from 2.5 mg/day to 10 mg/week) or a conventional arm (starting dose of 10 mg/day) (26). The primary endpoint of the study was met. The incidence of grade ≥2 stomatitis episodes was significantly lower in the escalation arm. There was not a significant difference either in other adverse events or in the relative dose intensity in the two arms. Numerically more everolimus discontinuation occurred due to adverse event in the conventional arm and due to disease progression in the escalation arm. These differences were not statistically significant, but they may question the equal efficacy of the escalating dosing. The rate of stomatitis grade ≥2 with gradually increasing everolimus dose was 18.8% in the DESIREE trial. In a study with two different mouth rinses the incidence of grade ≥2 stomatitis was similar (12–18%) and in another trial using dexamethasone mouthwash the incidence was even lower (2%) (27,28).

Table 2 Pivotal trials in advanced breast cancer

Name of study	Population [number of patients]	Phase	Therapy [number of subjects]	Primary objective	Main results (months)	Grade 3/4 adverse events	Notes
BOLERO-1 (6)	HER2+, first-line [ITT: 719, HR+: 311]	3	Weekly paclitaxel + trastuzumab + everolimus [480] vs. weekly paclitaxel + trastuzumab + placebo [239]	mPFS in ITT and in HR− patients	mFU: 41.3; ITT: 14.9 vs. 14.49 (hazard ratio: 0.89); HR−: 20.27 vs. 13.8 (hazard ratio: 0.66)	Neutropenia: 25% vs. 15%; stomatitis: 13% vs. 1 %; anemia: 10% vs. 3%; diarrhea: 9% vs. 4%	AE related death 17 (4%) vs. none
BOLERO-2 (2,3)	HR+/HER2−, postmenopausal, after NSAI [724]	3	Exemestane + everolimus [485] vs. exemestane + placebo [239]	mPFS	6.9 vs. 2.8 (hazard ratio: 0.43)	Stomatitis: 8% vs. 1%; anemia: 6% vs. <1%; dyspnea: 4% vs. 1 %; hyperglycemia: 4% vs. <1%; fatigue:4% vs. 1%; pneumonitis: 3% vs. 0%	mOS: 31 vs. 26.6 months; AE related death 7 (1%) vs. 1; PRO similar
BOLERO-3 (7)	HER2+, trastuzumab resistant, taxane pretreated [569]	3	Weekly paclitaxel + trastuzumab + everolimus [284] vs. weekly paclitaxel + trastuzumab + placebo [285]	mPFS	7 vs. 5.78 (hazard ratio: 0.78)	Neutropenia: 73% vs. 62%; leucopenia 38% vs. 29%; anemia 19% vs. 6%; FN: 16% vs. 4%; stomatitis: 13% vs. 1%; fatigue: 12% vs. 4%; death: 2 vs. 2 (patients)	mOS: 23.46 vs. 24.08 months; ORR: 40.8% vs. 37.2%; CBR: 59.2% vs. 53.3%
BOLERO-4 (8)	HR+/HER2−, postmenopausal, first- [202] and second-line [50]	2	First-line: everolimus + letrozole [202]; second-line (everolimus continuation offered): everolimus + exemestane [50]	mPFS (first-line)	22	Stomatitis: 6%; anemia: 10%; weight decreased: 6%; dyspnea: 4%; nausea/vomiting: 4%; hypertriglyceridemia: 6%; hyperglycemia: 3%; fatigue: 3%; pneumonia: 3%; pneumonitis: <1%	mPFS second-line: 3.7 months
BOLERO-5 (9)	HR+/HER2−, Chinese, postmenopausal, after NSAI [159]	2	Exemestane + everolimus [80] vs. exemestane + placebo [79]	mPFS	7.4 vs. 2 (hazard ratio: 0.52)	Hyperglycemia: 10% vs. 0; stomatitis:7.5% vs. 1.3%; anemia: 3.8% vs. 3.8%; weight decrease: 1.3% vs. 0	ORR: 8.8% vs. 1.3%; CBR: 35% vs. 16.5%
BOLERO-6 (10)	HR+/HER2−, postmenopausal, after NSAI [309]	2	Everolimus + exemestane [104] vs. everolimus [103] vs. capecitabine (1,250 mg/m²) [102]	mPFS (everlimus + exemestane vs. everolimus)	8.4 vs. 6.8 (hazard ratio: 0.74)	Stomatitis: 9% vs. 5% vs. 7%; fatigue: 8% vs. 3% vs. 8%; diarrhea: 5% vs. 3% vs. 8%; anemia: 13% vs. 105 vs. 7%; pneumonia:7% vs. 3% vs. 2%	mPFS everolimus + exemestane vs. capecitabine: 8.4 vs. 9.6 months (hazard ratio: 1.26); mOS: 23.1 vs. 29.3 vs. 25.6 months; discontinuation due to AE: 17% vs. 19% vs. 19%

