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

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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

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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

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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 (2,19). Several trials were conducted to gather more information on the safety of everolimus (4EVER, BALLET, EVA, BRAVO, STEPOUT) with concordant results (18,20-23). 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 (19). 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/m^2) [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; FN, febrile neutropenia; 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 (18)	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 (19)	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 1,159 (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.

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.

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Footnote

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Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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