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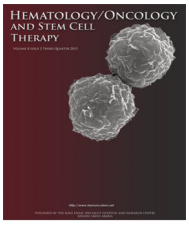

Current frontline endocrine treatment options for women with hormone receptor-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative advanced-stage breast cancer

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Abstract
Despite the recent advances in breast cancer early detection and awareness, a significant portion of patients present with an advanced-stage disease and more patients will progress to stage IV despite adequate treatment of their initial early-stage disease. Hormone receptor (HR)-positive, Human Epidermal Growth Factor Receptor-2 (HER2)-negative subtype is the commonest among all breast cancer subtypes. The management of the advanced-stage disease of this subtype has evolved significantly over the past few years. The emergence of estrogen receptor down regulators (fulvestrant), mTOR-inhibitors and the recent introduction of CDK4/6 inhibitors, like palbociclib, abemaciclib and ribociclib, has resulted in a significant and a historical improvement in treatment outcomes.
In this paper, we review many of the recently reported clinical trials that led to the approval of these new drugs in the first-line settings, along with the current international guidelines.

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Introduction

Breast cancer remains the commonest cancer among females worldwide [1]. Despite screening mammography and early-detection programs, some patients may still present with an advanced-stage disease, more so in underdeveloped countries. Additionally, and despite the recent advances in anticancer therapy, some patients may progress to stage IV disease while still on treatment or years after.

Patients who present with advanced-stage breast cancer are an extremely heterogeneous group. Treatment options vary remarkably depending on the clinical symptoms, location of metastasis, number of sites involved, hormone-receptor status and HER2 overexpression. The main goals of treating such patients are to slow the disease progression, improve quality of life and possibly prolong survival [2].

Endocrine therapy is considered an adequate treatment option for those who present with low-volume disease, asymptomatic, progress slowly and with no visceral crisis. It is extremely important to highlight that patients with advanced-stage breast cancer may survive long enough to consider their disease a chronic illness allowing the clinical utilization of multiple lines of endocrine therapy (ET) and chemotherapy.

The last decade has witnessed the introduction of many new drugs that down-regulate estrogen receptors (ER) like fulvestrant, or tackle the resistant state that many patients develop like mTOR-inhibitors (everolimus) and CDK4/6 inhibitors (palbociclib, ribociclib, abemaciclib).

Patients who present with de novo metastatic disease or progress after at least 12 months of finishing adjuvant endocrine therapy are considered, by recently-published and ongoing clinical trials, for frontline ET and such definition is used in our discussion.

Methods

The Pubmed/Medline, site was searched for all published literature using the key words: palbociclib, ribociclib, abemaciclib, fulvestrant, CDK4/6 inhibitors, aromatase inhibitors (AI) and endocrine therapy. Clinical trials website (www.clinicaltrials.gov) was also searched for all registered clinical trials utilizing the same key words.

Endocrine therapy

Almost 80% of breast cancer patients express estrogen receptor (ER) and/or progesterone receptors (PR) and as such are considered hormone-receptor positive and eligible for ET [3]. Classically, ET works by either depleting estrogen or through targeting its receptors.

Estrogen depletion

In premenopausal women, the ovaries are the primary source of estrogen. Oophorectomy can rapidly deplete the estrogen level. Estrogen suppression can also be accomplished using Luteinizing Hormone-Releasing Hormone (LHRH) agonists (goserelin, leuprolide).

In the postmenopausal state, estrogen is produced by converting adrenal precursors testosterone and dehydroepiandrostenedione (DHEA) by aromatase enzymes. Estrogen depletion in postmenopausal women can be accomplished by specific new third-generation AI; two of them (letrozole and anastrozole) are non-steroidal azole derivatives, while the third one (exemestane) is a 17-hydroxy steroid.

