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REVIEW

A paradigm shift for the treatment of hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) advanced breast cancer: a review of CDK inhibitors

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Abstract

In the last 3 years, a novel class of targeted therapy has been approved for patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+/HER2-) breast cancer. There are currently three approved agents, which are oral cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. All of the approved drugs exhibit progression-free survival benefit when compared to standard of care and generally have less adverse events compared to traditional chemotherapeutic options. The treatment of HR+/HER2- advanced breast cancer is a continuously evolving landscape, and the addition of CDK4/6 inhibitors is the newest mechanism for treatment. In this review, we summarize all available data, highlight the unanswered questions, and discuss pharmacological differences between each CDK4/6 inhibitor.

Keywords: breast cancer, targeted therapy, endocrine therapy, cyclin-dependent kinase 4, cyclin-dependent kinase 6.

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Introduction

Breast cancer is the most prevalent cancer among women in the United States. In 2017, breast cancer was responsible for 30% of all neoplasms.[1] The most common subtype of breast cancer (72.3%) is hormone receptor-positive (HR+) and human epidermal growth factor receptor 2-negative (HER2-).[2] In the United States, approximately 6% of patients have metastatic disease at the time of diagnosis. In addition, 20–30% of patients with early stage disease will become metastatic throughout the course of their disease.[3,4]

For many decades, blockade of estrogen receptor signaling was the basis for local, advanced, and metastatic HR+/HER2- breast cancer treatment; however, all advanced breast cancer patients eventually developed resistance to endocrine therapy (ET) throughout the course of their disease.[5]

The Cancer Genome Atlas found that HR+/HER2- breast tumors have a cyclin D1 amplification 29–58% of the time and a cyclin-dependent kinase (CDK) 4 amplification in 14–25% of cases.[4] Cyclin and CDK amplification might impact tumor hormone-blockade resistance.[4]

Cyclins and CDKs play a very important role in the cell cycle, regulating the transition from the phase G1 to the phase S. CDK4 and CDK6 bind cyclin D promoting the hyperphosphorylation, and thus deactivation of the retinoblastoma protein (pRb).[6] Hyperphosphorylated pRb releases E2F to express genes needed to proceed to S-phase. Therefore, in its physiological role, hypophosphorylated pRb acts as a tumor suppressor by slowing the progression of the cell cycle to the S-phase.[7]

The use of a CDK inhibitor prevents hyperphosphorylation of the pRb, resulting in cell arrest in the G1-phase, which has an indirect antitumor effect in cancer cells with an intact Rb-mediated checkpoint.[8]

Considering the importance of CDK4/6 activity in the regulation of cell proliferation and the mechanisms by which this pathway is known to be activated in HR+/HER2- breast cancer, selective

inhibition of CDK4/6 has emerged as an attractive therapeutic strategy for those patients.[9]

The first-generation CDK4/6 inhibitors had low specificity, resulting in inadequate clinical efficacy and intolerable toxicities; however, second-generation agents are now available and have demonstrated a higher efficacy compared to hormone therapy alone for advanced HR+/HER2- breast cancer and also a more manageable toxicity profile.[8] These agents include palbociclib, ribociclib, and abemaciclib.[8] The United States Food and Drug Administration (FDA) has approved CDK inhibitors for commercial use in the United States, although there is no study comparing them head to head. Therefore, this article will summarize the main clinical data of each drug.

Palbociclib

Palbociclib is a selective CDK4/6 inhibitor, which has activity in tumor cell lines driven by cyclin D1-CDK4 or cyclin D2/D3-CDK6.[10] The FDA initially approved palbociclib plus fulvestrant for patients with HR+/HER2- advanced breast cancer after progression on ET.

The randomized phase III trial, PALOMA-3, enrolled 521 women with advanced breast cancer whose disease progressed on ET or within 12 months of completion of adjuvant ET. Palbociclib plus fulvestrant achieved a median progression-free survival (mPFS) of 9.5 months versus 4.6 months achieved by placebo plus fulvestrant (hazard ratio [HR] 0.46, 95% confidence interval [CI] 0.36–0.59).[11] The main findings of the PALOMA-3 trial are summarized in Table 1.

The FDA also approved palbociclib plus an aromatase inhibitor (AI) for previously untreated advanced breast cancer patients based upon two studies (PALOMA-1 and PALOMA-2). PALOMA-1 was a randomized phase II study that enrolled 165 women and found a mPFS benefit for palbociclib plus AI versus placebo plus AI (median of 20.2 months versus 10.2 months, respectively; HR 0.488, 95% CI 0.319–0.748).[12] PALOMA-2 was a phase III study that enrolled 666 patients and found a statistically significant benefit for palbociclib plus AI versus placebo plus AI. The mPFS improved from 14.5 months for AI alone to 24.8 months for the combination (HR 0.58, 95% CI 0.46–0.72).[13] The data from PALOMA-1 and PALOMA-2 are summarized in Table 1.