BOLERO, Breast Cancer Trials of Oral Everolimus; HER2+, human epidermal growth factor receptor 2-positive; ITT, intention-to-treat; HR−, hormone-receptor-negative; mPFS, median progression-free survival; mFU, median follow-up; AE, adverse event; HR+, hormone-receptor-positive; HER2−, human epidermal growth factor receptor 2-negative; mOS, median overall survival; PRO, patient-reported outcome; ORR, overall response rate; CBR, clinical benefit rate; NSAI, non-steroid aromatase inhibitor.

Table 3 Post-marketing trials involving more than 200 advanced breast cancer patients with everolimus plus exemestane

Trial	Inclusion criteria	Population (evaluable)	Response	mPFS (months)	Safety (adverse events)
4EVER (19)	progression after NSAI, no restrictions on the time of progression after NSAI, prior chemotherapy for advanced disease or previous exemestane	n=299; prior chemotherapy: 151 (53.7%), endocrine therapy: 204 (72.6%), ≥4 prior lines for MBC: 87 (31%), prior exemestane: 89 (31.7%)	OR: 25 (8.9%); SD: 69 (24.6%)	5.6 (irrespective of prior exemestane)	All: stomatitis (49.2%), fatigue (36.1%), diarrhea (26.4%), nausea (26.1%), decreased appetite (25.4%), and dyspnea (24.7%) Grade 3/4: stomatitis (8.4%), general physical health deterioration (6.7%), dyspnea (4.7%), and anemia (4.3%) Permanently discontinued study treatment due to AEs: 74 (24.7%). The most common AEs leading to study treatment discontinuation were stomatitis (4.3%), dyspnea (2.3%), nausea (2.0%), pneumonitis (2.0%), and vomiting (2.0%). At least one dose reduction: 151 (53.7%), most commonly (85.7%) due to AEs Five deaths due to AE
BALLET (18)	progression after NSAI, no restrictions on the number of prior anticancer treatment lines received, and NSAIs did not have to be the last treatment administered before enrolment	n=2,131; prior chemotherapy: 1,284 (60%), prior exemestane 521 (24%)	NR	Progressive disease at 6 months: 554 (26%)	All: pneumonitis 206 (10%), stomatitis 1159 (54%), asthenia/fatigue 757 (36%), and weight loss 217 (10%) Grade 3/4: pneumonitis 42 (2%), stomatitis 202 (10%), asthenia/fatigue 103 (5%), and weight loss 2 (~0%) Permanently discontinued due to AEs (16%), most frequently pneumonitis (2%), stomatitis (2%), and asthenia (2%)
EVA (20)	Measurable or evaluable lesions	n=404; prior chemotherapy: 45 (11.1), ≥3 prior lines for MBC: 51 (12.6%)	OR: 31.6%; DCR: 60.7%	NR	All: stomatitis 206 (60.8%), fatigue 134 (39.5%), rash 86 (25.4%), pneumonitis 63 (18.6%), hypercholesterolemia 63 (18.6%), and hyperglycemia 60 (17.7%) Grade 3/4: stomatitis 38 (11.2%), fatigue 11 (3.2%), rash 9 (2.7%), pneumonitis 13 (3.8%), and hyperglycemia 3 (0.9%)
BRAWO (21,22)	As label indication	n=866; ≥4 prior lines for MBC: 23%, prior exemestane: 18.1%	–	Multivariate analysis: body mass index, therapeutic line, presence of visceral metastases and ECOG status at the beginning of the therapy correlated significantly with the PFS	All: stomatitis: 45.8% Grade 3: 2.7% (87% of patients received preventive treatment for stomatitis)
STEPOUT (23)	As label indication	n=225; 91 patients everolimus starting dose 5 mg	OR: 15 (6.4%)	9.5. The mPFS with 10 vs. 5 mg everolimus starting dose (9.9 vs. 8 months, P=0.5533). Dose escalation from 5 to 10 mg: 7.8 months. Dose de-escalation from 10 to 5 mg: 9.5 months. As first-line: 14 months	All: stomatitis 127 (53.8%), diarrhea 40 (17%), exanthema, rash 70 (29.7%), fatigue 47 (19.9%), and pneumonitis 35 (14.8%) Grade 3/4: stomatitis (only grade 3) 11 (4.75), diarrhea 3 (1.3%), exanthema, rash 1 (0.4%), fatigue 25 (10.6%), and pneumonitis (only grade 3) 5 (2.1%) Dose reduction: 18%

mPFS, median progression-free survival; NSAI, non-steroid aromatase inhibitor; MBC, metastatic breast cancer; OR, overall response; SD, stable disease; AE, adverse event; NR, not reported; DCR, disease control rate; ECOG, Eastern Cooperative Oncology Group.