Targeting the estrogen receptor

Estrogen receptor signaling can be targeted by using selective estrogen receptors modulators (SERMs) or selective estrogen receptor down-regulators (SERDs). Tamoxifen, the main SERM used in the treatment of breast cancer, was discovered in 1967 [4] and is listed in the World Health Organization's (WHO) list of essential drugs [5]. Tamoxifen itself is a prodrug, having relatively little affinity for ER. It is metabolized in the liver by the cytochrome P450 isoform CYP2D6 and CYP3A4 into the active metabolite endoxifen [6]. Efforts to use genetic variants of CYP2D6 to optimize the clinical response to tamoxifen resulted in conflicting data and is not utilized clinically [7,8].

Tamoxifen has both antagonist effects; exerted mainly on the breast, and agonist effects exerted both on the bone and the endometrium [9,10].

Fulvestrant, an analog of 17-beta estradiol, is the main selective estrogen receptor down-regulator and was the first-in-class to be approved for breast cancer treatment in 2002. Once bound to the estrogen receptor, it increases its turnover, inhibits nuclear uptake of the receptor, blocks ER dimerization and DNA binding and ultimately to its degradation [11,12].

Treatment selection

Tamoxifen vs. aromatase inhibitors

Several clinical trials had clearly shown that any of the three available third generation AI (letrozole, anastrozole and exemestane) are superior to tamoxifen in overall response rate, time to treatment failure and clinical benefit [13—16]. This clinical advantage was clearly shown in a meta-analysis that included more than 8500 patients recruited into 23 randomized studies. Compared to tamoxifen, third-generation AI, when used as first-line therapy, were associated with survival advantage (HR = 0.89, 95% CI, 0.80—0.99; $P = 0.03$), too [17].

Though pharmacokinetic studies had shown that letrozole might be more effective than anastrozole [18,19], several clinical trials had shown that no one AI is better than the other [20,21]. Due to its irreversible binding to aromatase, exemestane was also thought to be superior to non-steroidal AIs [22]. In one study, 128 patients were randomized to receive anastrozole or exemestane for metastatic breast cancer. The objective response in visceral sites was 15% in both groups. Clinical benefit was achieved in 32% of the patients treated with anastrozole and 38% of the patients treated with exemestane. Median survival was not statistically significantly different; 33.3 months and 30.5 months in the anastrozole and exemestane groups, respectively [23].

Fulvestrant

Several clinical trials had shown that fulvestrant, when used for patients who progressed on prior ET was noninferior, but not superior to AI [24]. However, following the publication of the CONFIRM trial that showed better outcome with the higher dose (500 mg) compared to the 250 mg dose used in earlier studies, more recent studies used the higher dose of fulvestrant [25].

Fulvestrant was also used as a first line with remarkable success. In a phase II, randomized, open-label, multicenter study (FIRST Study), 205 postmenopausal patients with locally advanced or metastatic breast cancer were recruited. No prior endocrine therapy for advanced disease was allowed, however, adjuvant endocrine therapy for early disease completed more than 12 months before enrollment was permitted. Patients were randomly assigned to receive either the high-dose fulvestrant (500 mg) intramuscular injections on days 0, 14, 28 and every 28 days thereafter or anastrozole (1 mg) daily. Objective response rate (ORR) was similar in both arms: 36.0% for fulvestrant and 35.5% for anastrozole. Clinical benefit rate (CBR) was also similar for fulvestrant and anastrozole, 72.5% and 67.0%, respectively (odds ratio, 1.30; 95% CI, 0.72—2.38; $P = 0.386$). Time to progression (TTP) was significantly longer for fulvestrant (median TTP not reached) versus 12.5 months for anastrozole (HR = 0.63; 95% CI, 0.39—1.00; $P = 0.0496$ [26].

Two other trials tested the use of fulvestrant in combination with AI (anastrozole) versus anastrozole alone. The FACT (Fulvestrant and Anastrozole in Combination Trial) randomized 514 postmenopausal women, or premenopausal women receiving LHRH agonist, at first relapse to fulvestrant (low-dose: 250 mg) plus 1 mg of anastrozole daily or to 1 mg of anastrozole daily alone. Median TTP was similar in both arms: 10.8 and 10.2 months in the combination versus standard arm, respectively (HR = 0.99; 95% CI, 0.81—1.20; $P = 0.91$). Additionally, no difference in overall survival (OS) was observed: 37.8 months in the combination arm and 38.2 months in the anastrozole-alone arm (HR = 1.0; 95% CI, 0.76—1.32; $P = 1.00$). The combination was associated with more adverse events: hot flashes were reported in 24.6% in the combination arm versus 13.8% in the standard arm ($P = 0.0023$) [27].

