Perspective

CDK4/6 inhibitors in advanced hormone receptor-positive breast cancer

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Abstract: Approximately 70% of breast cancers (BC) are classified as hormone receptor-positive (HR-positive), comprising those expressing estrogen receptors and/or progesterone receptors. BC deaths are ultimately caused by metastatic disease. In this setting, although estrogen pathway blockade is an initially highly effective therapy, virtually all patients will develop resistance to endocrine therapy (*de novo* or acquired). Further understanding of the underlying mechanisms related to endocrine therapy resistance is vital and can ultimately lead to new therapies for this population. Recently, cyclin-dependent kinase (CDK) 4/6 inhibitors have emerged as one of the most important groups of drugs that synergize with endocrine therapy. In this perspective article we will discuss the recent data from the phase III MONALEESA-2 trial, which evaluated the addition of ribociclib with letrozole in the first line of treatment for patients with advanced HR-positive BC, and we will put the results in context with clinical data of other CDK 4/6 inhibitors. In addition, we will discuss future directions in the field.

Keywords: Breast cancer (BC); cyclin-dependent kinase inhibitors; palbociclib; abemaciclib; ribociclib

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Breast cancer (BC) is the most frequently diagnosed cancer and the most common cause of cancer death in women worldwide (1). Approximately 70% of these cancers are hormone receptor-positive (HR-positive), comprising those expressing estrogen receptors and/or progesterone receptors (2). Despite continuous medical progress, many patients diagnosed with early BC, especially those with node-positive disease, remain at high risk of recurrence and death from metastatic disease (3). Moreover, in the United States and Western Europe, 5% of women first diagnosed with BC present with *de novo* metastatic disease (4). Estrogen pathway blockade is a highly effective therapy initially for patients with HR-positive tumors, however, virtually all patients will develop resistance to endocrine therapy (*de novo* or acquired), and will ultimately die from metastatic disease (5). Therefore, understanding the underlying mechanisms related to endocrine therapy is vital and can eventually lead to new therapies for this population.

Currently, the most studied molecular alterations contributing to endocrine resistance have been (I) point mutations in the estrogen receptor 1 (*ESR1*) gene; (II) genomic alterations in the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway; and (III) genomic alterations in different components of the cyclin-dependent kinases (CDKs) 4 and 6/D-type-cyclin/retinoblastoma (Rb) tumor suppressor protein. While mutations in *ESR1* seem to be predominantly acquired following treatment with aromatase inhibitors (AI) (6,7), molecular alterations in the other two pathways are commonly deregulated in primary HR-positive BC (8). Based on strong preclinical data showing close interaction between these signaling pathways and ER signaling, several clinical trials have evaluated different agents targeting components of PI3K-AKT-

mTOR or CDK4/6 pathways in HR-positive/HER2-negative patients with advanced disease. These studies have led to the approval of new targeted therapies, the mTOR inhibitor everolimus (9) (Afinitor®, Novartis) and the CDK4/6 inhibitor palbociclib (10-12) (Ibrance®, Pfizer), used in combination with endocrine therapy for patients with advanced HR-positive/HER2-negative BC.

Hortobagyi *et al*. published the results of the MONALEESA-2 trial in the *New England Journal of Medicine* (13). This was a randomized, placebo-controlled, international and multicenter phase III trial that evaluated the efficacy and safety of the selective CDK4/6 inhibitor ribociclib combined with letrozole for first-line treatment in women with HR-positive/HER2-negative recurrent or metastatic BC who had not received previous systemic therapy for advanced disease. The trial randomized 668 patients in a 1:1 ratio stratified by the presence of liver and/or lung metastases. Approximately 94% of patients included in this trial had *de novo* metastatic disease or a disease-free interval (DFI) longer than 24 months, and 59% of patients had visceral disease. Patients received 600 mg of ribociclib daily (3 weeks on and 1 week off) or placebo, in combination with 2.5 mg of letrozole daily. The primary endpoint of the trial was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), clinical benefit rate, health-related quality of life, safety, and tolerability. After a preplanned interim analysis demonstrated superiority of the ribociclib plus letrozole arm, the Independent Data Monitoring Committee recommended stopping the trial early as it met the primary endpoint. The median PFS was significantly longer in the ribociclib group than in the placebo group (hazard ratio, 0.56; 95% CI, 0.43–0.72; P=3.29×10–6 for superiority). Moreover, in patients with measurable disease at baseline, the ORR in the ribociclib group compared to the placebo group was 52.7% and 37.1%, respectively (P<0.001). The most common grade 3 or 4 adverse events were neutropenia (59.3% in the ribociclib group *vs*. 0.9% in the placebo group) and leukopenia (21.0% *vs*. 0.6%); the rates of discontinuation due to adverse events were 7.5% and 2.1%, respectively. Nonetheless, neutropenia occurred mainly within the first 4 weeks of treatment and resulted in only five cases (1.5%) of febrile neutropenia in the ribociclib group. Grade 3 or 4 elevations in alanine and aspartate aminotransferase levels were also seen, and reported in 9.3% and 5.7%, respectively, of patients receiving ribociclib in this study. Importantly, the majority of these cases were isolated and asymptomatic, and reversible with dose adjustment.

