Palbociclib in Metastatic Breast Cancer

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Abstract

The mainstay treatment for hormone receptor-positive metastatic breast cancer focuses on varying methods to reduce estrogen receptor signaling. Unfortunately, resistance to such therapies ultimately develops. The search for mechanisms of resistance to hormonal therapy has focused primarily on growth factor pathways and networks, while pathways involving cell cycle regulation seemed less influential. However, it is well known that the dysregulation of the cell cycle plays a role in oncogenesis. Cyclin- dependent kinases (CDKs) have been shown to play a role in the growth of estrogen positive breast cancer, in particular CDK 4 and 6, which promote progression from the G1 to S phase of the cell cycle. The recent approval of palbociclib, a specific inhibitor of CDK 4/6, for estrogen-receptor positive human epidermal growth factor receptor 2-negative advanced breast cancer has added an important tool to the available treatment armamentarium. We will focus this review on palbociclib, the first CDK 4/6 inhibitor to receive regulatory approval, and we will also provide an overview of the other CDK 4/6 in development.

Key words: breast cancer, hormone receptor-positive, palbociclib, metastatic, cyclin-dependent kinases

Introduction

The progression through the cell cycle is strictly controlled by cyclin dependent kinases (CDKs), which are key regulatory proteins. CDKs exist in an inactive form, but when quiescent cells are stimulated by mitogenic signals, CDK4 and CDK6 are activated by association with D-type cyclins.[1,2] This initiates phosphorylation of the retinoblastoma (Rb) tumor suppressor protein that negatively regulates cell proliferation through activation of the E2F family transcription factors.[3] CDK inhibitory (CKI) proteins including p15, p16, p18, and p19 are also involved in the cell cycle regulation. These proteins can inhibit cell cycle progression through direct association with activated CDK-cyclin complexes, thus acting as important effectors of anti-mitogenic stimuli.

Recent advancements in our understanding of tumor biology have led to a greater appreciation of the critical role that cell cycle dysregulation plays in malignant cell replication. Initially, CDK inhibitors were investigated as single agents; later, in combination with traditional cytotoxic drugs to overcome cell-cycle mediated drug resistance. In breast cancer, however, there are data supporting significant activity in hormone receptor (HR)-positive disease and potential synergy between CDK inhibition and hormonal therapy. Estrogen is involved in cell cycle progression by regulating the expression of cyclin D1, thereby activating cyclin E-CDK2 complexes. In vitro studies using palbociclib (PD-0332991),[4] an oral inhibitor of CDK 4/6, demonstrated a significant decrease in cell cycle progression[5] and growth inhibition in HR-positive breast cancer cell lines,[6] with the least activity in nonluminal/basal cells except for those with human epidermal growth factor receptor 2 (HER2)- amplification. In addition, data from The Cancer Genome Atlas point to an association between dysregulation of the cyclin D-CDK 4/6-Rb pathway and luminal B type breast cancer.[7] Luminal B tumors compared with luminal A tumors are more frequently associated with CCND1 (cyclin D1) gene amplification (58% vs 29%, respectively), gain of CDK4 (25% vs 14%, respectively), and loss of negative regulators, including p16 and p18. Dysregulation of the CDK pathway in luminal tumors may explain the increased activity of these drugs in HR+ cell lines.

Based on these findings, blockage of CDK 4/6 is a rational approach to restoring cell cycle control in ER-positive breast cancer. Palbociclib is the first CDK 4/6 that has received regulatory approval; other CDK 4/6 inhibitors are in active development.

Clinical Efficacy

Phase I

Palbociclib was initially evaluated as a single agent in 2 phase I dose-escalation trials in patients with advanced malignancies.[8,9] In the first published trial, 33 patients with Rb-positive advanced solid tumors or non-Hodgkin lymphoma refractory to standard treatment received palbociclib once daily for 14 days followed by

7 days off (2 weeks on/1 week off).[8] Overall, it was well tolerated with dose-limiting toxicities (DLTs) related primarily to myelosuppresion. There was 1 partial response (PR) and 9 patients had stable disease (SD). The recommended phase II dose (RP2D) was 200 mg. In the second study,[9] 41 patients with Rb-positive advanced solid tumors were enrolled, including 5 patients with breast cancer. In this trial, palbociclib was administered on a different dose schedule, with 21 days on followed by 7 days off (3 weeks on/1 week off). Neutropenia was the only dose-limiting effect, and the most common nonhematologic grade 3/4 adverse events (AEs) included fatigue, nausea, and abdominal pain. Of the 37 patients evaluable for tumor response, 10 had SD. The RP2D was 125 mg. This study defined the dosage used for subsequent trials. Further information on the safety and tolerability of palbociclib follows.

