



Editorial to “Palbociclib and letrozole in advanced breast cancer”

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Palbociclib is a first-in-class inhibitor of cyclin-dependent kinases 4 and 6 (CDK4/6) that inhibits cell proliferation and DNA synthesis by preventing cell-cycle progression from G1 to S phase (1). In cell line models of ER-positive breast cancer, estrogen activates CDK4/6 via cyclin D1, resulting in hyperphosphorylation of retinoblastoma (Rb) gene product, which leads to entry of the cell cycle (2). Endocrine resistance has been shown to depend on cyclin D1 and CDK4/6 *in vitro*. Based on the impressive progression-free survival (PFS) found in the phase 2 study PALOMA-1 (3), palbociclib was granted accelerated approval in 2015 by the Food and Drug Administration (FDA) for treatment of estrogen-receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC).

Key results of PALOMA-2

PALOMA-2, is a double-blind, placebo-controlled, randomized phase 3 study of palbociclib plus aromatase inhibitor (AI) letrozole in women with ER-positive, HER2-negative ABC who had no prior treatment for advanced disease (4). Patients were randomized in a 2:1 ratio to received palbociclib plus letrozole or placebo plus letrozole. The primary end point was PFS. Secondary end points included overall survival (OS), objective response (OR), clinical benefit response (CBR) and safety.

The study successfully randomized 666 women within 17 months. Median duration of follow up was 23 months. The primary endpoint was met—the addition of palbociclib to letrozole, as compared with placebo-letrozole, increased the median PFS from 14.5 months [95% confidence interval (CI), 12.9 to 17.1] to 24.8 months (95% CI, 22.1 to not estimable) [hazard ratio (HR) 0.58, 95% CI, 0.46

to 0.72; $P < 0.001$]. The treatment efficacy was confirmed by a blinded independent review committee. Subgroup analyses of PFS according to study stratification factors and other baseline characteristics confirmed a consistent benefit across all subgroups evaluated (HR ranges, 0.35–0.67). In short, the benefit was seen irrespective of race, disease-free survival, visceral involvement, prior hormonal therapy, the type of recent hormonal therapy, or prior chemotherapy.

The rate of OR for all randomly assigned patients in palbociclib-letrozole group versus placebo-letrozole group was 42.1% (95% CI, 37.5 to 46.9) and 34.7% (95% CI, 28.4 to 41.3) (odds ratio 1.4, 95% CI, 0.98 to 2.01; $P = 0.06$), and among patients with measurable disease according to RECIST the corresponding rate of OR was 55.3% (95% CI, 49.9 to 60.7) and 44.4% (95% CI, 36.9 to 52.2) respectively (odds ratio 1.55, 95% CI, 1.05 to 2.28; $P = 0.03$). The rate of CBR among all patients randomized was 84.9% (95% CI, 81.2 to 88.1) for palbociclib-letrozole group and 70.3% (95% CI, 63.8 to 76.2) for placebo-letrozole group (odds ratio 2.39, 95% CI, 1.58 to 3.59; $P < 0.0010$). Similarly, in those with measurable disease, the rate of CBR in these two groups was 84.3% (95% CI, 80.0 to 88.0) and 70.8% (95% CI, 63.3 to 77.5) respectively (odds ratio 2.23, 95% CI, 1.39 to 3.56; $P < 0.001$).

The more common grade 3 or 4 adverse events (AEs) in the palbociclib-letrozole group were neutropenia (66%), leukopenia (25%), and anemia (5%). Febrile neutropenia occurred in 1.8% of patients in this group. Serious (grade 4) AEs of any cause occurred in 19.6% of patients in the palbociclib-letrozole group and 12.6% of patients in the placebo-letrozole group. Permanent treatment discontinuation due to AEs was 9.7% in the palbociclib-letrozole group and 5.9% in the placebo-letrozole group.

Discussion

PALOMA-2 showed superior efficacy for palbociclib plus letrozole in first line treatment of ER-positive HER2-negative ABC with an unprecedented PFS of 2 years. Subgroup analysis suggested all patients, including those with prior exposure to hormonal therapy or chemotherapy, derived benefit from this approach. This study confirms the important roles of CDK4/6 inhibition in the management of ER-positive HER2-negative ABC. CDK 4/6 inhibition in combination with hormonal therapy is clearly a new standard.

The results of PALOMA-2 echo those of PALOMA-1 that led to FDA approval. PALOMA-1 differs from PALOMA-2, besides being a phase 2 trial, in that it adopted a 1:1 randomization. There were also small differences in the subgroup analysis, such as inclusion of the newly diagnosed metastatic disease subgroup. Nevertheless, both studies showed significant survival benefit of palbociclib and similar toxicity profiles. Longer follow up is needed for the effect on overall survival.

Ribociclib is another CDK 4/6 inhibitor in clinical development. MONALEESA-2 is a double-blind, placebo-controlled, phase 3 study of ribociclib plus letrozole and mirrors PALOMA-2 for the target patient population (5). Patients were randomized 1:1 to ribociclib-letrozole or placebo-letrozole. The study, similar to PALOMA-2, demonstrated that the addition of ribociclib to letrozole significantly improved PFS giving a comparable HR of 0.56 for disease progression or death ($P < 0.001$), as well as a similar overall response rate. Of note, PALOMA-2 included more Asians than MONALEESA-2, and recruited 20% more patients who had endocrine resistance (DFS ≤ 12 months) at baseline. Although neutropenia and leukopenia were the most common AEs for both CDK 4/6 inhibitors and the rate of occurrence was similar in both trials, there were some differences in the toxicity profile worth noticing. It appeared that anemia, thrombocytopenia and possibly stomatitis were more common in patients receiving palbociclib-letrozole and most of these AEs were mild. On the other hand, elevated alanine aminotransferase and aspartate aminotransferase have been observed in patients given ribociclib-letrozole and grade 3 or 4 transaminitis could happen in up to 9% of these patients. Prolonged QTcF was also a concern for a small proportion of patients in MONALEESA-2. Although palbociclib and ribociclib have comparable spectrum of CDK activity (6), the minor disparities in their chemical structure might explain these differences in toxicity profile. The median

follow up time for MONALEESA-2 was only 15.3 months and more mature PFS data is awaited. The comparison between these two clinical trials is summarized in *Table 1*.