The first overall survival (OS) data were shown in the PALOMA-1 study after a follow-up of 7 years.[14] The median OS was 37.5 months for 60 patients treated with palbociclib plus letrozole versus 34.5 months for 56 patients in the control arm of letrozole alone (HR 0.897, 95% CI 0.623–1.294).[14]

The average bioavailability of 125 mg of palbociclib is around 46% and reaches a maximum serum concentration between 6 and 12 hours after oral administration. Palbociclib is extensively metabolized in the liver by CYP3A and SULT2A1.[15] It has a half-life of 29 hours, and the metabolites are mainly excreted via renal (17.5%) and fecal (74.1%).[15]

The occurrence of uncomplicated grade 3/4 neutropenia suggests that the mechanism of myelosuppression with palbociclib may differ from that of traditional cytotoxic chemotherapy.[16] The rarity of neutropenic fever or infection suggests that bone marrow progenitors, suppressed during treatment, may still be functional in the face of an infectious challenge, as suggested by preclinical studies.[16]

Ribociclib

Ribociclib is an oral inhibitor of CDK4/6. Ribociclib also prevents hyperphosphorylation of pRb, which results in G1 cell cycle arrest.[17] In clinical trials, ribociclib demonstrated clinical activity as a single agent in advanced solid tumors and in combination with letrozole or fulvestrant for premenopausal or postmenopausal women with HR+/HER2- advanced breast cancer.[18–21]

The MONALEESA-2 study enrolled 668 treatment-naïve patients to ribociclib plus letrozole or placebo plus letrozole and achieved a statistically significant improvement in mPFS for ribociclib plus letrozole (25.3 months versus 16.0 months; HR 0.56, 95% CI 0.43–0.72).[18,19]

Recently, the MONALEESA-2 authors published an update OS among 50 women on ribociclib plus letrozole and 66 on placebo plus letrozole.[19] The median OS has not been reached in the ribociclib arm and was 33.0 months in the placebo plus letrozole arm (HR 0.746, 95% CI 0.517–1.078).[19]

MONALEESA-3 evaluated ribociclib plus fulvestrant versus placebo plus fulvestrant for first- or second-line treatment (381 patients were treatment-naïve and 345 patients received prior ET).[20]

MONALEESA-7 randomized premenopausal treatment-naïve patients using goserelin monthly to ribociclib plus letrozole or placebo plus letrozole. Both studies showed a mPFS benefit for ribociclib compared to the control arms.[20,21] All of the MONALEESA trials' data are included in Table 1.

The pharmacokinetic analysis determined that ribociclib is rapidly absorbed with a time to maximum concentration of 1 to 5 hours, and a half-life between 33 and 42 hours. In Japanese patients, blood levels of ribociclib appeared higher than in non-Japanese patients, although considerable variability was observed among patients.[22]

The most common grade 3/4 adverse events reported in the ribociclib plus letrozole arm of MONALEESA-2 were neutropenia (62%), nausea (8%), fatigue (10%), and diarrhea (8%).[19] Although neutropenia is the most common adverse event associated with ribociclib, febrile neutropenia is rare (1.5%).[18] Some cardiovascular adverse reactions occurred: peripheral edema (12–15%) and prolonged Q–T interval on ECG (1–6%).[19]

Abemaciclib

Abemaciclib is the third orally bioavailable inhibitor of CDK4/6 to be successfully developed from preclinical to clinical

Table 1. Summary of the main findings of all studies.

Trials	Setting	Type	n (menop)	Arms	OS (months)	mPFS (months)	ORR (%)	CBR (%)
PALOMA-1[12,14]	1st line	Phase 2	165 post	Palbociclib plus letrozole	37.5	20.2	43	81
				Placebo plus letrozole	34.5	10.2	33	58
PALOMA-2[13]	1st line	Phase 3	666 post	Palbociclib plus letrozole		24.8	42.1	84.9
				Placebo plus letrozole		14.5	34.7	70.3
PALOMA-3[11,30]	2nd line	Phase 3	521 pre or post	Palbociclib plus fulvestrant	34.9	9.2	10.4	34
				Placebo plus fuvestrant	28.0	3.8	6.3	19
MONALEESA-2[18,19]	1st line	Phase 3	668 post	Ribociclib plus letrozole	NR	16.0	40.7	76.9
				Placebo plus letrozole	33.0	25.3	27.5	72.7
MONALEESA-3[20]	1st line 2nd line allowed	Phase 3	76 post	Ribociclib plus fulvestrant		20.5	32.4	69.4
				Placebo plus fulvestrant		12.8	21.5	59.7
MONALEESA-7[21]	1st line	Phase 3	672 pre	Ribociclib plus ET		23.8	51	80
				Placebo plus ET		13	36	67
MONARCH-2[24]	2nd line	Phase 3	669 pre or post	Abemaciclib plus fulvestrant		16.4	35.2	72.2
				Placebo plus fulvestrant		9.3	16.1	56.1
MONARCH-3[25]	1st line	Phase 3	493 post	Abemaciclib plus AI		NR	48.2	78.0
				Placebo plus SAI		14.7	34.5	71.5

