

## Original Article

### Efficacy of Palbociclib and Endocrine Treatment in Heavily Pretreated Hormone Receptor-positive Her2-negative Advanced Breast Cancer: Retrospective Multicenter Trial

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#### ABSTRACT

**Introduction:** The synthesis of CDK4/6 inhibitors with treatment of endocrine in start two series of treatment has been widely accepted as the standard for Estrogen (ER)-positive MBC (metastatic breast cancer) patients. In spite of, the activity of CDK4/6 inhibitors in MBC patients who had progressed despite receiving multiple lines of treatment is not well understood.

**Aim:** We aimed to report on the activity and safety of a CDK4/6 inhibitor (palbociclib) for patients who had failed at least three lines of treatment for ER+/ MBC.

**Study Design:** Multi-center retrospective observational cohort study

**Methods:** In this retrospective observational cohort study, we included 43 patients, whom were given palbociclib after at least 3 lines of systemic treatment for ER-positive/HER2-negative MBC.

**Results:** Overall, the median progression-free survival in our population was 7 months (25th percentile = 4, 75th percentile = 10) (Figure 1) and median overall survival was 11 months (25th percentile = 6, 75th percentile = 19). Although there were some adverse events, palbociclib was generally well tolerated, so dose reduction was needed for only 6 (14%) patients.

**Conclusion:** We demonstrated that the efficacy of palbociclib among heavily treated hormone receptor-positive/HER2-negative advanced BC patients was acceptable clinical benefit, and it was generally well tolerated among this population.

**Keywords:** Breast cancer, cdk4/6 inhibitors, palbociclib

Breast cancer (BC) is the by a majority cancer in women. Despite the numerous therapeutic options at our disposal, it still remains incurable, earning it the notorious reputation of being the second most common cause of cancer death in western population, following lung cancer (1). BC is a heterogeneous disease and it has variety of subgroups according to clinical, pathological and molecular features (2).

Approximately 80% of all BC cases are estrogen receptor-positive (ER+) /human epidermal growth factor receptor 2 negative (HER2-). According to current guidelines, sequential endocrine therapy (ET) is the main treatment recommendation for premenopausal and postmenopausal women with ER+/HER2- stage 4 BC (except for extensive visceral involvement) (3,4). Unfortunately, resistance to ET (acquired or de novo) will develop in the vast majority of these cases during therapy (5). Cyclin dependent kinases and mammalian target of rapamycin (mTOR) signaling pathways are the main mechanism of resistance to ET (6). Currently, the most commonly recommended therapeutic options to overcome ET resistance are mTOR inhibitor (everolimus) and CDK4/6 inhibitor (palbociclib, abemaciclib and ribociclib) (7-9).

Combination of CDK4/6 inhibitors with ET in start two series of treatment have been widely accepted as the standard treatment for ER+ MBC patients (10-12). However, the activity of CDK4/6 inhibitors in MBC patients progressing after multiple treatment lines is not well known. In this multi-center retrospective study we report on the activity and safety of a CDK4/6 inhibitor (palbociclib) for patients who had failed at least three lines of treatment for ER+/MBC.

### Methods

In this retrospective observational cohort study, between 14 September 2015 and 14 March 2019, we included 43 patients from different medical oncology clinics in Turkey. Clinic whom were given palbociclib after at least three lines of systemic treatment for ER+ and HER2-negative MBC (confirmed at diagnosis or on a metastatic lesion). Patients using fulvestrant or aromatase inhibitors with palbociclib were accepted for study. Initially defined date of first drug intake. All patients provided signed informed consent, and ethical approval was given by our ethical committee (Date: 12.09 2019, Number: 2019-14/34).

Main outcomes of this trial were overall survival (OS) and progression free survival (PFS). OS was determined from the date of initiation of therapy until death or last visit date. PFS was the time window between the beginning of treatment to radiological progression, death or last visit date. We also reported the frequency of adverse events related to therapy (neutropenia, anemia, thrombocytopenia, diarrhea etc...).

We included MBC patients whom progressed according to RECIST Criteria despite at least three lines of standard therapy. Our exclusion criteria were as follows; radiotherapy, surgery or systemic treatment with in two weeks, past medical history of cardiovascular disease (arrhythmias including atrial fibrillation, torsades de pointes, long or short QT interval, prior myocardial infarction, coronary artery bypass grafting, heart failure and pulmonary embolism), hypersensitivity of palbociclib and suicidal behavior.

### Statistical Analysis

The data was analyzed using descriptive statistical methods. Continuous variables are given in mean  $\pm$  standard deviation, whilst categorical variables are given in percentages. Kaplan Meier curves were performed to determine overall survival and progression free-survival. SPSS v.21 was used to analyze the data and generate graphical content.