Page 6 of 12

Rubovszky. Moving forward with everolimus in metastatic breast cancer

Table 4 Possible future directions in everolimus investigations

Option	Results	Future perspectives
Predictive biomarker exploration	Genetic alterations in PI3K-AKT-mTOR pathways and other frequent genes failed	Search on proteomic level
	Genetic subtypes (PAM50) failed	Exploration with new combinations
Different combination partners	Chemotherapy failed	Endocrine based triplet combination
	Other endocrine partners	Other targeted compound
	Other targeted compound (trastuzumab failed)	
	Other non-target partner (i.e., Merckformin)	
Side effect management	Active prevention and treatment of side effects is beneficial	Improbable to gain new data
Pharmacological monitoring	Early results with alternative dosing and therapeutic drug monitoring method	Dosing optimization and personalization

Limitations of everolimus treatment and how to overcome them

Everolimus is a targeted drug. Appropriate patient selection is essential to maximize the benefits of its use. In general, there are many options for improving the benefit-risk ratio of a targeted drug (*Table 4*).

Until now, there is no accepted predictive biomarker for everolimus therapy. Genetic alterations commonly found in breast cancer (in *PIK3CA*, *CCND1*, *TP53*, *FGFR1*, and *ESR1*) were not associated with the efficacy of everolimus (29-31), however, according to a combined biomarker analysis of trials with everolimus and chemotherapy (BOLERO-1 and BOLERO-3) *PIK3CA* mutations, *PTEN* loss or hyperactive *PI3K* pathway have been identified as biomarkers of everolimus efficacy (32). In a retrospective study, Prat *et al.* analyzed 261 samples from BOLERO-2 patients and the PAM50 subtyping resulted in that 46.7% of samples were luminal A, 21.5% HER2-enriched, 15.7% luminal B, 14.2% normal-like, and 1.9% basal-like (33). Although the mPFS was more favorable with everolimus in luminal than in non-luminal cases, and in non-HER2-enriched than in HER2-enriched cases, the interaction was not statistically significant and in all subtypes everolimus seemed beneficial. At the present no biomarker can currently be utilized to select or enrich for patients who may benefit from everolimus, consequently all HR+/HER2− advanced breast cancer patients are candidates for everolimus treatment. In one trial, the immune system and angiogenesis-related biomarkers correlated with the response to everolimus-based treatment, but it was a retrospective analysis of trials without a control arm (34). In a small prospective trial, CD4+ effector cells were associated with result and natural killer cells with lung toxicity (35). These early results warrant further validation. Proteomics reflecting the functional state of the cell, the discovery of the mutational state of cell-free DNA, and the reevaluation of traditional biomarkers in new combinations of targeted therapies can be future research areas in this regard (36).

There were efforts to explore the feasibility of therapeutic partners other than a hormonal agent. Everolimus combined with eribulin showed modest activity in a phase 1 trial (37). The vinorelbine combination was investigated in patients with brain metastasis and also as a second-line treatment in two phase 2 trial without signal of additive effectiveness (38). The study with paclitaxel plus bevacizumab backbone also failed (unpublished data, available at http://www.clinicaltrials.com, NCT00915603). In accordance with the present trial results it is improbable that everolimus would improve the therapeutic benefit if combined with chemotherapy. A potential way to enhance efficacy is to eliminate the resistance mechanism. It could be done with extended combinations. In the TRINITY-1 single-arm trial, the combination of ribociclib, everolimus, and exemestane resulted in a clinical benefit rate of 41.1% at week 24 of treatment after progression on CDK4/6 inhibitor (39), while a phase II study with the combination of palbociclib, exemestane and everolimus showed very modest activity after progression on a CDK4/6 inhibitor (clinical benefit rate only 12.5%) (40). The horizontal double targeting of PI3K-AKT-mTOR pathway was

investigated in a phase 1 dose-finding trial; however, no efficacy data has been available so far (41). Trials with lapatinib or trastuzumab combinations were terminated (NCT01272141, NCT00912340).