Phase II

The results seen in phase I led to a single arm phase II study of palbociclib given as monotherapy in patients with Rb-positive advanced breast cancer.[10] Primary endpoints were disease response and tolerability. Thirty-seven patients were enrolled and 19% had a clinical benefit rate, defined as PR and SD for 24 months or longer. Median progression-free-survival (PFS) was 3.7 months overall, but was significantly longer for those with HR-positive disease compared with HR-negative disease (4.5 months vs 1.5 months; $P = .03$). Although biomarker assessment was a secondary endpoint, neither Rb nuclear expression, Ki67 proliferation index, p16 loss, nor CCND1 amplification was associated with response.

Based on preclinical data demonstrating synergy of palbociclib with anti-estrogen therapy,[6] Finn et al conducted the PALOMA-1 trial.[11] This multicenter, open-label phase II trial enrolled 165 postmenopausal women with ER-positive, HER2-negative, advanced breast cancer who had not received previous systemic treatment for advanced disease. Patients were randomized in a 1:1 fashion to letrozole 2.5 mg daily or letrozole 2.5 mg daily plus palbociclib. Investigator (inv)-assessed PFS was the primary endpoint. Median inv-assessed PFS was 20.2 months (95% CI, 13.8-27.5) in the palbociclib plus letrozole arm and 10.2 months (95% CI, 5.7-12.6) in the letrozole alone arm (hazard ratio [HR], 0.488; 95% CI, 0.319-0.748). In addition, the overall response rate (ORR) in patients with measurable disease was higher in the palbociclib plus letrozole compared with the letrozole alone arm (55.4% vs 39.4%). Initially patients were enrolled in 2 separate cohorts: in cohort 1, patients were enrolled on the basis of ER-positive and HER2-negative biomarker status alone, whereas in cohort 2, they were also required to have *CCND1* amplification or loss of p16, or both. Accrual to cohort 2 was later stopped after an interim analysis suggested that patient selection based on CCND1 or p16 loss was unlikely to improve patient outcome. At the time of this analysis, PFS for the palbociclib plus letrozole group was 26.1 months in cohort 1 compared to 18.1 months in cohort 2.

TABLE 1. Dose Modification and Management – Hematologic Toxicities

CTCAE Grade	Dose Modifications
Grade 1 or 2	No dose adjustment is required.
Grade 3 (except lymphopenia)	No dose adjustment is required. Consider repeating CBC monitoring 1 week later. Withhold initiation of next cycle until recovery to Grade≤2.
Grade 3 ANC (<1000 to 500/mm^3) + fever≥38.5°C and/or infection	Withhold palbociclib and initiation of next cycle until recovery to Grade≤2 (≥1000/mm^3). Resume at next lower dose.
Grade 4 (except lymphopenia)	Withhold palbociclib and initiation of next cycle until recovery to Grade≤2. Resume at next lower dose.

Phase III

Although the results of the phase II study PALOMA-1 are encouraging, a phase III randomized double-blind placebo controlled trial was designed to definitely evaluate the role of palbociclib in metastatic breast cancer: PALOMA-2.[12] Eligible patients are postmenopausal women with ER-positive HER2-negative disease who have not received prior therapy for advanced breast cancer, prior CDK 4/6 inhibitors, or prior (neo)adjuvant treatment with letrozole or anastrozole with a disease free interval less than 12-months from completion of treatment. Patients were assigned to letrozole with palbociclib 125 mg once daily for 3 weeks on/1 week off or to letrozole with placebo. This study has accrued its planned 666 patients and data are maturing with results expected in 2016.