### Results

The median age of patients was 51 (25<sup>th</sup> percentile 44, 75<sup>th</sup> percentile 58) years. All patients were diagnosed with mBC and 30 (69.7%) patients were initially stage I-III. All of them were ER positive and five (11.6%) ER positive/PR negative. The vast the greater part of our patients were pathologically classified as having invasive ductal carcinoma (n=41, 95.3%). All patients were given at least three lines of treatment for mBC, including chemotherapy and endocrine therapy (ET). For most of the patients adjuvant ET was tamoxifen (n=19, 44.1%), other combinations were as follows; letrozole (n=6, 13.9%) and anastrozole (n=3, 6.9%). Five patients (11.6%) had received both a steroidal and a nonsteroidal AI. Fulvestrant was used in 39.5% (n = 17) patients before palbociclib/AI. Twenty-one premenopausal women had undergone surgical or medical castration as part of combination HT. Only one patient had been treated with the exemestane/everolimus combination. Most of our patients (55%; n = 23) had received sequential mono chemotherapy with standard drugs including taxanes, capecitabine, gemcitabine and anthracyclines, while a small minority had received combination chemotherapy regimens such as capecitabine/docetaxel (XT), fluorouracil, doxorubicin and cyclophosphamide (FAC) or doxorubicin/docetaxel (AT) or a combination of both approaches. The baseline characteristics of patients in the study cohort were outlined in Table 1.

According to RECIST criteria; No complete response was observed. There were partial response (PR) in six patients (13.9%), stable disease (SD) in 28 patients (65.1%) and progressive disease (PD) in 9 (21%) patients. The disease control rate was 79% and the objective response rate was 13.9%. The median PFS in our population was 7 months (25<sup>th</sup> percentile=4, 75<sup>th</sup> percentile= 10) (Figure 1), and the median overall survival was 11 months

(25<sup>th</sup> percentile=6, 75<sup>th</sup> percentile= 19) (Figure 2). All deaths in our study cohort were associated with disease progression.

Although there were some side effects, palbociclib was generally well tolerated, as a result, dose reduction was needed for only 6 (14%) patients. The most common non-hematological side effect was nausea (n=30, 69.7%). Elevated transaminases levels were also frequent (n=25, 58.1%). Grade 3 neutropenia occurred in 12 (27.9%) patients and febrile neutropenia was seen in 2 (4%) patients (Table 2).

### Discussion

CDK4/6 inhibitors critical step in the abolishment of ET resistance among ER-positive, HER2-negative patients. Many Phase II and III clinical trials have been carried out to investigate the efficacy and safety of CDK4/6 inhibitors among this population (8-11). In the PALOMA-1 trial, the median PFS was 20.2 months in letrozole/palbociclib arm whereas 10.2 months in the letrozole/placebo arm (HR: 0.488; 95% CI: 0.319–310.748; p = 0.0004) (13). Similarly, in the PALOMA-2 trial, median PFS was 24.8 months in palbociclib/letrozole arm and 14.5 months in letrozole/placebo arm (HR: 0.58; 95% CI: 0.46–40.72; p < 0.001) (14). PALOMA-3 trial was performed to find out the efficacy of palbociclib and fulvestrant combination among 521 HR+/-mBC patients as second line treatment option. Palbociclib-fulvestrant combination improved PFS significantly compared to placebo-fulvestrant arm (9.2 vs 3.8 months, p <0.001) (9). Another CDK4/6 inhibitor abemaciclib was also tested in second line treatment in MONARCH 2 trial. The results were promising, abemaciclib/fulvestrant combination prolonged PFS significantly (median PFS; 16.4 vs 9.3 months, p=0.001) (11).

In spite of the efficiency and reliance of CDK4/6 inhibitors were well investigated among ER-positive, HER2-negative patients, there are no large number of phase 3 studies showing efficacy after treatment. Ban et al. published a retrospective analysis of 24 heavily pre-treated ER+/HER2- mBC patients. All patients in their trial received a minimum of four lines of treatment for mBC including chemotherapy and ET. They reported that 58.3% of patients achieved stable disease and median progression-free survival was 4.8 months; median overall survival was 11 months. They reported that grade III neutropenia occurred in 54.1% (n = 13) patients, grade IV neutropenia in 12.5% (n = 3) of patients and grade III thrombocytopenia in 12.5% (n = 3) of patients. The most commonly reported treatment-related nonhematologic adverse events were nausea (12.5%; n = 3). These side effects were consistent with our trial. (15). In our trial, we achieved more stable patients compared to this trial (65.1% vs 58.3) and our PFS was a bit longer (7 vs 4.8 months) which may be explained by the use different of treatment lines between trials (min. 3 lines vs min. 4 lines) but the overall survival was similar with our study. A recent retrospective analysis also aimed to investigate the role of palbociclib among heavily treated (more than 4 previous CT lines) mBC patients. They reported the utility of palbociclib among 118 HR positive HER2-negative advanced breast cancer patients. Clinical benefit rate was 47.5%, overall response rate 15.8%, median PFS 4.5 months and median OS 15.8 months. In terms of therapeutic efficacy PFS and response rates were comparable with our results but our results were again favorable. Hematological side effects were consistent with our trial; 89.7% developed neutropenia (grade ≥ 3 in 56.8%), 5.1% experienced febrile neutropenia. However, dose reductions and discontinuation rates were higher in that trial compared to our trial; 48.3% had dose decreases after side effects and 3.4% had palbociclib discontinued due to toxicity. (16).