Everolimus also can be co-administered with fulvestrant (42,43), tamoxifen (44) or a non-steroidal aromatase inhibitor. In the phase 2 MIRACLE trial 199 patients were randomized to letrozole plus everolimus or letrozole alone arm. All patients received goserelin. The mPFS was longer in the combination arm (19.4 vs. 12.9 months, hazard ratio: 0.64, P=0.008) (45). In the similar LEO study recruiting 137 participants the mPFS was numerically longer, although not significant (17.5 vs. 13.8 months, P=0.245) (46). Studies with estrogen receptor degraders are currently underway (NCT05306340, NCT0551769). It is not known yet whether ESR1 mutation predicts more benefit of fulvestrant or a new oral selective endocrine degrader as a combination partner.

In contrast to the combination with chemotherapy plus trastuzumab, the triplet everolimus, letrozole, and trastuzumab therapy showed encouraging activity in HR$^+$/HER2$^+$ breast cancer in a first-in-human trial: five partial responses in 26 treatment-refractory breast cancer patients, another 9 patients with stable disease at 6 month and mPFS 7.5 months. It seemed that the efficacy of this triplet combination was independent of previous therapy, the presence of HER2 mutation or overexpression, and *PI3K* or *ESR1* mutation, although small cohort size limits the validity of this observation (47). Glucose metabolism regulation, like insulin-like growth factor-1 (IGF1) plays an important role in survival and proliferation of cancer cells through the IGF1-dependent activation of *PI3K/AKT/mTOR* pathway. The antidiabetic metformin and everolimus therapy tested in one phase 2 trial in overweight and obese postmenopausal patients resulted in only a moderate activity compared to the BOLERO-2 results (mPFS: 6.3 months, OS: 28.8 months) (48). Xentuzumab, a humanized IgG1 IGF monoclonal antibody targeting the IGF1 and IGF2 did not improve mPFS in a phase 2 study in addition to everolimus and exemestane (49).

Everolimus has a very sensitive pharmacokinetic (PK) profile and consequently, there is considerable intrapatient and interpatient variability in PK values (50). There are several factors which have an impact on the PKs of everolimus. The PK properties of everolimus justify the dosing rules specified in the label (5). The medicine must be taken at the same time every day, and can be taken with or without food. High fat meals reduced area under the curve (AUC) by 22% and peak concentration (C_{max}) by 54%, light fat meals did it by 32% and 42%, respectively, but without an effect on the post absorption phase concentration-time profile. The drug is metabolized through CYP3A4. Moderate inhibitors may increase AUC by 2.7–4.4 times and strong inhibitors by 15 times; therefore, the co-administration of strong inhibitors is contraindicated. Moderate-strong inductors of CYP3A4 can decrease serum levels and may diminish efficacy. The metabolites of everolimus are about 100 times less active and must not be taken into account. Hepatic impairment can also increase serum level, and the drug is usually contraindicated in Child-Pugh C stage, but there is no restriction in renal failure as long as the glomerular filtration rate is above 11 mL/min (5).

Knowing the unpredictable variability of serum levels of everolimus, regular measurement of PK values and adjusting the treatment according to it possibly provides a more personalized treatment with the prospect of greater efficacy and less toxicity. In a randomized cross-over trial Verheijen and colleagues compared the standard once 10 mg daily dose to splitting the same dose to 5 mg twice a day. With twice-daily everolimus dose the C_{max} decreased, C_{min} increased and AUC maintained. The authors assumed that lower C_{max} may be associated with fewer side effects, and consequently better adherence to therapy, while higher C_{min} with improved efficacy (50). The PK-guided therapy, called therapeutic drug monitoring-based precision dosing now tested in a Dutch multicenter study. The investigated pharmacokinetically guided interventions (emphasizing compliance, adjusting concomitant medication due to drug-drug interactions, considering food effect or splitting intake moments) and dose increase of oral targeted therapies deemed feasible and it markedly reduced the proportion of underexposed patients (with 39% compared to historical data), although it did not reach the prespecified boundary of 50% (51). Besides the encouraging results the method should be further developed and clarified. They could apply successful intervention in the study in only 38% of patients (113 out of 294), who had at least one PK sample below the preset target at a certain time point during treatment. The relative low number of successful intervention was mostly due to severe side effects. The study results may be true also for everolimus, despite only 9 of enrolled patients took everolimus in this study and the split-dose was not tested, therefore further investigation of PK guided dosing of

everolimus is warranted.

Strengths and limitations

The advantage of this work is that it is based on a review of both a literature database and a clinical trial database. However, it also has limitations, because I chose a single literature database and did not take into account unpublished results or results published only at conferences. It is also a limitation that the literature review was conducted by a single person.