This same concept was tested in another study; the Southwest Oncology Group (SWOG) S0226 trial, which randomized 707 women with metastatic breast cancer to anastrozole alone or anastrozole plus fulvestrant. Most of the patients received the low dose (250 mg), but after the release of the CONFIRM study [23], patients were allowed to use the high-dose (500 mg). Combined treatment resulted in a longer PFS (15.0 versus 13.5 months; HR = 0.80, 95% CI, 0.68—0.94, $P = 0.007$) and a trend to better OS (47.7 versus 41.3 months; HR = 0.81, 95% CI, 0.65—1.00, $P = 0.049$). The rates of grade 3 or more toxic effects were not different between the two groups. In a subgroup analysis, significant advantage was observed in both PFS and OS in the subgroup of patients who never received tamoxifen in the adjuvant setting ($n = 414$). Those who received tamoxifen ($n = 280$) had no PFS or OS benefit, Table 1 [28]. Many factors may have contributed to this outcome difference in the two combination studies (FACT and SWOG). Higher number of endocrine-naïve patients were included in the SWOG study (60%) than in the FACT study (32%). Additionally, the FACT study allowed the accrual of locally advanced (non-metastatic) patients while the SWOG study restricted patients' entry to metastatic disease only.

More recently, fulvestrant was tried against anastrozole in a phase III trial (FALCON). Patients ($n = 462$) with metastatic breast cancer, including those with de novo metastatic disease, who had not received prior ET were randomized to receive fulvestrant or anastrozole in a dose and a schedule similar to the FIRST trial discussed earlier [26]. At a median follow-up of 25.0 months, PFS was significantly longer in the fulvestrant group (16.6 months) than in the anastrozole group (13.8 months, HR = 0.797, 95% CI, 0.637—0.999, $P = 0.0486$) [29].

Cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors

CDK4 and CDK6 are cyclin-dependent kinases that control cellular transition between the G1 and S-phases of the cell cycle. Selective CDK4/6 inhibitors turn off kinases that lead to dephosphorylation of the retinoblastoma protein (Rb) resulting in cell-cycle arrest and the prevention of cancer

Table 1 Subgroup analysis of the SWOG-S0226; PFS and OS according to prior tamoxifen therapy.

End point	Anastrozole + Fulvestrant	Anastrozole alone	HR (95% CI)	p-Value
Median PFS (Months) (n = 694)	15.0	13.5	0.80 (0.68—0.94)	0.007
• No previous adjuvant tamoxifen (n = 414)	17.0	12.6	0.74 (0.59—0.92)	0.0055
• Previous adjuvant tamoxifen (n = 280)	13.5	14.1	0.89 (0.69—1.15)	0.37
Median OS (Months) (n = 694)	47.7	41.3	0.81 (0.65—1.00)	0.049
• No previous adjuvant tamoxifen (n = 414)	47.7	39.7	0.74 (0.56—0.98)	0.0362
• Previous adjuvant tamoxifen (n = 280)	49.6	44.5	0.91 (0.65—1.28)	0.59

PFS: Progression-Free Survival; OS: Overall Survival; HR: Hazard Ratio; CI: Confidence Interval

cell proliferation [30,31]. In breast cancer cells, CDK4/6 activity is typically deregulated and overactive leading to cellular proliferation and overgrowth.

Extensive studies had shown that inhibiting both kinases (CDK4/6) resulted in the inhibition of cell cycle and thus the inhibit cellular proliferation [32]. Flavopiridol was the first pan-CDK inhibitor, the clinical development of which was aborted due to significant adverse events [33]. More effective and less toxic specific inhibitors (palbociclib, ribociclib and abemaciclib) were recently introduced.