In summary; our trial adds important information about the use of palbociclib among highly treated HR positive HER2-negative advanced breast cancer patients for literature. We demonstrated a comparable PFS and OS rates among advanced patients in a real life trial, and palbociclib was well tolerated among such a severe patient population except for febrile neutropenia. Main limitation of our study is its retrospective nature and relatively small number of patients. Additionally, we only determined progression free survival and overall survival so we could not get any information about quality of life measures.

### Conclusion

We demonstrated that the efficacy of palbociclib among heavily treated HR positive HER2-negative advanced breast cancer patients were comparable and it was generally well tolerated among this population. But, further randomized controlled studies with larger number patients are needed to confirm our findings and define patients who may benefit even in late stage disease.

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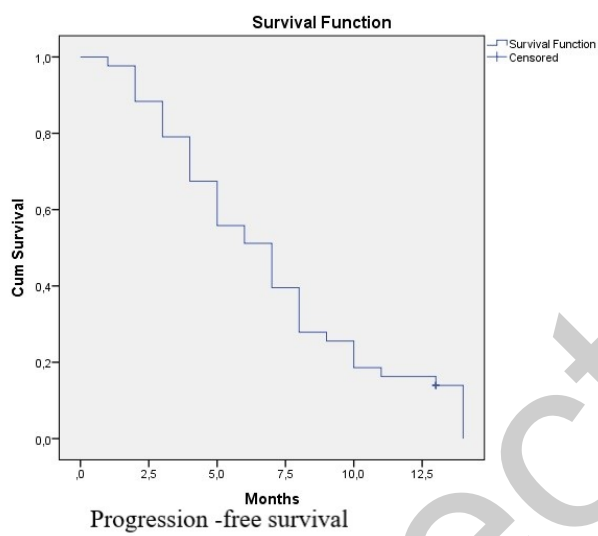
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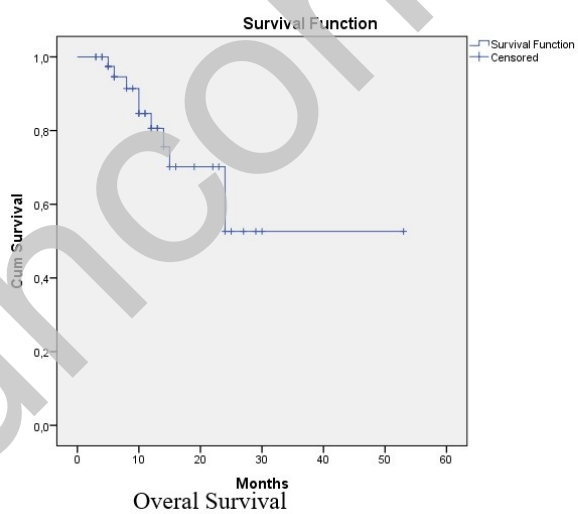
**TABLE 1.** Baseline characteristics of patients in the study cohort

Age (years) (25 <sup>th</sup> percentile-75 <sup>th</sup> percentile)	51 (44-58)
Hormone receptor status	
-ER +/PR+	n=38 (88.3%)
-ER+/PR-	n=5 (11.6%)
Histological diagnosis	
-Ductal invasive	n=41 (95.3%)
-Lobular invasive	n=2 (4.6%)
Stage of disease	
-Stage I-III	n=30 (69.7%)
-Stage IV	n=13 (30.3%)
Menopausal status (post-menopausal patients )	n=22 (51.1%)
Adjuvant endocrine therapy	
-Tamoxifene	n=19 (44.1%)
-Letrozole	n=6 (13.9%)
-Anstrazole	n=3 (6.9%)
Site of metastasis	
-Bone	n=11 (25.6%)
-Visceral	n=27 (62.8%)
-Brain	n=5 (11.6%)

<b>TABLE 2.</b> Adverse events during palbociclib treatment	
Elevated transaminases	25 (58.1%)
Any neutropenia	12 (27.9%)
Febrile neutropenia	2 (4%)
Nausea any grade	30 (69.7%)
Dose reduction due to side effects	6 (14%)



**FIG. 1.** Progression-free survival graphic by Kaplan–Meier curve



**FIG. 2.** Overall survival graphic by Kaplan–Meier curve