Novel strategies to improve the endocrine therapy of breast cancer

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Abstract

Endocrine therapy (ET) constitutes the usual first-line of therapy for patients in the treatment of metastatic hormone receptor-positive breast cancer. Unfortunately, not all patients respond to first-line endocrine treatment due to intrinsic resistance, while others may initially respond but eventually progress with secondary acquired resistance leading to disease progression. Mechanisms of resistance to anti-estrogen therapy include, loss of expression for estrogen or progesterone receptor, upregulation of epidermal receptor growth factor 2, increased receptor tyrosine kinase signaling, leading to activation of various intracellular pathways that are involved in signal transduction such as PI3K/AKT/mammalian target of rapamycin, and others. Growing understanding of the signal cascade of estrogen receptors and the signaling pathways that interact with estrogen receptors has revealed the complex role of these receptors in cell growth and proliferation, and on the mechanism in development of resistance. These insights have led to the development of targeted therapies that may prove to be effective options for the treatment of breast cancer and may overcome hormone therapy resistance. In this review we summarize some of the mechanisms of endocrine resistance, selected clinical trials of ET and targeted therapies, which might interfere with estrogen receptor pathways and might reduce or reverse resistance to traditional, sequential, single-agent ET.

Introduction

The role of estrogen in the growth of breast cancer has been recognized for over a century. George Beatson, a Scottish surgeon, in 1896 described surgical castration as the first systemic therapy for breast cancer.[1] Beatson was able to recognize the benefits of this approach, even though hormones had not been yet discovered.

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Estrogen mediates its biological effects by binding to ERα and ERβ, which are members of the nuclear receptor superfamily of ligand-inducible transcription factors.[2] ERα is encoded by *ESR1*, a 300 kb gene located on chromosome 6, and has six functional domains, A to F, which include both ligand-binding and DNA-binding domains.[3] Approximately 75% of breast cancers express ERα and belong to the molecular subtypes luminal A or luminal B.[4] Estrogen receptor positive (ER+) and negative (ER-) disease differ in terms of clinical behavior, prognosis, patterns of recurrence, and aggressiveness. Patients with ER+ disease are likely to have more indolent disease, bone metastases, and late recurrences.[5]

Given their proven efficacy and generally favorable toxicity profile, with the exception of patients with advanced visceral disease, most patients will receive endocrine therapies (ET) in the treatment of metastatic ER+ breast cancer (BC). In premenopausal women, tamoxifen, pharmacological or surgical ovarian ablation are standard, while in postmenopausal women, aromatase inhibitors (AI) are prescribed to block the conversion of weak androgens of adrenal origin to estrogen in peripheral tissues as well as breast cancer tissue itself.[6] Fulvestrant is an ER downregulator and a more potent antiestrogen that reduces ER levels in cells.[7] Unfortunately, not all patients respond to first-line ET due to intrinsic resistance, while others may initially respond but eventually progress with secondary acquired resistance leading to disease progression and endocrine resistance.[8] The response to second line ET has a tendency to be brief, as demonstrated in clinical trials including, the EFECT (Evaluation of Faslodex *versus* Exemestane Clinical Trial), SoFEA (Study Of Faslodex with or without concomitant Arimidex *vs* Exemestane following progression on non-steroidal aromatase inhibitors) with progression free survival (PFS) of around 4-5 months in all study groups.[9,10]

Mechanisms of resistance to anti-estrogen therapy include, ER loss over time in the tumor which occurs in about 20% of patients treated with ET, acquired mutations in ERα (*ESR1*), constitutive activation cyclin-dependent kinases (CDK) 4 and 6.[8] Upregulation of epidermal receptor growth factor 2 (HER2) by either acquisition of gene amplification or overexpression, HER2 may subsequently assume the driving role in tumor progression by serving as an alternative survival pathway or by reducing the level of ER, thus rendering the tumor less responsive to estrogen.[11,12] Progesterone receptor (PR) is lost more frequently than ER while patients undergo ET. This loss leads to tumor aggressiveness and worse survival outcome than patients who maintain PR expression after resistance to ET.[13] Other mechanisms of resistance are associated with increased receptor tyrosine kinase signaling, leading to activation of various intracellular pathways involved in signal transduction, such as PI3K/AKT/mammalian target of rapamycin (mTOR), including loss of phosphatase and tensin homolog (PTEN) function, PI3K mutations, aberrant activation of AKT, mitogen activated kinase (MAPK)/ERK, fibroblast growth factor receptor and insulin-like growth factor-1 receptor.[14-19] Also described are alterations in cell cycle and apoptotic machinery; Epigenetic modification including dysregulation of DNA methy-