The major toxicity of palbociclib was neutropenia and it led to dose reduction in 29% of patients. Its significance wasn't discussed in this paper. PALOMA-3 is a study of palbociclib in combination with fulvestrant in patients who progressed on first line hormonal therapy (7). Detailed analysis showed that dose modification of palbociclib for grade 3 and 4 neutropenia had no adverse effect on PFS (8). PALAMO3 also demonstrated that the quality of life (QoL) among patients on palbociclib was better maintained than those given placebo. Together with a low frequency of febrile neutropenia, all these results supported palbociclib is a drug well tolerated.

AI has been the standard of care for first line treatment of patients with ER-positive HER2-negative ABC. Besides CDK 4/6 inhibitors, recently this standard is also challenged by another hormonal therapy fulvestrant. Fulvestrant is a selective ER degrader. In the phase 3 FALCON trial, patients given monthly injection of fulvestrant at 500 mg had significantly longer median PFS of 16.6 months (95% CI, 13.83 to 20.99) compared with those of 13.8 months (95% CI, 11.99 to 16.59) given oral anastrozole 1 mg daily (HR 0.797, 95% CI, 0.637 to 0.999; $P = 0.0486$) (9). This approach showed that the ceiling PFS ceiling of hormonal therapy could be stretched to 20 months in some patients.

With the emergence of new treatment options and increasing financial burden associated with them, the practical questions would be how to choose the first line hormonal therapy. Current guidelines lay the general clinical principle that treatment recommendation should be based on if the patient is naïve to endocrine therapy, the type of adjuvant therapy, length of disease free interval and if disease relapsing less than 12 months from the end of adjuvant AI (10,11). More updated and detailed guidelines are anticipated later this year in light of recent breakthrough findings.

At the age of personalized medicine, we would like study of predictive biomarkers could enlighten us on how to optimize treatment choice. Biomarkers studied for palbociclib include cyclin D1 amplification and p16 loss in PALOMA-1 (3), ER expression, Rb level, p16 loss, cyclin D1 amplification and Ki67 index in PALOMA-2 (12), as well as hormone-receptor expression level, *PIK3CA* mutation status, and plasma circulating tumor DNA *ESR1* mutation status in PALOMA-3 (13,14). Unfortunately, all these analyses were negative. A better understanding in biology of endocrine resistance and study of fresh biopsy at the time of disease recurrence or

Table 1 Comparison between PALOMA-2 and MONALEESA-2

Compared items	PALOMA-2	MONALEESA-2
CDK4/6 inhibitor	Palbociclib	Ribociclib
Sample size [#]	444 vs. 222	334 vs. 330
Median follow up (months)	23	15.3
Median PFS (months) [#]	24.8 vs. 14.5 (HR 0.58; P<0.001)	Not reached vs. 14.7(HR 0.56; P<0.001)
Overall response rate in patients with measurable disease [#]	55.3% vs. 44.4%	52.7% vs. 37.1%
Subgroup characteristics		
Asian	14.3%	7.6%
DFS ≤12 months	22.1%	2.1%
G3/4 AEs >5%		
All	75.7%	81.2%
Neutropenia	66.5%	59.3%
(Febrile neutropenia)	1.8%	1.5%
Leukopenia	24.8%	21.0%
Anemia	5.4%	1.2%
Elevated ALT	None reported	9.3% (all grade 15.6%)
Elevated AST	None reported	5.7% (all grade 15.0%)
Serious AEs of any cause	13.5%	15.0%
Other AEs showing difference pattern:		
Thrombocytopenia	15.5% (G3/4 1.6%)	None reported
Stomatitis	15.3% (G3/4 0.2%)	None reported
ECG changes		
QTcF >60 msec from baseline	None reported	2.7%
Average QTcF >480 msec	None reported	3.3%

[#], CDK4/6-letrozole vs. placebo-letrozole. PFS, progression-free survival; HR, hazard ratio; DFS, disease-free survival; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DFS, disease free survival; AEs, adverse events; ECG, electrocardiography; QTcF, QT interval corrected with Fridericia's formula.

progression might provide valuable insight in this field.

A proportion of patients given adjuvant hormonal therapy relapse eventually. The impressive response in metastatic setting and decent QoL data of palbociclib opens door for the development of this drug in adjuvant setting. A number of adjuvant trials for palbociclib are ongoing. PALLAS evaluates the outcome of adding 2 years of palbociclib to standard endocrine therapy (NCT02513394). PENELOPE-B studies the role of adding palbociclib to standard endocrine therapy in patients with high relapse risk after neoadjuvant chemotherapy (NCT01864746). These studies should also provide insights on tolerability of this drug in the healthy population.

Palbociclib is a first-in-class CDK 4/6 inhibitor in clinical use. It is a game changer for first line ER-positive HER2-

negative ABC and for patients with endocrine resistance. There is an unmet need for biomarker of response to guide management decision. Further studies on the benefit of continuing CDK 4/6 inhibitor beyond progression or optimal treatment strategy after resistance to CDK 4/6 inhibitor would also be needed.

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