The results of MONALEESA-2 have confirmed the striking benefit of adding CDK4/6 inhibition to first-line endocrine-therapy in patients with HR-positive/HER2-negative BC that had been previously demonstrated with the addition of palbociclib to letrozole in the PALOMA-2 trial. The magnitude of benefit in terms of PFS favoring the ribociclib arm was the same as with palbociclib in a similar population. Although both trials included a similar population overall, PALOMA-2 had more patients with a short DFI (≤12 months) (22.3% *vs*. 1.2% in MONALEESA-2), and fewer patients with visceral disease (48.2% *vs*. 59.0%). Both phase III trials confirmed the data of the phase II PALOMA-1 trial, which led to the accelerated Food and Drug Administration (FDA) approval of palbociclib in combination with letrozole in first-line setting for women with advanced HR-positive/HER2-negative BC. In addition, the FDA approved the use of palbociclib in combination with fulvestrant for the treatment of pre- and postmenopausal patients with advanced HR-positive/HER2-negative BC following progression to a previous line of endocrine therapy (12). Of note, accrual for the phase III trial MONALEESA-3 (NCT02422615), in which postmenopausal patients with advanced HR-positive/HER2-negative BC are randomized to receive fulvestrant with or without ribociclib in the first- or second-line setting, is complete and results are anticipated in 2017.

Abemaciclib is another CDK4/6 inhibitor in late clinical development (LY2835219; Lilly). Although the data from phase 3 clinical trials evaluating abemaciclib in first (MONARCH 3; NCT02246621) and second line (MONARCH 2; NCT02107703) are still pending, this agent has promising clinical activity in combination with endocrine therapy (14). Unlike ribociclib or palbociclib, abemaciclib demonstrated an impressive ORR of 19.7% (95% CI, 13.3–27.5%) as monotherapy in heavily pretreated patients with metastatic HR-positive BC (15). Although the reason for the higher monotherapy response rate compared to other CDK4/6 inhibitors is not clear, it may be related to greater potency for CDK4 inhibition, or may be due to it continuous administration, possibly driving senescence and ultimate tumor regression to a greater degree (16). While the toxicity profiles of ribociclib and palbociclib are similar to one another, with the most common toxicities being neutropenia and fatigue (10,13), abemaciclib has a different toxicity profile, with the most common toxicities being diarrhea and fatigue (15). The lower rate of neutropenia seen

with abemaciclib may be due to its greater selectivity for CDK4 compared to CDK6, as CDK6 inhibition is thought to contribute to the neutropenia seen with these agents.

While we do not yet have data for overall survival from these above mentioned clinical trials, the improvement doubling in progression free survival seen with the addition to CDK 4/6 inhibition to endocrine therapy represents a breakthrough in the treatment of patients with metastatic HR-positive BC. Given these compelling results and manageable toxicity profiles seen, the combination of an AI plus a CDK 4/6 inhibitor should be the standard first line treatment for the majority of patients with advanced HR-positive BC. However, there still remain several questions regarding the use of CDK 4/6 inhibitors in patients with advanced BC.

To date, besides estrogen receptor status, there is no other biomarker to predict response to CDK4/6 inhibitors. The search for predictive biomarkers of response and/or resistance to CDK4/6 inhibitors is of interest, especially due to the high costs associated with these agents, and the possibility of sparing patients from unnecessary toxicity. The phase II of the PALOMA-1 trial, which evaluated the role of palbociclib in postmenopausal women with advanced HR-positive BC, failed to demonstrate that *CCND1* amplification and loss of p16INK4A could be predictive of response to the drug (11).

Another important issue requiring evaluation is whether the benefit of CDK 4/6 inhibitors will will also apply in the early-stage setting. Currently, there are two randomized, multicenter, international ongoing phase III trials evaluating the role of adding palbociclib as adjuvant therapy for patients with early stage HR-positive BC: the Palbociclib Collaborative Adjuvant Study (PALLAS, NCT 02513394) was designed to recruit 4,600 patients with stage IIa–III disease and the primary endpoint is invasive disease-free survival in patients treated with palbociclib for 2 years; the PEBELOPE-B (NCT 01864746) trial was designed to accrue 1,100 women with residual invasive disease after neoadjuvant therapy and the primary endpoint is invasive disease-free survival in patients treated with palbociclib for 1 year.