lation, histone modification, nucleosome remodeling and altered expression of specific microRNAs.[20,21]

Over the past few years a number of clinical trials have tested the addition of novel therapeutic agents to standard ET, with the purpose of improving the response and preventing the resistance to ET. This has resulted in the approval of three agents; the mTOR inhibitor everolimus and two CDK 4/6 inhibitors: palbociclib and ribociclib. Current ongoing studies will likely further improve the drug armamentarium for the treatment of locally advanced and metastatic breast cancer (MBC). In this review we summarize some of the clinical trials that have seeked to improve the response of ET in breast cancer by combining drugs that can help overcome intrinsic resistance of tumor and affect pathways associated with poor response to ET.

mTOR inhibitors

The PI3K-AKT (a serine/threonine kinase) pathway plays a central role in cell survival, proliferation and angiogenesis and is frequently deregulated in cancer.[22-24] A close interaction between the mTOR pathway and ER signaling has been reported. A substrate of the mTOR complex 1, S6 kinase 1 phosphorylates the activation function domain 1 of the ER, leading to ligand-independent receptor activation. Estrogen-dependent cells, cultured long term in estrogen-depleted medium, rely on mTOR signaling for growth and are excessively sensitive to its inhibition.[25] In addition, mTOR inhibition restores sensitivity of endocrine-resistant breast cancer cells to endocrine therapy.[26,27]

Prior to reports from m-TOR inhibitors studies in the metastatic setting (Table 1),[28-33] a phase II neoadjuvant endocrine therapy clinical trial of breast cancer, demonstrated synergistic effect to the combination of everolimus with letrozole. In this study, 270 postmenopausal women with operable ER+/HER2 negative breast cancer were randomly assigned to receive 4 months of neoadjuvant treatment with letrozole and either everolimus (10 mg/day) or placebo. The primary endpoint, response rate by clinical examination, was significantly improved from 59.1% to 68.1% in the combined treatment arm (P=0.062). The patients had mandatory biopsies at baseline and at day 15, allowing key biomarker analyses as a secondary endpoint. Downregulation of phospho-S6 and reduction in Ki67 expression was more frequently seen in the everolimus arm.[28]

Although active in renal cancer, the m-TOR inhibitor temsirolimus was not found to be effective in the treatment of advanced breast cancer. In the phase III HORIZON clinical trial 1112 postmenopausal patients with MBC were randomized to receive front line therapy with either letrozole daily combined with temsirolimus 30 mg intermittent daily (5 days every 2 weeks) or letrozole and placebo. The study was prematurely closed for futility at the preplanned second interim analysis with a PFS of 9 and 8.9 months respectively.[29] The disappointing results of this large randomized trial were followed by positive findings in a much smaller open-labeled phase II study. The TAMRAD clinical trial randomized 111 postmenopausal patients following progression to AI to receive tamoxifen 20 mg oral daily combined with everolimus or tamoxifen alone. The primary endpoint was clinical benefit rate (CBR) defined as objective response or stable disease for ≥24 weeks according to RECIST v 1.0 (Response Evaluation Criteria In Solid Tumors version 1.0). The CBR was higher in the combined treatment arm (61% *versus* 42%) and the time to progression (TTP) was increased from 4.5 months to 8.6 months favoring the investigational arm (hazard ratio [HR], 0.54; 95% CI, 0.36 to 0.81). The main toxicities were more common in the tamoxifen plus everolimus arm and included, fatigue (72% *vs* 53%) stomatitis (56% *vs* 7%), rash (44% *vs* 7%), anorexia (43% *vs* 18%), and diarrhea (39% *vs* 11).[30]