Palbociclib has also been investigated in the second-line setting. In PALOMA-3, a phase III randomized (2:1) double blind study, 521 patients with HR-positive, HER2-negative breast cancer that relapsed or progressed on previous endocrine therapy were assigned to fulvestrant with palbociclib or placebo.[13] Premenopausal or perimenopausal women were eligible if also treated with goserelin. Women on the experimental arm had more than double median PFS (primary endpoint) compared with those in the placebo arm (9.2 months vs 3.8 months; HR 0.42; P <.001). The relative difference in primary outcome between the placebo and palbociclib groups was consistent regardless of menopausal status of the patients. At the time of this preplanned interim analysis, data on overall survival (secondary endpoint) were immature. Although the efficacy benefit was not as large as seen in the first-line setting, these results may lead to an ex-

TABLE 2. Dose Modification and Management – Hematologic Toxicities

Study name	Description	Design	Primary Endpoint	Status
PALOMA-1[27]	Palbociclib + letrozole vs letrozole alone in postmenopausal women with ER+/HER2- locally advanced or newly diagnosed metastatic BC	Phase II	PFS	Completed, results published
PALOMA-2[28] (NCT01740427)	Palbociclib + letrozole vs letrozole for first-line therapy of postmenopausal women with ER+/HER2- advanced BC	Phase III Randomized (2:1), double blind	PFS	Active, not recruiting Results expected in early 2016
PALOMA-3[29] (NCT01942135)	Palbociclib +/- fulvestrant in ER+/HER2- metastatic BC after endocrine failure	Phase III Randomized (2:1), double blind	PFS	Completed, results published
PALOMA-4[30] (NCT02297438)	Palbociclib + letrozole vs placebo + letrozole for first-line treatment of Asian postmenopausal women with ER+/HER2- advanced BC	Phase III Randomized, double blind	PFS	Currently recruiting
PEARL[31] (NCT02028507)	Palbociclib + exemestane vs capecitabine in postmenopausal women with ER+/HER2- metastatic BC refractory to letrozole or anastrozole	Phase III Randomised (1:1), multicenter, open-label	PFS	Currently recruiting
PENELOPE-B[32] (NCT01864746)	Standard endocrine therapy + palbociclib vs placebo in patients with ER+/HER2- early-stage BC with high-risk features for recurrence after pre-op chemotherapy and surgery	Phase III Randomized (1:1), double blind, placebo controlled	DFS	Currently recruiting
PALLAS[33]	Standard adjuvant endocrine therapy +/- palbociclib for ER+/HER2- early-stage BC	Phase III Randomised (1:1), open label	DFS	Planned

BC indicates breast cancer; DFS, disease-free survival; ER+, estrogen-receptor positive; HER2-, human epidermal growth factor receptor 2 negative; PFS, progression-free survival.

pansion of the currently approved label of palbociclib in breast cancer.

Regulatory process and FDA approval

In December 2012, preliminary data of the PALOMA-1 study was presented at the Cancer Therapy & Research Center-American Association for Cancer Research (CTRC-AACR) San Antonio Breast Cancer Symposium and showed a marked improvement in median PFS in women who received palbociclib (26.1 months compared with 7.5 months).[14] Based on these results, palbociclib received Breakthrough Therapy designation by the FDA for the potential treatment of patients with breast cancer on April 10, 2013. This designation is a relatively recent mechanism intended to accelerate the development and review of potential new medicines being developed to treat serious or life-threatening conditions.[15]

In April 2014, detailed efficacy and safety data on PALOMA-1 were presented at AACR meeting.[16] In February 3, 2015 after study results were published, the FDA granted accelerated approval to palbociclib (IBRANCE) in combination with letrozole for first-line therapy of postmenopausal women with locally advanced or metastatic ER-positive HER2-negative breast cancer. The recommended dosage and schedule of palbociclib is 125 mg daily for 21 consecutive days followed by 7 days off treatment with letrozole 2.5 mg daily continuously throughout the 28-day cycle. Accelerated approval by the FDA allows drugs to be approved based on a surrogate endpoint, but requires further trials to confirm the perceived clinical benefit. In a public statement from Pfizer on May 30, 2015 the company announced the intention to file a Marketing Authorisation Application for palbociclib to the European Medicines Agency (EMA) in the second half of 2015.[17]

