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Mini Review

# Clinical Benefit with Palbociclib in Estrogen Receptor–Positive, Her2-Negative Metastatic Breast Cancer: New Concepts

**Morales S***

Hospital Arnau de Vilanova, Lleida, Calle Lleida 147, Alpicat 25110, Lleida, Spain

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## 1. Mini Review

The main objective in patients with MBC(Metastatic Breast Cancer) is the prolongation of survival as well as of improvements in time to progression and duration of response [1]. The most important advanced in the improvement of survival has been the development of specific biological agents targeting specific cell pathways in the different breast cancer subtypes [2].

Treatment with cyclin-dependent kinase 4/6 inhibitor in estrogen receptor-positive, HER2-negative metastatic breast cancer (luminal phenotype) has shown its efficacy based on an interesting mechanism of action through the suppression of the cyclin D pathway through the CDK4/6 inhibitors that acts as a modulator of hormonal activation. Growth of HR-positive breast cancer is dependent on cyclin-dependent kinases (CDK) 4 and 6 that promote progression from G1 to the S phase of the cell cycle. CDK inhibitors block the cyclin D1-CDK 4/6 complex, prevent RB protein phosphorylation, stop the cell cycle from progressing to the S phase, thereby preventing cancer cell proliferation [3].

The first CDK 4/6 inhibitor, palbociclib, received accelerated FDA approval in February 2015 based on phase II data from the PALOMA 1 trial [4]. This trial randomized women with no prior therapy for advanced breast cancer and no AI therapy within 12 months of randomization to letrozole alone or letrozole plus palbociclib. The combination therapy arm showed an improved in progression free survival (PFS) of 20.2 months compared to 10.2 months with letrozole alone (HR.49).

In the PALOMA 2 trial [5], a randomized phase III study evaluating the same study population as in PALOMA 1.666 postmenopausal women with ER-positive MBC were randomized (2:1) between letrozole and palbociclib versus letrozole and placebo. The combination therapy arm showed similar benefit to the phase II trial with a PFS of 24.7 months compared to 14.5 months in the single-agent letrozole arm (HR 0.58). There was a non-statistically significant improvement in OS.

The combination of palbociclib and fulvestrant was studied in the PALOMA 3 [6] trial in luminal MBC who progressed on prior endocrine therapy or chemotherapy for advanced breast cancer, or within 12 months of completing adjuvant hormonal therapy. Whereas an improvement in overall survival has been shown in the hormonosensitive subgroup (39 to 29 months. HR :0.72), the non-hormonosensitive subgroup has not shown this improvement (20 to 26,2 months. HR: 1,14).

In the PEARL trial that will be presented in the next SABCS 2019 congress; 10-13 December 2019 San Antonio, USA; do not find any survival advantage of palbociclib compared to capecitabine in patients whose disease progressed on aromatase inhibitors. We also analyzed a cohort of patients treated with hormonotherapy plus CDK4/6 inhibitors and shows a greater difference in the patients treated in first line (median disease free survival of 18 months) in contrast to second

***Corresponding Author (s):** Serafin Morales Murillo, Hospital Arnau de Vilanova, Lleida, Calle Lleida 147, Alpicat 25110, Lleida, Spain, Tel: 696729451, Email: serafin-morales01@gmail.com*



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lines (6 months). Data will be presented at ABC-5- Advanced Breast Cancer Fifth International Consensus Conference. 14-16 November 2019 Lisbon, Portugal.

So far, several studies have shown interesting results of biomarkers of response to inhibitors of CDK4/6 although they have not yet been used in clinical practice as determinants of resistance to these drugs although they show resistance to cyclin inhibitors, also continue to maintain a resistance to conventional hormonal treatment [7].

Preclinical studies have shown that cell lines resistant to pure anti-estrogens such as fulvestrant have an increase in the expression of CDK6 measured by immune histochemistry and the expression of CCND1, CDK4, CDK6, CDKN2A, and Rb in 2 models of MCF cell lines resistant to Fulvestrant measured by RT-PCR. In addition, it has also been shown that blocking the expression of CDK6 with cyclin inhibitors results in greater cell death with fulvestrant, showing the role of CDK6 in fulvestrant resistance [8]. This phenomenon has also been seen in metastatic breast cancer patients treated with fulvestrant, patients who had a high expression of CDK4/6 had a progression-free survival of 2.8 months versus 8 months for those with low expression [8].

Survival benefit has even been reported in patients previously treated with fulvestrant who, once again treated with the combination of fulvestrant + palbociclib, have shown a median progression-free survival of 6 months, similar to those who did not receive prior treatment with fulvestrant and greater than the 4 months that are reached in most of the series treated with fulvestrant in second line monotherapy [9].

Therefore, it seems that treatment with palbociclib does not work well in patients with hormonal resistance. This would go against the concept of the mechanism of action of cyclin inhibitors that do not behave as inhibitors of hormonal resistance but as enhancers of hormonal treatment in patients with hormonesensivity, which would justify their great effect in the first line of treatment.

In conclusion it will be very important to know the status of the hormonal sensitivity and if resistance mechanism induced in the second hormomotherapy line is mediated by cyclin activation or by another independent mechanism to improve the results of treatment with CDK4/6 inhibitors.

## Reference

1. Howlader N, Noone AM, Krapcho M et al. (eds). SEER cancer statistics review, 1975e2013. Bethesda, MD: National Cancer Institute. based on November 2015 SEER data submission, posted to the SEER web site, updated September 12, 2016, http://seer.cancer.gov/ csr/1975_2013/.

2. Kobayashi K, Ito Y, Matsuura M, Fukada I, Horii R, Takahashi S et al. Impact of immunohistological subtypeson the long-term prognosis of patients with metastatic breast cancer. Surg Today 2016; 46(7): 821-826.

3. Morikawa A, Henry NL. Palbociclib for the treatment of estrogen receptor–positive, HER2-negative metastatic breast cancer. Clin Cancer Res. 2015;21(16):3591-3596.

4. Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16(1):25-35.

5. Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375(20):1925-1936.

6. Turner NC, Slamon DJ, Ro J, Bondarenko I, Im SA, Masuda N et al. Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer.N Engl J Med. 2018;379(20):1926-1936.

7. Fang H, Huang D, Yang F, Guan X2. Potential biomarkers of CDK4/6 inhibitors in hormone receptor-positive advanced breast cancer. Breast Cancer Res Treat. 2018;68(2):287-297.

8. Alves CL, Elias D, Lyng M, Bak M, Kirkegaard T, Lykkesfeldt AE et al.High CDK6 Protects Cells from Fulvestrant-Mediated Apoptosis and is a Predictor of Resistance to Fulvestrant in Estrogen Receptor-Positive Metastatic Breast Cancer.Clin Cancer Res. 2016;22(22): 5514-5526.

9. Du Rusquec P, Palpacuer C, Campion L, Patsouris A, Augereau P, Gourmelon C et al. Efficacy of palbociclib plus fulvestrant after everolimus in hormone receptor-positive metastatic breast cancer. Breast Cancer Res Treat. 2018;68(2):559-566.