The encouraging results from the TAMRAD study led to the design of the randomized phase III BOLERO-2 clinical trial. In this study 724 postmenopausal HR+/HER2 negative patients with advanced BC were randomized in a 2:1 ratio favoring the investigational arm to receive either everolimus at the dose of 10 mg daily in combination with exemestane or exemestane and placebo. All patients suffered from recurrence of breast cancer 12 months after the end of adjuvant treatment or during treatment for MBC with either anastrozole or letrozole. Other previous anticancer endocrine treatments and a single prior chemotherapy regimen for advanced disease were also allowed. The trial met the primary end point, PFS; the median PFS, on the basis of central assessment were 10.6 months and 4.1 months, respectively favoring the everolimus containing arm (P<0.001).[31] Based on results of this phase III clinical trial everolimus is currently approved for the treatment of ER+, HER2 negative advanced breast cancer in combination with exemestane in patients resistant to nonsteroidal aromatase inhibitors.

The use of everolimus in the frontline setting of MBC is being evaluated in the phase 2 BOLERO-4 trial, where 202

Table 1. Selected clinical trials of m-TOR inhibitors + ET.

Study	Design	Drug combination	N	Results
Baselga *et al*.[28]	Phase II Neoadjuvant	Letrozole-everolimus	270	RR by clinical examination, 59.1% to 68.1%
TAMRAD[30]	Phase II MBC pretreated	Tamoxifen-everolimus *vs* tamoxifen	111	TTP increased from 4.5 to 8.6 m
HORIZON[29]	Phase III MBC 1st line	Letrozole-temsirolimus *vs* letrozole	1112	No improvement in PFS 9 vs 8.9 m
BOLERO-2[31]	Phase III MBC pretreated	Exemestane-everolimus *vs* exemestane	724	Increase in PFS from 4.1 to 10.6 m
BOLERO-4[32]	Phase II MBC 1st line	Letrozole-everolimus *vs* letrozole	202	Median PFS not reached at 17.5 m
PrECOG 0102[33]	Phase II MBC pretreated	Fulvestrant-everolimus *vs* fulvestrant	131	Increase in PFS 10.4 to 5.1 m

m, months; PFS, progression free survival; MBC, metastatic breast cancer; RR, response rate; TTP, time to progression.

Postmenopausal patients with HR+/HER2 negative metastatic or locally advanced BC with no prior advanced disease therapy received everolimus at the dose of 10 mg/day combined with letrozole. At disease progression, patients were offered everolimus and exemestane 25 mg/day until further progression or unacceptable toxicity. Patients with stomatitis completed the Oral Stomatitis Daily Questionnaire and were randomized to local standard of care or alcohol-free dexamethasone 0.5 mg/5 mL oral rinse, where commercially available. Median PFS has not been reached at the median follow-up of 17.5 months. Researchers estimated the 6-month and 12-month PFS rates to be 83.6% (95% CI, 77.3-88.2) and 71.4% (95% CI, 64.0-77.5), respectively. The overall response rate was 42.6% (95% CI, 35.7-49.7) the CBR for the combination was 74.3% (95% CI, 67.7-80.1).[32]

PrECOG 0102 sought to evaluate the combination of everolimus with fulvestrant vs fulvestrant plus placebo in 131 postmenopausal women HR+/HER2 negative inoperable BC (locally advanced or metastatic) previously treated with an AI for metastatic disease or relapsing on adjuvant AI. One prior chemotherapy regimen for metastatic disease was allowed. Patients were randomized in a 1:1 ratio in a blinded manner to fulvestrant (500 mg/d on days 1 and 15 of cycle 1, then day 1 of cycles 2–12 given every 28 days) plus oral everolimus (10 mg/d) or the same dose of fulvestrant plus placebo during the induction phase. Treatment continued until disease progression or unacceptable toxicity, for a maximum of 12 cycles (48 weeks). The study met the primary endpoint for PFS by investigator assessment, patients receiving the combination of fulvestrant and everolimus had a significant improvement in PFS of 10.4 *versus* 5.1 months for the group receiving fulvestrant/placebo. The hazard ratio was 0.60 (P=0.02).[33] There was no difference in OS, the combination was associated with more toxicity, including more frequent known everolimus therapy grade 3 adverse events.