Safety and Tolerability

Palbociclib is well tolerated overall, either as monotherapy or in combination with anti-estrogen therapies. However, quite often,

dosage reductions or treatment delays are required, primarily due to hematologic toxicity. In the phase I study reported by Flaherty KT et al,[9] neutropenia was the dose-limiting toxicity and there was a relatively small incidence of grade 3 neutropenia (12%) and anemia (7%). Surprisingly, in the single arm phase II study where palbociclib was also given as monotherapy, neutropenia was significantly higher and grade 3/4 neutropenia, anemia, and thrombocytopenia were reported in 51%, 5%, and 22% of patients, respectively. Of note, 24% of patients had treatment interruption and 51% had dose reductions, all due to cytopenias.[10]

In the PALOMA-1 study,[11] the most common grade 3/4 toxicities were also hematologic. What seemed to be unexpected was the finding that although grade 3/4 neutropenia was reported in 54% of patients in the experimental arm, no cases of febrile neutropenia or neutropenia-related infections were seen. Grade 3 or 4 thrombocytopenia was reported in only 2% of patients. Among the nonhematologic all-grade AEs, the most common were fatigue (40%), nausea (25%), arthralgia (23%), and diarrhea (21%). Importantly, 43% of patients enrolled had received previous chemotherapy in the neoadjuvant or adjuvant setting.

In the PALOMA-3 study[13] the toxicity profile was not different and neutropenia was the most common AE occurring in 78.8% of patients receiving palbociclib-fulvestrant (any grade). Grade 3/4 neutropenia occurred in 62% of patients in the palbociclib arm compared with 0.6% in the placebo arm. In this study, low rates of neutropenia-related complications and febrile neutropenia were also confirmed and reported in 0.6% of patients in each arm. Compared with PALOMA-1, more patients received chemotherapy prior to enrollment (72.3% in the experimental arm and 79.3% in the placebo arm) that could contribute to the higher incidence of neutropenia. Remarkably, 31.6% of patients required dosage reduction of palbociclib.

For patients scheduled to initiate treatment with palbociclib, complete blood cell count (CBC) is required. In addition, CBC should be monitored at the beginning of each cycle, on day 14 of the first 2 cycles, and as clinically indicated. Dose modifications are recommended for management of AEs, with a first reduction to 100 mg and a second to 75 mg. For hematologic AEs, no dose adjustment is necessary for grade 3 events. Repeating CBC at 1 week is suggested and the next cycle should be resumed after recovery to grade 2 or lower. For grade 3 neutropenia with fever or other evidence of infection and for grade 4 events, palbociclib should be withheld until recovery to grade ≤2 then restarted at the next lower dose (**Table 1**).[18] If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as per best clinical practice. If the retreatment parameters are met within 3 weeks of dose interruption, palbociclib may be resumed as per recommended dose modification guidelines. If retreatment parameters have not been met after more than 3 weeks of dose interruption, the patient should permanently discontinue palbociclib treatment. However, if a patient is deemed to be suitable for a lower dose of palbociclib, treatment may be resumed at a lower dose at the physician's discretion.

In terms of safety, another important consideration is related to the concomitant use of strong CYP3A inhibitors such as clarithromycin, indinavir, and ketoconazole. These drugs should be avoided whenever possible. If one must be used, it is recommended that the palbociclib dose be reduced to 75 mg. Eating grapefruit or drinking grapefruit juice should be avoided, as well as other natural products and supplements that may interfere with the metabolism of palbociclib.

Future Directions

Additional studies of palbociclib in advanced/metastatic breast cancer and in early breast cancer are open and enrolling patients (**Table 2**). For example, PENELOPE-B and PALLAS are 2 phase III placebo controlled studies evaluating the role of palbociclib (for 1 or 2 years, respectively) in addition to standard endocrine therapy in patients with HR-positive HER2-negative high-risk early stage breast cancer. Other earlier phase trials are evaluating palbociclib in the neoadjuvant setting and when given with chemotherapy and with HER2-targeted therapies.