n, number of included patients; menop, menopausal status; OS, overall survival; mPFS, median progression-free survival; ORR, objective response rate; CBR, clinical benefit rate; ET, endocrine therapy; pre, pre-menopausal; post, post-menopausal; NR, not reached.

practice. It is structurally different from palbociclib and ribociclib, as it exhibits greater selectivity for CDK4.[23]

The MONARCH-2 randomized phase III trial enrolled 669 patients and compared abemaciclib plus fulvestrant versus placebo plus fulvestrant.[24] The addition of abemaciclib led to a statistically significant increase in mPFS from 9.3 months to 16.4 months (HR 0.553, 95% CI 0.449–0.681).[24]

The MONARCH-3 phase III study randomized 493 previously untreated patients to abemaciclib plus letrozole or placebo plus letrozole.[25] The mPFS for patients treated with abemaciclib plus letrozole has not been reached compared to placebo plus letrozole of 14.7 months (HR 0.54, 95% CI 0.41–0.72).[25] Table 1 summarizes the main findings from MONARCH-2 and MONARCH-3.

The main pharmacokinetic feature of abemaciclib compared to the other CDK4/6 inhibitors is its ability to cross the blood–brain barrier, with drug concentrations in the cerebrospinal fluid comparable to those in the plasma.[26]

The main adverse event that occurred in patients taking abemaciclib was diarrhea, which occurred in 81.3% of patients (all grades).[25] Likewise, fatigue in all grades occurred in 40.1% of subjects.[25] These toxicities were reversible and occurred

predominantly within the first 2 weeks after initiation of treatment.[25]

Abemaciclib produces less neutropenia and can be administered continuously without breaks, potentially leading to senescence and final tumor regression to a greater degree.[27] In addition, the varying toxicity profiles may be due to the increased selectivity of this compound to CDK4 than to CDK6.[27]

Discussion

It is unclear as to which CDK inhibitor provides the most benefit and what the optimal treatment sequencing is. The major benefits in terms of mPFS were seen for first-line treatment, although the complete overall survival (OS) data is yet to mature.

Differences between each CDK inhibitor

Although there is not any clinical trial comparing CDK inhibitors head-to-head, their efficacy appear to be similar with differing adverse events. Ribociclib, palbociclib, and abemaciclib are all oral molecules that bind to the ATP-motif of CDK4 and CDK6; however, abemaciclib appears to bind more selectivity to CDK4 than ribociclib and palbociclib, with the half maximal inhibitory concentration (IC_{50}) five times lower than those of the two other compounds.[27] In contrast, ribociclib and palbociclib appear to have higher lipophilicities of the binding site side chains than abemaciclib, which may reduce the number of ATP-binding sites of the off-target kinase with which they interact.[27]

CDK inhibitors for all patients?

Although CDK inhibitors have proven efficacy among different patient subgroups (e.g. treatment-naïve and previously treated patients or premenopausal and postmenopausal patients), further studies to select patients who will benefit most are needed.

A combined analysis of MONARCH-2 and MONARCH-3 presented at the San Antonio Breast Cancer Symposium in 2017 found that patients with progression after more than 3 years after adjuvant endocrine therapy completion and patients with bone-only metastatic disease might receive only a modest benefit of abemaciclib plus ET versus ET-alone.[28,29]

CDK inhibition as soon as possible?

A majority of patients with HR+/HER2- breast cancer is diagnosed at an early stage, and ET is the current standard of care in the adjuvant setting. Although many patients can be cured, relapse occurs for up to 15% of patients within 5 years after ET. Patients at higher risk of recurrence may be identified based on the clinical characteristics (e.g. lymph node involvement or the need for adjuvant chemotherapy) and pathologic characteristics (e.g. high grade or Oncotype *Dx* > 25) of disease. Thus, optimizing adjuvant therapy for these patients is an important clinical need. Considering the benefits previously reported among patients with metastatic disease, there are several ongoing trials evaluating CDK inhibition plus ET in the adjuvant setting (e.g. NCT03155997, NCT02513394, and NCT03078751).

Conclusion

Inhibition of CDK4/6 represents a promising approach to overcome resistance to ET in HR+/HER2- advanced breast cancer. More studies are needed in order to find the optimal treatment sequence and who will benefit most from these novel compounds.

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