Anti-HER 2 therapy

Prior to establishing the standard of care for ER+/HER2 negative MBC, the combination of a taxane with trastuzumab and pertuzumab.[34] Clinical trials evaluated the feasibility and therapeutic effect of combining ET with anti-HER 2 agents (Table 2).[35,36] The first of these studies the TAnDEM phase III clinical trial, included 207 postmenopausal patients with HR+/HER 2 positive MBC, who were randomly assigned to received anastrozole alone (n=104) or trastuzumab plus anastrozole (103). Patients in the trastuzumab plus anastrozole arm experienced a significant improvements in PFS of 4.8 months compared with patients receiving anastrozole alone 2.4 months (P=0.0016).[35] Similarly a phase III clinical trial randomized 1286 postmenopausal patients with either HR+/HER2 positive or HR+/HER2 negative MBC to receive letrozole plus lapatinib *vs* letrozole plus placebo. In the HR+/HER2 positive patients (n=219), addition of lapatinib to letrozole significantly reduced the risk of disease progression with a median PFS of 8.2 months in comparison to 3.0 months in the letrozole-placebo group (P=0.019). No improvement in PFS was observed among patients with HER2 negative disease.[36]

These two studies highlight the fact that the PFS in patients with HR+/HER2 positive MBC treated with endocrine therapy alone is very brief when compared to HR+/HER2 negative.[6] Also, that despite the fact that the addition of anti-HER2 therapy to ET is effective, results are inferior to what is seen with chemotherapy and anti-HER2 therapy.[34] These findings are the reason why endocrine therapy in combination with anti-HER2 therapy is reserved for patients with very indolent disease or in those who are not candidates for chemotherapy.[37]

Inhibition of the proteasome

The proteasome is a multi-catalytic, multi-subunit protease complex that is responsible for the ubiquitin-dependent turnover of cellular proteins.[38] The proteolytic component of this system, the 26S proteasome, consists of two 19S regulatory particles, involved in substrate recognition and unfolding and a core particle, the 20S proteasome. Since proteasomes play a central role in the cytoplasmic turnover of the vast majority of proteins, the manipulation of proteasomal activity is a key goal in controlling the stability of regulatory proteins.[39] Inhibition of the proteasome results in abnormal accumulation of many intracellular proteins, thereby disrupting cellular homeostasis and results in the induction of tumor cell apoptosis.[40]

Preclinical studies have demonstrated that proteasome inhibition might be a potential therapeutic tool for the treatment of endocrine resistant breast cancer. Mechanisms of this effect include, inhibition of mitogen activated protein kinase phosphatase-1 (MKP-1),[41] and inhibition of signaling cascades that are key regulators of hormone independence and anti-endocrine resistance.[42-44]

The combination of fulvestrant and bortezomib has been studied in a group of postmenopausal women, who had experienced progressive disease following AI therapy. The study randomized 118 patients to receive fulvestrant alone at the dose of 500 mg or in combination with bortezomib (1.6 mg/m^2 IV on days 1, 8, 15). The primary endpoint was PFS. At 12 months, the PFS was 13.6% for the fulvestrant alone group *vs* 28.1% in patients treated with fulvestrant and bortezomib (P=0.03).[45] This study indicates that proteasome inhibitors could have some activity delaying progression to ET and perhaps further studies should be performed evaluating these agents.

Histone deacetylase inhibitors

Histone acetylation is an important determinant of gene expression. Acetylation is generally associated with elevated transcription, while deacetylated histones are often associated with

Table 2. Selected clinical trials of anti-HER2 + endocrine therapy.