In a preclinical study, 47 human breast cancer cell lines were treated with palbociclib. Cell lines representing luminal ER-positive subtype were most sensitive to growth inhibition by palbociclib while nonluminal/basal subtypes were most resistant. Sensitive cell lines, but not resistant ones, showed G0/G1 cell cycle arrest and blocking of Rb phosphorylation [34].

Both palbociclib and ribociclib were studied extensively, first in heavily pretreated patients and then as a front line therapy. The PALOMA-1 study was a small phase-II, open-label randomized trial which evaluated the efficacy and safety of palbociclib in combination with letrozole versus letrozole alone in the first-line setting of patients with advanced-stage breast cancer. Eighty-four patients were randomized to receive palbociclib plus letrozole while 81 others received letrozole alone. After a median follow-up of almost 30 months, the median PFS was 10.2 months (95% CI, 5.7—12.6) for the letrozole group and 20.2 months (13.8—27.5) for the palbociclib plus letrozole group (HR = 0.488, 95% CI, 0.319—0.748; $P = 0.0004$) [35]. Results were recently updated; median OS was similar across the two arms of the study: 37.5 months for palbociclib plus letrozole vs 33.3 months for letrozole alone ($P = 0.813$) [36].

The PALOMA-2 was a larger phase III, double-blind study that was designed to confirm the efficacy and safety data of PALOMA-1. In this study, 666 patients were randomly assigned in a 2:1 ratio to receive palbociclib plus letrozole or letrozole alone. Median PFS was longer (24.8 months) among a group of 444 patients treated with letrozole and palbociclib compared to 14.5 months among the 222 patients randomized to letrozole alone (HR = 0.58, 95% CI, 0.46—0.72, $p < 0.001$). Additionally, the response rate was higher in the combination group (42.1%) compared to 34.7% in the letrozole-alone group, $P = 0.031$. Subgroup analyses of PFS according to stratification factors and other baseline characteristics confirmed a consistent benefit of palbociclib-letrozole across all subgroups (visceral versus nonviceral disease, prior hormonal therapy versus none and disease-free interval; less than 12 months or more than 12 months [37].

Ribociclib, another CDK4/6 inhibitor, was tested in multiple clinical trials (MONALEESA program). The MONALEESA-2 study, tested ribociclib in the front line setting among 648 advanced-stage breast cancer patients. Previous neoadjuvant or adjuvant therapy with a nonsteroidal aromatase inhibitor was not allowed, unless the disease-free interval was more than 12 months. Patients were randomized to receive ribociclib plus letrozole versus letrozole alone. Similar to the PALOMA-2 trial, the response rate was also better in the combination group (52.7%) versus 37.1% in those treated with letrozole alone, $p < 0.001$. After a median follow up of 15.3 months, the median PFS was not reached in the ribociclib combination group versus 14.7 months in the letrozole-alone group (HR = 0.56, 95% CI, 0.43—0.72, $P = 3.29 \times 10^{-6}$) [38]. In both studies (PALOMA-2 and MONALEESA-2), neutropenia was observed in a higher percentage of patients who received the CDK4/6 inhibitors (79.5% and 59.3%) in the palbociclib and ribociclib groups, respectively versus less than 7% among the letrozole groups in both studies. Though neutropenia was frequent, very few patients experienced febrile neutropenia (Grade 3 or 4); 8 patients (1.8%) in the palbociclib-letrozole group and in 5 patients (1.5%) in the ribociclib group and in none in the placebo group in both studies, Table 2. In addition to neutropenia, grade3/4 anemia was reported among 5.4% of patients treated with palbociclib while almost 10% of patients treated with ribociclib had grade 3/4 elevation of their liver enzymes. Prolongation of the QTc interval, defined as QTc > 450 ms, is relevant mostly for ribociclib (reported in 3.3% of the patients) and has not been reported with the other two CDK4/6 inhibitors [38]. Biomarkers of response were an exploratory endpoint of the trial. Using archival or fresh tumor samples obtained at screening, the first biomarker analysis of the MONALEESA-2 trial failed to turn up any predictors of response. The benefit in PFS was seen in all subgroups regardless of the biomarker status [39].