Conclusions

Presently, the standard first-line therapy for advanced HR$^+$/HER2$^-$ breast cancer is the combination of endocrine therapy (aromatase inhibitor or fulvestrant) and a CDK4/6 inhibitor based on OS benefit shown in phase 3 trials (1). According to research results in the literature, no significant progress has been made with everolimus therapy since its introduction into daily practice. Prevention and early treatment of dose-limiting side effects such as stomatitis and pneumonia may improve efficacy, but we have no data to support this assumption. In a network meta-analysis for postmenopausal patients whose disease progressed after a non-steroidal aromatase inhibitor, the addition of CDK4/ inhibitor or everolimus to the endocrine therapy resulted in similar PFS benefit compared to endocrine therapy alone (52). Therefore, everolimus combination (exemestane, fulvestrant, tamoxifen) is still a valid treatment option in later lines; however, everolimus combination has failed in the adjuvant setting (53). For *PI3K*-mutated tumors the alpelisib plus fulvestrant combination is also recommended after CDK4/6 inhibitor, although therapeutic benefit is not proven over the everolimus combination (54).

Most promising research directions seem to be the further investigations in quest of useable predictive biomarkers, for combinations with other targeted drugs (even in triple combinations) and for the feasibility of pharmacologically guided dosing method.

Acknowledgments

Footnote

References

1. NCCN Guidelines for Breast Cancer V.4.2022. Available online: https://www.nccn.org/guidelines/guidelines-process/transparency-process-and-recommendations/GetFileFromFileManagerGuid?FileManagerGuidId=d01730d4-cb06-4ec8-b20b-c4f34a8109af
2. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med 2012;366:520-9.

3. Piccart M, Hortobagyi GN, Campone M, et al. Everolimus plus exemestane for hormone-receptor-positive, human epidermal growth factor receptor-2-negative advanced breast cancer: overall survival results from BOLERO-2†. Ann Oncol 2014;25:2357-62.

4. The ESMO-MCBS Scorecards provides a centralised location of cancer medicines that have been scored and published by ESMO. Available online: https://www.esmo.org/guidelines/esmo-mcbs/esmo-mcbs-scorecards?mcbs_score_cards_form%5BsearchText%5D=everolimus

5. Afinitor. Product information. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/afinitor#product-information-section

6. Hurvitz SA, Andre F, Jiang Z, et al. Combination of everolimus with trastuzumab plus paclitaxel as first-line treatment for patients with HER2-positive advanced breast cancer (BOLERO-1): a phase 3, randomised, double-blind, multicentre trial. Lancet Oncol 2015;16:816-29.

7. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol 2014;15:580-91.

8. Royce M, Bachelot T, Villanueva C, et al. Everolimus Plus Endocrine Therapy for Postmenopausal Women With Estrogen Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer: A Clinical Trial. JAMA Oncol 2018;4:977-84.

9. Shao Z, Cai L, Wang S, et al. 238P BOLERO-5: A phase II study of everolimus and exemestane combination in Chinese post-menopausal women with ER+/HER2- advanced breast cancer. Ann Oncol 2021;32:S463.

10. Jerusalem G, de Boer RH, Hurvitz S, et al. Everolimus Plus Exemestane vs Everolimus or Capecitabine Monotherapy for Estrogen Receptor-Positive, HER2-Negative Advanced Breast Cancer: The BOLERO-6 Randomized Clinical Trial. JAMA Oncol 2018;4:1367-74.

11. Watanabe K, Kuwahara S, Tachikawa H, et al. P66-6 Efficacy of everolimus in HR+ HER2-metastatic breast cancer patients after progression on CDK4/6 inhibitors. Ann Oncol 2022;33:S538.

12. Raphael J, Lefebvre C, Allan A, et al. Everolimus in Advanced Breast Cancer: A Systematic Review and Meta-analysis. Target Oncol 2020;15:723-32.

13. Decker T, Söling U, Hahn A, et al. Final results from IMPROVE: a randomized, controlled, open-label, two-arm, cross-over phase IV study to determine patients'

preference for everolimus in combination with exemestane or capecitabine in combination with bevacizumab in advanced HR-positive, HER2-negative breast cancer. BMC Cancer 2020;20:286.

14. Yardley DA, Bosserman LD, O'Shaughnessy JA, et al. Paclitaxel, bevacizumab, and everolimus/placebo as first-line treatment for patients with metastatic HER2-negative breast cancer: a randomized placebo-controlled phase II trial of the Sarah Cannon Research Institute. Breast Cancer Res Treat 2015;154:89-97.

15. Decker T, Marschner N, Muendlein A, et al. VicTORia: a randomised phase II study to compare vinorelbine in combination with the mTOR inhibitor everolimus versus vinorelbine monotherapy for second-line chemotherapy in advanced HER2-negative breast cancer. Breast Cancer Res Treat 2019;176:637-47.