Study	Design	Drug combination	N	Results
TAnDEM[35]	Phase III MBC 1st line	Anastrozole-trastuzumab *vs* anastrozole	207	Increase in PFS 2.4 *vs* 4.8 m
Johnston *et al.*[36]	Phase III MBC 1st line	Letrozole-lapatinib *vs* letrozole	219	Increase in PFS 3.0 *vs* 8.2 m

m, months; PFS, progression free survival; MBC, metastatic breast cancer.

gene repression.[46] Histone deacetylases (HDACs) are critical regulators of gene expression that enzymatically remove the acetyl group from histones. With HDAC inhibition, epigenetic changes may lead to the loss of ERα and make it more difficult to inhibit this receptor.[47] A possible approach to reverse hormone resistance in the treatment of breast cancer, is the use of histone deacetylase inhibitors (HDACI) to re-sensitize breast cancer cells to hormone manipulation.[48] Entinostat is an HDACI that has been shown to increase expression of both ER and the enzyme aromatase in a dose-dependent manner both *in vitro* and *in vivo*, which then sensitized breast cancer cells to estrogen and subsequent inhibition by the AI letrozole.[49]

The combination of the AI exemestane with entinostat was evaluated in the phase II ECORE 301 clinical trial. In this study 130 postmenopausal patients with history of advanced breast cancer that had progressed on a non-steroidal AI were randomized to receive exemestane with entinostat 5 mg or placebo weekly. 33% of the patients had received chemotherapy in the advanced breast cancer setting. Although small, this trial did demonstrate a statistically significant improvement in the PFS favoring the investigational arm (4.28 *vs* 2.27 months). The most striking findings of the trial was that the addition of entinostat led to a 10 month improvement in overall survival, from 19.8 months with exemestane alone to 28.1 months with the combination (P=0.04).[50] Correlative studies suggest that HDAC2 expression could be a predictive biomarker, and that histone hyper-acetylation may be a valid pharmacodynamic marker for the efficacy of this combination.[51] The phase III E2112 trial will further evaluate entinostat plus exemestane in 600 metastatic patients. Importantly, prior treatment with everolimus is allowed in this study (NCT02115282).

Antiangiogenic agents

High vascular endothelial growth factor (VEGF) levels in breast tumors have been associated with a decreased response to ET.[52,53] The feasibility and activity of the VEGF inhibitor bevacizumab in combination with endocrine agents had been previously tested in a phase II clinical trial with encouraging results.[54] Based on these findings, the phase III randomized LEA clinical trial evaluated bevacizumab with ET in the first line setting of postmenopausal patients with HR+/HER2 negative MBC. In this study 380 patients were randomly assigned to receive ET alone or in combination with bevacizumab. Of the patients, 342 received letrozole and 38 fulvestrant. Although PFS in this study was increased to 18.4 months with the addition of bevacizumab *vs* 13.4 without, it did not reach statistical significance (P=0.14). The combination had a significantly higher incidence of hematologic and non-hematologic toxicities therefore does not appear to be a promising approach to enhance first line therapy.[55]

Agents targeting the FGFR pathway

Fibroblast growth factors (FGFs) are involved in cancer cell proliferation and new blood vessel formation. FGFs are a family of related extracellular proteins that normally regulate cell proliferation and survival in humans.[56] They act by binding to and activating FGF receptors (FGFRs), which are cell surface proteins that transmit growth signals to cells. Certain FGFs promote growth of multiple solid tumors by binding and activating FGFRs.[57] The FGF family consists of 22 known proteins called ligands that exert their physiological effect on cells by binding to four FGFRs (FGFR1, 2, 3 and 4).[58]

In addition to FGFR1 gene amplification, certain tumors contain an excessive number of gene copies encoding FGF ligands 3, 4 and 19. Because these genes are located together on chromosome 11, amplification of FGF 3, 4 and 19 is commonly referred to as 11q amplification. The amplification of these genes in the tumor cell has the potential to increase FGFR activation and tumor growth.[59]