Based on these studies, both palbociclib and ribociclib were approved by the US FDA in combination with letrozole in the front line treatment of postmenopausal women with HR-positive, HER2-negative advanced-stage breast cancer.

Table 2 Phase-III clinical trials addressing the role of CDK4/6 inhibitors in front line setting.

Study	Treatment arms	Progression-free survival		Response rate		Neutropenia (Grade 3/4)	Neutropenic fever
		(Months)	p-value	%	p-value		
PALOMA-2 [37]	Letrozole + Palbociclib (444)	24.8[a]	<0.001	42.1	0.031	79.5%	1.8%
	Letrozole (222)	14.5[a]		34.7		6.3%	Zero
MONALEESA-2 [38]	Letrozole + Ribociclib (334)	Not reached[b,c]	3.29×10^{-6}	52.7	<0.001	59.3%	1.5%
	Letrozole (314)	14.7[c]		37.1		0.9%	Zero
MONALEESA-7 [40]	Tamoxifen/AI + Goserelin + Ribociclib (335)	23.8	9.83×10^{-8}	40.9	0.00098	60.6%	2%
	Tamoxifen/AI + Goserelin + Placebo (337)	13.0		29.7		3.6%	1%
MONARCH-3 [42]	Letrozole/Anastrozole + Abemaciclib (328)	Not reached[d,e]	0.000021	59.2	0.004	21.1%	NA
	Letrozole/Anastrozole (165)	14.7[e]		43.8		1.2%	NA

AI: Aromatase inhibitors.
[a] HR = 0.58, 95 CI 0.46—0.72.
[b] Median duration of follow-up was 15.3 months. At 18 months, PFS was 63.0% for the combination versus. 42.2% for letrozole.
[c] HR = 0.56, 95 CI 0.43—0.72.
[d] After a median follow up of 17.8 months.
[e] HR = 0.543, 95% CI 0.409—0.723.

Ribociclib has been tested in premenopausal patients. The results of MONALEESA-7 trial, the first phase-III study evaluating CDK4/6 inhibition as a frontline therapy for premenopausal women, were recently reported (40th annual San Antonio Breast Cancer Symposium, 6—10 December 2017). In this trial, 672 premenopausal women with advanced HR-positive, HER2-negative breast cancer were randomized to ribociclib ($n = 335$, median age 43 years) in combination with tamoxifen ($n = 87$) or AI ($n = 248$) plus goserelin. The control arm ($n = 337$, median age 45) received placebo in combination with tamoxifen ($n = 90$) or AI ($n = 247$) plus goserelin. The median PFS was 23.8 months for the ribociclib arm and 13.0 months for patients in the placebo arm (HR = 0.553, 95% CI, 0.441—0.694, $P = 9.83 \times 10^{-8}$). Response rate was also higher in the ribociclib arm (40.9%) compared to the placebo arm (29.7%), $P = 0.00098$. Grade-3 and grade-4 neutropenia were more common in the ribociclib arm; 50.7% and 9.9% compared to 3.0% and 0.6% in the placebo arm. However, in most patients, neutropenia was asymptomatic and was associated with fever in only 2% and 1%, respectively [40].

Abemaciclib is another potent CDK4/6 specific inhibitor, the activity of which was demonstrated in a phase II study (MONARCH-1) among 132 heavily pretreated patients with HR-positive breast cancer. As a single agent, abemaciclib resulted in a response rate of 19.7%; higher than had been seen with palbociclib or ribociclib as monotherapy. Median progression-free survival was about 6 months, and overall survival was 22 months [41].