16. Guarneri V, Giorgi CA, Cinieri S, et al. Everolimus plus aromatase inhibitors as maintenance therapy after first-line chemotherapy: Final results of the phase III randomised MAIN-A (MAINtenance Afinitor) trial. Eur J Cancer 2021;154:21-9.

17. Anand K, Patel T, Niravath P, et al. Targeting mTOR and DNA repair pathways in residual triple negative breast cancer post neoadjuvant chemotherapy. Sci Rep 2021;11:82.

18. Ciruelos E, Jerusalem G, Martin M, et al. Everolimus plus exemestane in hormone-receptor-positive, HER2-negative locally advanced or metastatic breast cancer: incidence and time course of adverse events in the phase IIIb BALLET population. Clin Transl Oncol 2020;22:1857-66.

19. Tesch H, Stoetzer O, Decker T, et al. Efficacy and safety of everolimus plus exemestane in postmenopausal women with hormone receptor-positive, human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer: Results of the single-arm, phase IIIB 4EVER trial. Int J Cancer 2019;144:877-85.

20. Cazzaniga ME, Airoldi M, Arcangeli V, et al. Efficacy and safety of Everolimus and Exemestane in hormone-receptor positive (HR+) human-epidermal-growth-factor negative (HER2-) advanced breast cancer patients: New insights beyond clinical trials. The EVA study. Breast 2017;35:115-21.

21. Fasching PA, Grischke EM, Schuetz F, et al. Analysis of everolimus starting dose as prognostic marker in HR+ mBC patients treated with everolimus (EVE)+ exemestane (EXE): Results of the 3rd interim analysis of the non-interventional trial BRAWO. J Clin Oncol 2017;35:1061.

22. Lueftner D, Schuetz F, Grischke EM, et al. Breast

Page 10 of 12

Rubovszky. Moving forward with everolimus in metastatic breast cancer

cancer treatment with everolimus and exemestane for ER+ women: Results of the first interim analysis of the noninterventional trial BRAWO. J Clin Oncol 2014;32:578.

23. Steger GG, Egle D, Bartsch 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.

24. Niikura N, Nakatukasa K, Amemiya T, et al. Oral Care Evaluation to Prevent Oral Mucositis in Estrogen Receptor-Positive Metastatic Breast Cancer Patients Treated with Everolimus (Oral Care-BC): A Randomized Controlled Phase III Trial. Oncologist 2020;25:e223-30.

25. Nakatsukasa K, Niikura N, Kashiwabara K, et al. Secondary endpoints analysis in patients with estrogen receptor-positive metastatic breast cancer treated with everolimus and exemestane enrolled in Oral Care-BC. BMC Cancer 2021;21:34.

26. Schmidt M, Lübbe K, Decker T, et al. A multicentre, randomised, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (DESIREE). ESMO Open 2022;7:100601.

27. Jones VE, McIntyre KJ, Paul D, 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.

28. Rugo HS, Seneviratne L, Beck JT, et al. Prevention of everolimus-related stomatitis in women with hormone receptor-positive, HER2-negative metastatic breast cancer using dexamethasone mouthwash (SWISH): a single-arm, phase 2 trial. Lancet Oncol 2017;18:654-62.

29. O'Shaughnessy J, Thaddeus Beck J, Royce M. Everolimus-based combination therapies for HR+, HER2- metastatic breast cancer. Cancer Treat Rev 2018;69:204-14.

30. Kruger DT, Opdam M, van der Noort V, et al. PI3K pathway protein analyses in metastatic breast cancer patients receiving standard everolimus and exemestane. J Cancer Res Clin Oncol 2020;146:3013-23.

31. Hortobagyi GN, Chen D, Piccart M, 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. André F, Hurvitz S, Fasolo A, et al. Molecular Alterations

and Everolimus Efficacy in Human Epidermal Growth Factor Receptor 2-Overexpressing Metastatic Breast Cancers: Combined Exploratory Biomarker Analysis From BOLERO-1 and BOLERO-3. J Clin Oncol 2016;34:2115-24.

33. Prat A, Brase JC, Cheng Y, et al. Everolimus plus Exemestane for Hormone Receptor-Positive Advanced Breast Cancer: A PAM50 Intrinsic Subtype Analysis of BOLERO-2. Oncologist 2019;24:893-900.

34. Schettini F, Sobhani N, Ianza A, et al. Immune system and angiogenesis-related potential surrogate biomarkers of response to everolimus-based treatment in hormone receptor-positive breast cancer: an exploratory study. Breast Cancer Res Treat 2020;184:421-31.