The FGFR1 and/or 11q gene amplification has been observed in up to 25% of breast malignant tumors.[60] Several studies are evaluating FGFR inhibitors in the treatment of breast cancer with or without antiestrogen therapies.[61-64] Dovitinib (TKI258) a small molecule inhibitor of FGFR1-3, VEGFR1-3, c-KIT, fms-related tyrosine kinase 3 (FLT3), platelet-derived growth factor receptor (PDGFR) β, c-KIT, and FLT3, is being evaluated in combination with fulvestrant in postmenopausal patients with locally advanced or metastatic HER2 negative, HR breast cancer who have progressed during or following endocrine therapy.[63] Lucitanib (E-3810) a small molecule inhibitor of VEGFR1-3, FGFR1-2, and colony stimulating factor 1 receptor has demonstrated anti-angiogenic and anti-tumor activity in preclinical models. A phase 2 study of lucitanib is ongoing in patients with ER + FGFR1-amplified and non-amplified metastatic breast cancer (NCT02053636).

Inhibitors of cyclin-dependent kinase 4/6

Cell cycle regulation is identified as an attractive target for targeted drug therapy. Inhibitors of cyclin-dependent kinase (CDK) 4 and 6, together with cyclin D, promote G1-to-S phase transition by phosphorylating the retinoblastoma protein, which releases the E2F transcription factor and activates downstream target genes.[64] CDK4/6 is particularly activated in ER+ breast cancer via the ER, along with other oncogenic signaling pathways.[65] Given their kinase activity, the cyclin dependent kinases have been pursued as drug targets.[66] After disappointing results of first and second generation CDK inhibitors mainly due to low single agent efficacy and increased toxicity,[67] the development of specific CDK 4/6 inhibitors has produced results never before seen in the treatment of breast cancer[68] (Table 3).[69-77]

Palbociclib was the first of these agents to gain approval, it did so by demonstrating activity in the phase II open label randomized PALOMA 1 clinical trial. In this study, 165 postmenopausal women with advanced ER+ and HER2 negative breast cancer, who had not received any systemic treatment for their advanced disease were randomly assigned in a 1:1 to receive continuous letrozole or letrozole daily plus oral palbociclib 125 mg, given once daily for 3 weeks followed by 1 week off over 28-day cycles. The major efficacy outcome measure was investigator-assessed PFS of 10.2 months for the letrozole group and 20.2 months for the palbociclib plus letrozole group (P=0.0004).[69] These results were confirmed in the larger phase III PALOMA-2 clinical trial. This study randomized 666 patients 2:1 to receive the same dose and frequency of letrozole or letrozole plus palbociclib. Patients in the palbociclib containing arm experienced a PFS of 24.8 months in comparison to the control arm of 14.5 months (P<0.000001). Over all response rate (ORR) was also higher with palbociclib with 55.3% of patients who had measurable disease experiencing a reduction in size *vs* 44% (P=0.013). In terms of side effects, neutropenia (79.5 *vs* 6.3%) and fatigue (37.4 *vs* 27.5%) were more noticeable in the investigational arm; neutropenic fever was only seen in 2.5 % of the patients.[70]

Similarly, in the second line setting the PALOMA-3 double-blind phase III clinical trial, randomized 427 patients whose dis-

ease had progressed within 12 months of adjuvant therapy or within one month of endocrine therapy for HR+/HER2 negative MBC to receive palbociclib plus fulvestrant *versus* fulvestrant plus placebo. In conjunction with study treatment, premenopausal and perimenopausal women were required to take goserelin. The study met the primary endpoint, PFS which was 9.2 months in the palbociclib and fulvestrant arm *versus* 3.8 months in the fulvestrant and placebo arm (P<0.001).[71]