The efficacy of abemaciclib in the first-line therapy of postmenopausal women with hormone receptor-positive, HER2-negative advanced-stage breast cancer was recently shown in a phase-III randomized, double-blind trial (MONARCH-3) that randomized 493 patients to nonsteroidal AI (NSAI), anastrozole or letrozole, and abemaciclib or NSAI and placebo. Previous adjuvant or neoadjuvant therapy with aromatase inhibitors in the last 12 months was not allowed. Results of the interim analysis, after median follow-up of 17.8 months, were recently published. Median PFS was not reached in abemaciclib arm compared to 14.7 months in placebo arm; HR = 0.543 (95% CI, 0.409—0.723, $P = 0.000021$). Additionally, patients with measurable disease treated with abemaciclib had a better objective response rate (59%) compared to 44% in the placebo arm ($P = 0.004$). A progression-free survival benefit was demonstrated across all prespecified subgroups. In addition to neutropenia (Table 2), the most frequent grade-3 adverse events (no grade-4) in the combination arm were diarrhea (9.5%) and anemia (5.8%) compared to none in the NSAI-alone arm. Venous thromboembolic events (VTE) were also higher (4.9%) in the abemaciclib arm compared to 0.6% in the NSAI-alone arm [42].

Several other clinical trials are ongoing testing the combination of CDK4/6 inhibitors, including abemaciclib, as upfront therapy in combination with tamoxifen, AI, or fulvestrant [43—48], Table 3.

Conclusions and future directions

Current front line endocrine treatment options for HR-positive, HER2-negative advanced stage breast cancer are

Table 3 Ongoing clinical trials addressing the role of CDK4/6 inhibitors as a first line endocrine therapy for advanced-stage breast cancer.

Study [Reference]	ClinicalTrials.gov Identifier	Patients included	Experimental arm	Control arm	Status
FATIMA [43]	NCT02917005	Premenopausal women	Goserelin 3.6 mg every 28 days, plus Exemestane, plus Palbociclib	Goserelin 3.6 mg every 28 days, plus exemestane	Not yet recruiting
PARSIFAL [44]	NCT02491983	Postmenopausal women	Palbociclib and Letrozole	Palbociclib and Fulvestrant	Recruiting
FLIPPER [45]	NCT02690480	Postmenopausal women	Fulvestrant 500 mg and Palbociclib	Fulvestrant 500 mg alone	Recruiting
BTCRC-BRE15-016 [46]	NCT02668666	Both pre- and post-menopausal women	Palbociclib and Tamoxifen	No controlled arm	Recruiting
COMPLEEMENT-1 [47]	NCT02941926	Both pre- and post-menopausal women	Ribociclib + letrozole	No controlled arm	Recruiting
MONARCH-Plus [48]	NCT02763566	Postmenopausal	Abemaciclib + NSAI or Abemaciclib + Fulvestrant	Placebo + NSAI or Placebo + Fulvestrant	Recruiting

NSAI: Non-steroidal aromatase inhibitor.

becoming really wide; varying from as little as tamoxifen to as sophisticated as a combination of both CDK4/6 inhibitor and AI [49,50].

Additionally, the value of the agents were investigated with fulvestrant in second line setting among patients who had disease progression during prior endocrine therapy; PALOMA-3 (palbociclib) [51], MONALEESA-3 (Ribociclib) [52] and MONARCHE-2 (abemaciclib) [53] are among such land mark trials.

Several points should be considered when choosing ET in the front-line setting: First, HR-positive, HER2-negative metastatic breast cancer, with low-volume disease, is considered a chronic illness allowing us to deliver many therapeutic options. Second, we are not sure that the way we sequence ET plays an important role in treatment outcomes [54]. These points and many others are difficult to address. Clinical trials testing the optimal sequencing of ET are highly needed but, obviously, difficult to perform.

Prospective biomarker-driven trials that identify patients who will likely be responsive and the upcoming overall survival data should help identify patients who will benefit from which CDK4/6 inhibitor(s) [55].

Currently, the National Comprehensive Cancer Network (NCCN) guidelines lists the combination of AI and CDK4/6 inhibitors or fulvestrant; alone, or in combination with AI, as category-I [56]. Particular adverse event profiles may help selecting a particular agent. Neutropenia and fatigue are more common with palbociclib, while elevation of the liver enzymes and EKG changes are more common with ribociclib and diarrhea is more with abemaciclib.

Conflict of interest

Nothing to declare.

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