35. Willemsen AECAB, He X, van Cranenbroek B, et al. Baseline effector cells predict response and NKT cells predict pulmonary toxicity in advanced breast cancer patients treated with everolimus and exemestane. Int Immunopharmacol 2021;93:107404.

36. Sim SH, Yang HN, Jeon SY, et al. Mutation analysis using cell-free DNA for endocrine therapy in patients with HR+ metastatic breast cancer. Sci Rep 2021;11:5566.

37. Lee JS, Yost SE, Blanchard S, et al. Phase I clinical trial of the combination of eribulin and everolimus in patients with metastatic triple-negative breast cancer. Breast Cancer Res 2019;21:119.

38. Van Swearingen AED, Siegel MB, Deal AM, et al. LCCC 1025: a phase II study of everolimus, trastuzumab, and vinorelbine to treat progressive HER2-positive breast cancer brain metastases. Breast Cancer Res Treat 2018;171:637-48.

39. Bardia A, Hurvitz SA, DeMichele A, et al. Phase I/II Trial of Exemestane, Ribociclib, and Everolimus in Women with HR(+)/HER2(-) Advanced Breast Cancer after Progression on CDK4/6 Inhibitors (TRINITI-1). Clin Cancer Res 2021;27:4177-85.

40. Barroso-Sousa R, Li T, Trippa L, et al. A phase I/IIb study of palbociclib (PALBO) plus everolimus (EVE) and exemestane (EXE) in hormone-receptor positive (HR+)/HER2-metastatic breast cancer (MBC) after progression on a CDK4/6 inhibitor (CDK4/6i): Results of the phase II study. Cancer Res 2020;80:P5-11-04.

41. Curigliano G, Martin M, Jhaveri K, et al. Alpelisib in combination with everolimus ± exemestane in solid tumours: Phase Ib randomised, open-label, multicentre study. Eur J Cancer 2021;151:49-62.

42. Massarweh S, Romond E, Black EP, et al. A phase II study of combined fulvestrant and everolimus in patients with

metastatic estrogen receptor (ER)-positive breast cancer after aromatase inhibitor (AI) failure. Breast Cancer Res Treat 2014;143:325-32.

43. Kornblum N, Zhao F, Manola J, 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.

44. Bachelot T, Bourgier C, Cropet C, 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.

45. Fan Y, Sun T, Shao Z, et al. Effectiveness of Adding Everolimus to the First-line Treatment of Advanced Breast Cancer in Premenopausal Women Who Experienced Disease Progression While Receiving Selective Estrogen Receptor Modulators: A Phase 2 Randomized Clinical Trial. JAMA Oncol 2021;7:e213428.

46. Jeong H, Jeong JH, Kim JE, et al. Final results of the randomized phase 2 LEO trial and bone protective effects of everolimus for premenopausal hormone receptor-positive, HER2-negative metastatic breast cancer. Int J Cancer 2021. [Epub ahead of print]. doi: 10.1002/ijc.33613.

47. Ballhausen A, Wheler JJ, Karp DD, et al. Phase I Study of Everolimus, Letrozole, and Trastuzumab in Patients with Hormone Receptor-positive Metastatic Breast Cancer or Other Solid Tumors. Clin Cancer Res 2021;27:1247-55.

48. Yam C, Esteva FJ, Patel MM, et al. Efficacy and safety of the combination of metformin, everolimus and exemestane in overweight and obese postmenopausal patients with metastatic, hormone receptor-positive, HER2-negative breast cancer: a phase II study. Invest New Drugs 2019;37:345-51.

49. Schmid P, Sablin MP, Bergh J, et al. A phase Ib/II study of xentuzumab, an IGF-neutralising antibody, combined with exemestane and everolimus in hormone receptor-positive, HER2-negative locally advanced/metastatic breast cancer. Breast Cancer Res 2021;23:8.

50. Verheijen RB, Atrafi F, Schellens JHM, et al. Pharmacokinetic Optimization of Everolimus Dosing in Oncology: A Randomized Crossover Trial. Clin Pharmacokinet 2018;57:637-44.

51. Groenland SL, van Eerden RAG, Westerdijk K, et al. Therapeutic drug monitoring-based precision dosing of oral targeted therapies in oncology: a prospective multicenter study. Ann Oncol 2022;33:1071-82.

52. Ayyagari R, Tang D, Patterson-Lomba O, et al. Progression-free survival with endocrine-based therapies following progression on non-steroidal aromatase inhibitor among postmenopausal women with hormone receptor positive, human epidermal growth factor receptor-2 negative metastatic breast cancer: a network meta-analysis. Curr Med Res Opin 2018;34:1645-52.