In the neoadjuvant setting, a phase II clinical trial evaluated the early introduction of CDK 4/6 inhibitors in the treatment of breast cancer. This is based on the observation that decreasing Ki 67 by complete cell cycle arrest, could have a positive effect on long term outcomes.[72] The study included patients with clinical stage II/III HR+, HER2 negative breast cancer. Patients received palbociclib and anastrozole for a four-month period and a proportion of patients was kept on palbociclib up until surgery; serial biopsies were performed. The primary end point was complete cell-cycle arrest, which was defined as a proportion of tumor cells positive for Ki 67 ≤2.7% on cycle 1, day 15 after 2 weeks of treatment with both drugs. Of the 45 evaluable patients 87% experienced complete cell-cycle arrest at cycle 1, day 15. Clinical responses were observed in 67%. Patients tended to have a rebound in Ki67 level in the washout period; however, this increase was not observed in patients who continued palbociclib.[73] The neoMONARCH phase II trial evaluated abemaciclib in combination with anastrozole in the neoadjuvant setting. In this study 173 women were randomized to receive abemaciclib plus anastrozole (n=56), abemaciclib monotherapy (n=58) or anastrozole monotherapy (n=59) for the first two weeks. At the conclusion of that regimen, all patients underwent a second core biopsy and then subsequently received the abemaciclib-anastrozole combination for 14 weeks. Abemaciclib was administered in 150 mg oral doses every 12 h, and anastrozole was administered in 1 mg oral doses daily. Patients also received loperamide as primary prophylaxis with each abemaciclib dose. The percentage of Ki67 responders, defined as patients with Ki67 levels <2.7% at week 2, was higher among those assigned the combination (69.6%) and abemaciclib monotherapy (68.4%) than anastrozole alone (22.7%), radiographic response rate (RR) was 54.7%.[74]

The results for ribociclib were reported in the MONALEESA-2 Phase III randomized, double blind, placebo controlled, and multicenter global registration trial. The study randomized 668 postmenopausal women with HR+/HER2 negative advanced breast cancer in a 1:1 stratified by the presence of liver and/or lung metastases. Patients received ribociclib 600 mg/daily (three weeks on and one week off), or placebo, in combination with letrozole 2.5 mg/daily. The first interim analysis showed a 44% improvement in median PFS and has not been yet reached at the data cut-off over 14.7 months seen in the placebo arm (P=0.00000329). As seen with other CDK4/6 inhibitors there is a significantly higher objective response rate when combined with AIs (53% *vs* 37%; P=0.00028). This agent is also associated with neutropenia which occurred in 59% of patients in the ribociclib arm compared to 1% of the placebo arm; leukopenia occurred in 21% *vs* 1%.[75,76] The MONALEESA-3 trial is evaluating ribociclib in combination with fulvestrant compared to fulvestrant alone in men and postmenopausal women with HR+/HER2 negative MBC in the second line endocrine therapy setting (NCT02422615).

Abemaciclib has demonstrated single agent activity as reported in the MONARCH 1 phase II single arm study where 132 patients received abemaciclib monotherapy 200 mg every 12 hours until progression of disease. Patients had a median of 3 lines of prior therapy for advanced disease, including a median of 2 lines of chemotherapy for advanced disease, 90.2% had visceral disease. At the 8 month interim the confirmed ORR (per RECIST v1.1) was 17.4%, the CBR defined as objective response or stable disease for ≥24 weeks was 42.4%, and median PFS was 5.7 months.[77] Two additional MONARCH trials are evaluating abemaciclib in breast cancer. MONARCH 3 is a Phase III trial of abemaciclib in combination with anastrozole in patients with HR+/HER2 negative locoregionally recurrent or metastatic breast cancer (NCT02246621). The monarcHER is evaluating abemaciclib plus trastuzumab (with or without fulvestrant) in women with HR+/HER2 positive locally advanced or metastatic breast cancer (NCT02675231).

Fulvestrant in the first line setting

Fulvestrant was initially approved at the dose of 250 mg following progression on an antiestrogen therapy, such as tamoxifen. However, pharmacokinetic findings from the phase III EFECT trial prompted researchers to explore a 500 mg dose.[9] Two clinical trials

Table 3. Selected clinical trials of CDK 4/6 inhibitors.