Along with palbociclib, 2 other orally available specific inhibitors of CDK 4/6 are being explored: abemaciclib and ribociclib (**Table 3**). In a breast cancer expansion arm of a phase I monotherapy study, abemaciclib (LY2835219) showed a response rate of 25% and a clinical benefit rate of 61%.[19] The dosage established for abemaciclib is 200 mg twice daily. It has more prominent gastrointestinal toxicity (diarrhea) and is currently being evaluated in a phase II monotherapy study (MONARCH 1) and in phase III trials with fulvestrant (MONARCH 2) or with nonsteroidal aromatase inhibitors (MONARCH 3). There is evidence suggesting that both abemaciclib and palbociclib may cross the blood-brain barrier.[20,21]

Ribociclib (LEE011) has also been evaluated in a phase I monotherapy study and shown to have an acceptable safety profile[22] with less prominent hematologic and gastrointestinal toxicity than the 2 other agents. Paired skin biopsies confirmed pharmacodynamic inhibition of cell proliferation measured by reductions of 50% or higher of phospho-pRb and Ki67. The recommended dose is 600 mg daily, 3 weeks on, 1 week off. It is currently in phase III development in the metastatic setting: in combination with letrozole (MONALEESA-2) or fulvestrant (MONALEESA-3) for postmenopausal women and with tamoxifen or aromatase inhibitors with goserelin for premenopausal women (MONALEESA-7).

Based on preclinical data demonstrating growth inhibition in breast cell lines showing HER2-amplification,[6] there are ongoing and planned clinical trials looking at the potential role of CDK 4/6 inhibitors in HER2-positive breast cancers.[23] Additionally, there is preclinical evidence that CDK 4/6 inhibitors improve

TABLE 3. Summary of the Major Clinical Trials With Other CDK 4/6 Inhibitors in Breast Cancer

Study name	Description	Design	Primary Endpoint	Status
Abemaciclib				
MONARCH 1[34] (NCT02102490)	Abemaciclib alone in women with previously treated ER+/HER2- metastatic BC	Phase II	ORR	Active, not recruiting
MONARCH 2[35] (NCT02107703)	Fulvestrant with abemaciclib vs placebo in women with ER+/HER2- advanced BC	Phase III Randomized double blind	PFS	Currently recruiting
MONARCH 3[36] (NCT02246621)	Nonsteroidal aromatase inhibitors with abemaciclib or placebo in postmenopausal women with ER+/HER2- advanced BC	Phase III Randomized double blind	PFS	Currently recruiting
Ribociclib				
MONALEESA-2[37] (NCT01958021)	Letrozole with ribociclib vs placebo for first-line treatment of postmenopausal women with ER+/HER2- advanced BC	Phase III Randomized double blind	PFS	Currently recruiting
MONALEESA-3[38] (NCT02422615)	Fulvestrant with ribociclib vs placebo for postmenopausal women with ER+/HER2- advanced BC who received no or only 1 line of prior endocrine therapy	Phase III Randomized double blind	PFS	Currently recruiting
MONALEESA-7[39] (NCT 02278120)	Ribociclib or placebo with tamoxifen and goserelin or a nonsteroidal aromatase inhibitor and goserelin for premenopausal women with ER+/HER2- advanced BC	Phase III Randomized double blind	PFS	Currently recruiting

BC indicates breast cancer; ER+, estrogen receptor positive; HER2-, human epidermal growth factor receptor 2 negative; ORR, overall response rate; PFS: progression-free survival.

the response to phosphotidyl inositol 3-kinase (PI3K) inhibitors[24] which has led to ongoing trials evaluating the combination of ribociclib with endocrine therapy and either isoform-specific PI3K inhibitor BYL219[25,26] or the pan-isoform inhibitor BKM120.[26]

The identification of specific predictive biomarkers of responsiveness remains of paramount importance. Thus far, only HR-positivity was found to be a significant predictor of response. Although preclinical development identified higher levels of Rb and cyclin D1 and lower levels of p16 as potential predictors of response to CDK4 inhibition, none of these has yet been validated in clinical trials. Possible explanations include various resistance mechanisms such as the use of other CDKs by cancer cells, loss of Rb function, or activation of other oncogenic pathways such as the PI3K-AKT pathway. Further work in this field with serial biopsies at baseline and during treatment may bring additional information in the near future.

Conclusion

The new class of CDK 4/6 inhibitors offers promise in the treatment of patients with HR-positive HER2-negative advanced breast cancer. To fully determine the role of these drugs in breast cancer, we must await definitive results from phase III studies and overall survival results from the studies that have already been presented. In parallel, and despite initial negative efforts to identify predictive markers of response, it is important to continue our endeavors to better define who benefits most from these therapies.

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