53. Bachelot T, Cottu P, Chabaud S, et al. Everolimus Added to Adjuvant Endocrine Therapy in Patients With High-Risk Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Primary Breast Cancer. J Clin Oncol 2022;40:3699-708.

54. Vernieri C, Corti F, Nichetti F, et al. Everolimus versus alpelisib in advanced hormone receptor-positive HER2-negative breast cancer: targeting different nodes of the PI3K/AKT/mTORC1 pathway with different clinical implications. Breast Cancer Res 2020;22:33.

First search

Literature search from 01.01.2014
to 10.02.2023 in PubMed with terms
"breast cancer" and "everolimus"

669 hits

⬇

Selecting clinical trials and
randomized controlled trials

84 hits

⬇

Selecting all phase 3 trials, phase 1-2
trials with not repetitive
information, and studies with
biomarker results.

Excluding early breast cancer trials,
subsequent publication of the same
trial, and trials with other indication

33 clinical trials

8 biomarker analyis

Second search

Literature search from 01.01.2020
to 10.02.2023 in PubMed with terms
"breast cancer" and "everolimus",

meta-analysis or systemic review

⬇

Selecting publications discussing
everolimus treatment.

4 hits

Third search

Search in clinicaltrials.gov with
terms "breast cancer" and
"everolimus"

133 hits

⬇

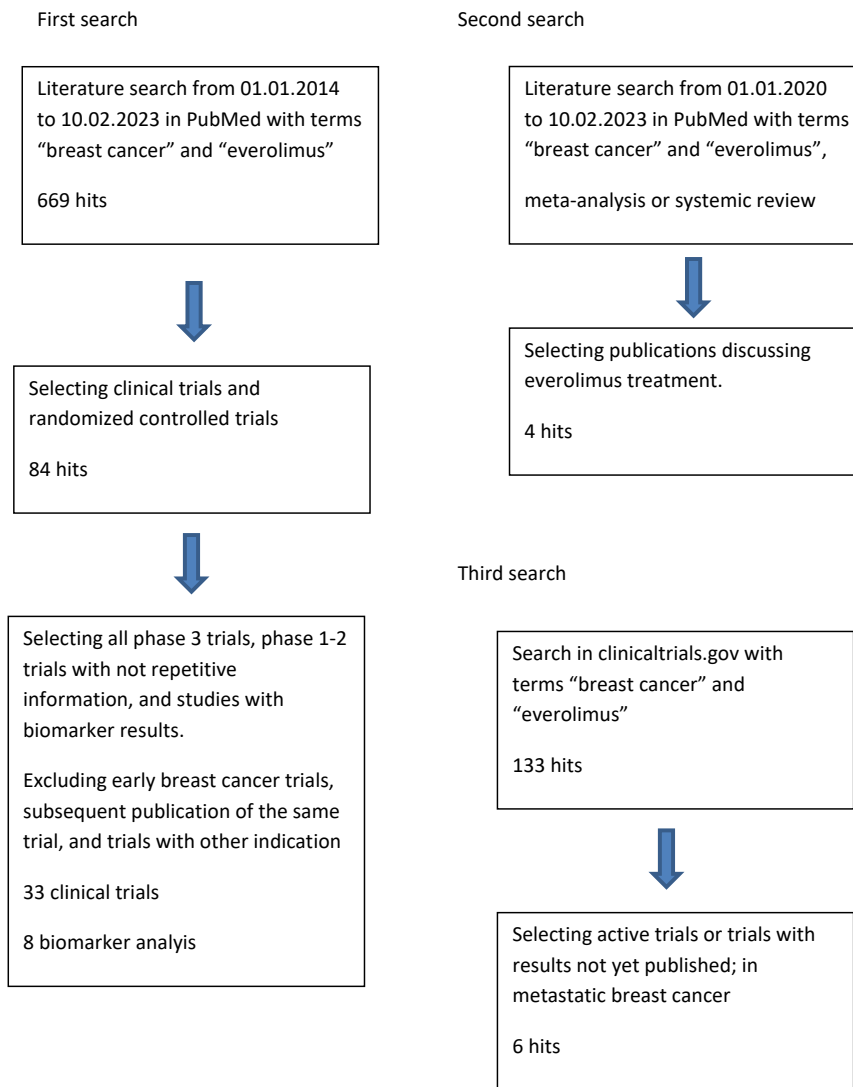Selecting active trials or trials with
results not yet published; in
metastatic breast cancer

6 hits

Figure S1 A detailed search strategy.