Study	Design	Drug combination	N	Results
Paloma 1[69]	Phase II MBC 1st line	Letrozole-palbociclib *vs* letrozole	165	Improvement in PFS from 10.2 to 20.2 m
Paloma 2[70]	Phase III MBC 1st line	Letrozole-palbociclib *vs* letrozole	666	Improvement in PFS from 14.5 to 24.8 m
Paloma 3[71]	Phase III MBC pretreated	Fulvestrant palbociclib *vs* fulvestrant	427	Improvement in PFS from 3.8 to 9.2 m
Ma *et al.*[73]	Phase II Neoadjuvant	Anastrozole-palbociclib	45	87% complete cell-cycle arrest at cycle 1, day 15. Clinical RR 67%
MONALEESA-2[76]	Phase III MBC 1st line	Letrozole-ribociclib *vs* letrozole	668	44% improvement in PFS 14.7 m *vs* NR for ribociclib
MONARCH-1[77]	Phase II MBC (heavily-pretreated)	Abemaciclib	132	ORR 17.4%, CB 42.4%, PFS 5.7 m
neoMONARCH[74]	Phase II Neoadjuvant	Abemaciclib + anastrozole *vs* abemaciclib *vs* anastrozole	173	Ki67 <2.7% at week 2. Combination (69.6%); abemaciclib (68.4%); anastrozole (22.7%). RR 54.7%

m, months; PFS, progression free survival; TTP, time to progression; ORR, over all response rate; RR, response rate; CB, clinical benefit.

have explored fulvestrant in the front line treatment of MBC. The FIRST phase II open-label study randomized postmenopausal patients with ER +/HER2 negative MBC to receive fulvestrant (n=102) or anastrozole (n=103). The study allowed for prior adjuvant endocrine therapy. The primary endpoint of the study was CBR, defined as objective response or stable disease for ≥24 weeks. 72.5% CBR was observed with fulvestrant compared with 67% with anastrozole (P=0.386). The study demonstrated an impressive TTP of 23.4 *versus* 13.1 months favoring fulvestrant (P=0.01).[78] OS was also improved to 54.1 months with fulvestrant compared with 48.4 months with anastrozole (P=0.041).[79] The confirmatory FALCON phase III clinical trial randomized 462 postmenopausal patients with advanced breast cancer in a 1:1 to receive the same dose and frequency of fulvestrant or anastrozole. The study met the primary end point PFS. Patients receiving fulvestrant had a PFS of 16.6 *vs* 13.8 months with anastrozole (P=0.0486).[80]

Conclusions

ET is central for many women with breast cancer, but resistance to therapy unavoidably occurs. The ER signaling pathway is a composite network of extensive crosstalk with growth-factor signaling pathways, cell cycle control pathways, and protein degradation pathways. These pathways provide many alternative targets for agents that may be useful in combination with ET to decrease resistance to treatment and to extend benefit to patients who do not achieve optimal benefit from ET alone. Aromatase inhibitors have been for decades the preferred front line therapy for MBC patients who are not experiencing a visceral crisis, fulvestrant has been reserved for the second line setting. Recent studies demonstrating improved results with first-line therapy fulvestrant indicate this agent can be considered in this setting. With the development of CDK 4/6 inhibitors significant improvement in PFS has been documented in each trial, where these agents have been combined with antiestrogen therapies. It is however, unknown if there is benefit to the continuation of these agents following progression. There is an ongoing studies looking into combining everolimus with ribociclib, following progression in the first-line ET in combination with a CDK 4/6 inhibitor (NCT02732119). Everolimus will likely continue to be used following progression to a CDK 4/6 inhibitor in combination with exemestane or fulvestrant. The toxicity profile of the CDK 4/6 inhibitors although favorable, caution should be taken in to adjusting the dose of these agents adequately as severe neutropenia and other side effects have been reported. With the broader use of molecular profiling, identifying patients with mutations in the FGFR could improve the participation of patients in clinical trials of these agents, with promising potential in the treatment of MBC.

The future looks very promising for the ET of patients with MBC, with unprecedented PFS findings on recent trials, it is likely that the overall survival of patients will continue to improve overtime. Part of the success of these agents is in overcoming intrinsic resistance of cancer and preventing acquired resistance over time. The question remains however, on which patients are these drug combinations needed, as adding these agents to ET increases toxicity and cost. Biomarkers that predict the benefit of these targeted therapies are greatly needed.

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