Another unresolved question is whether or not there is any role for continuation of CDK 4/6 inhibition beyond progression. These agents rely on the presence of the Rb, and although this protein is infrequently lost in primary HR-positive tumors (17), recent data presented at the 2016 San Antonio Breast Cancer Symposium showed that this phenomenon might be more common as an acquired event during evolution of advanced disease (18). Currently several clinical trials are ongoing to evaluate utility of continuation of CDK 4/6 inhibition after progression (NCT02732119, NCT02632045, NCT02871791, NCT02684032).

Whether the use of CDK4/6 inhibitors can be expanded to other BC subtypes is a matter of investigation. Goel *et al*. demonstrated that cyclin D1/CDK4 is implicated in resistance to anti-HER2 therapy in HER2-positive BC (19). Using patient-derived xenograft models, the authors were able to show that CDK4/6 inhibitors resensitize breast tumors with acquired resistance to HER2-targeted therapies and delay tumor recurrence *in vivo*. In the clinical setting, an interesting 36% (95% CI, 10.9–69.2%) ORR was seen in patients with HR-positive/HER2-positive advanced BC treated with abemaciclib monotherapy in the phase I JPBA trial (14). Gianni *et al*. presented preliminary data from the phase II Michelangelo study, which evaluated the efficacy of neoadjuvant therapy with the combination of trastuzumab, pertuzumab, palbociclib and fulvestrant in patients with HR-positive/HER2-positive BC suitable for preoperative treatment (20). The combination resulted in a promising 27% of pathological complete response. There are several ongoing clinical trials evaluating the combination of different anti-HER2 agents with ribociclib (NCT02657343), abemaciclib (NCT02675231), or palbociclib (NCT02774681, NCT02448420, NCT01976169, NCT02947685).

In the triple-negative subgroup, although it is well known that Rb loss is more common, preclinical data have emerged in the subset of luminal-androgen receptor (LAR) tumors, suggesting that these tumors may benefit from CDK4/6 inhibition (21). The expression of the androgen receptor correlated with the sensitivity to these inhibitors. Based on this rationale, there is an ongoing phase I/II clinical trial evaluating the safety and effectiveness of palbociclib with the anti-androgen bicalutamide for the treatment of triple-negative, androgen receptor-positive BC (NCT02605486).

Preclinical and clinical data have shown that abemaciclib crosses the blood-brain barrier and prolongs survival in intracranial human brain tumor xenografts (22). Better treatment for brain metastases due to BC is an unmet need and currently, the ongoing phase II JPBO trial (NCT02308020) is evaluating the efficacy of abemaciclib in patients with HR-positive BC, non-small cell lung cancer, or melanoma with brain metastasis. In addition, there is an ongoing phase II trial evaluating the role of palbociclib in patients with brain metastasis from different primary tumors, including BC (NCT02896335).

Given the success of CDK4/6 inhibitors in breast oncology, another very important question that is raised is whether CDK inhibitors are effective in combination with other therapeutic modalities (16). The rationale for combining CDK inhibitors and PI3K/AKT-mTOR inhibitors is based on the fact that the expression of cyclin D1 is in part regulated by this pathway (23). Preclinical and clinical data have showed synergistic activity between PI3K inhibitors and CDK 4/6 inhibitors (24). Several ongoing clinical trials are evaluating triplet combination of CDK 4/6 inhibitors, endocrine therapy and PI3K/AKT-mTOR inhibitors (NCT02871791; NCT02684032; NCT02684032; NCT02732119; NCT01857193; NCT02057133). Additionally, there is interest in combining CDK 4/6 inhibitors with immune checkpoint inhibitors. Recently, data from the phase II, preoperative trial neoMONARCH (NCT02441946) suggested treatment with abemaciclib correlated with an increase in total T cells and a greater ratio of cytotoxic/suppressor T cells in tumor microenvironment (25). Based on these data, there is an ongoing clinical trial evaluating the combination of abemaciclib and pembrolizumab in HR-positive/HER-2 negative advanced BC (NCT02779751).

In conclusion, the clinical development of CDK4/6 inhibitors represents the most important therapeutic advance in HR-positive BC in recent years. Relying on the results of large phase III trials, we do believe the combination of an AI plus a CDK 4/6 inhibitor should be the standard first line treatment for most patients with advanced HR-positive BC. Importantly, ongoing clinical trials are investigating the role of this class of drugs in the adjuvant setting. Finally, further investigation is required to determine whether the continuation of CDK4/6 inhibition beyond progression has any clinical benefit, as well whether the combination of these drugs with other targeted agents and with immune checkpoint inhibitors will translate into additional benefit.

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