

Original Article

## Outcome in patients of hormone receptor (HR) positive (Her 2) negative metastatic breast cancer treated with palbociclib – A real-world experience

Ajay Bapna<sup>1</sup>, A. Samar<sup>1</sup>, Pulkit Nag<sup>1</sup>, Sanjeev Patni<sup>2</sup>, Nidhi Patni<sup>3</sup>

<sup>1</sup>Department of Medical Oncology, Bhagwan Mahaveer Cancer Hospital, <sup>2</sup>Department of Surgical Oncology, Bhagwan Mahaveer Cancer Hospital & Research Centre, Bhagwan Mahaveer Cancer Hospital, <sup>3</sup>Department of Clinical and Radiation Oncology, Bhagwan Mahaveer Cancer Hospital & Research Centre, Jaipur, Rajasthan, India.



**\*Corresponding author:**

Ajay Bapna,  
Department of Medical  
Oncology, Bhagwan Mahaveer  
Cancer Hospital, Jaipur,  
Rajasthan, India.

drabapna@yahoo.com

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### ABSTRACT

**Objectives:** We present real-world outcome with the use of palbociclib in patients with HR-positive Her2-negative breast cancer treated at single center in India.

**Material and Methods:** We conducted a medical audit of consecutive patients with HR-positive Her2-negative metastatic breast cancer, who were treated with palbociclib at our center between November 2016 and May 2020. Palbociclib was commenced at a dose of 125 mg orally once daily and a schedule of 21 days on therapy followed by 7 days off therapy was followed. Survival analysis included the Kaplan–Meier method using Statistical Package for the Social Sciences software (Version 26). HRs were calculated using Cox proportional hazard regression models and 95% confidence intervals (CIs) for the incidence estimates.

**Results:** A total of 67 female patients were commenced on treatment with palbociclib between November 2016 and May 2020. The median age was 55 years (range 29–78 years). A total of 51 (76%) of these patients were postmenopausal and the remaining 16 were premenopausal. Baseline metastatic disease involved one organ/site in 23 (34%), two organs/sites in 32 (48%), three or more in 12 (18%). Bony metastasis alone was seen in 17 (25%) patients, visceral alone in 30 (45%), and the remaining 20 had both bony and visceral metastases. For these 67 patients, palbociclib was commenced as 1<sup>st</sup> line systemic therapy in 24 (36%) cases. Amongst the remaining 43 cases, it was 2<sup>nd</sup> line in 21 (31%); 3<sup>rd</sup> line and beyond in 22 (33%). Median PFS was 16.1 months (95% CI: 9.6–22.8) and median OS was 20.7 months (95% CI: 14.1–27.3). Median PFS for palbociclib use in first line was 18.7 months (95% CI: 4.6–32.9) while in subsequent lines, it was 13.8 months (95% CI: 9.8–17.9; log-rank  $P = 0.228$ ). Median OS in patients who received palbociclib in first line was 23.2 months (95% CI 20.1–26.3) and for those who received it in subsequent lines was 16.3 months (95% CI: 12.5–20.1;  $P = 0.069$ ). In total population, best response on imaging was CR in 11 (16%) cases (06 in 1<sup>st</sup> line setting and 05 in subsequent line setting); PR in 33 (49%); SD in 03; and progressive disease in 20. Median PFS with bone only metastasis: 20.9 months (95% CI: 5.9–36.0), while with visceral metastasis 16.1 months (95% CI: 9.8–22.5;  $P = 0.537$ ). Median OS with bone only metastasis: 22.7 months (95% CI: 17.8–27.5), while with visceral metastasis, it was 18.5 months (95% CI: 13.6–23.4;  $P = 0.314$ ).

**Conclusion:** Palbociclib is a useful addition in the management of HR +ve Her2 –ve breast cancer patients. Its benefit is confirmed in our real-world setting, both in the first and subsequent lines of therapy and the data are on similar lines as the global real-world data on palbociclib effectiveness.

**Keywords:** Overall survival, Progression-free survival, India, Patient assistance program, Cost benefit, Quality of life, Hormone receptor positive, her2 negative

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## INTRODUCTION

Palbociclib has been the first cyclin-dependent kinase 4/6 inhibitor that became available for use in patients with breast cancer.<sup>[1]</sup> It is now approved for use in all patients with hormone receptor (HR)-positive and human epidermal growth factor receptor 2(Her2)-negative metastatic tumors in combination with aromatase inhibitor (this combination as initial endocrine therapy in MBC patients) or fulvestrant (in patients progressed on prior endocrine therapy). Trials have shown that progression-free survival (PFS) is usually improved by 6–12 months with palbociclib.<sup>[2]</sup> Our objective was to evaluate the real-world outcome with the use of palbociclib in patients with HR-positive Her2-negative breast cancer treated at our center.

## MATERIAL AND METHODS

This is a medical audit of all consecutive patients with breast cancer who were treated with palbociclib at our center between November 2016 and May 2020. Data were collected up to December 31, 2020. Palbociclib was commenced at a dose of 125 mg orally once daily. A schedule of 21 days on therapy followed by 7 days off therapy was followed. Patients were regularly evaluated clinically and with imaging scans as per hospital policy. Prospectively collected data regarding duration of treatment, best response (as per RECIST criteria), additional therapy, adverse events, dose modifications, and status at last follow-up were analyzed. Survival analysis included the Kaplan–Meier method using Statistical Package for the Social Sciences software (Version 26). Hazard ratios (HRs) were calculated using Cox proportional hazard regression models and 95% confidence intervals (CIs) for the incidence estimates.<sup>[3]</sup> All *P*-values are two sided.

## RESULTS

A total of 67 female patients were commenced on treatment with palbociclib between November 2016 and May 2020. The median age was 55 years (range 29–78 years). A total of 51 (76%) of these patients were postmenopausal and the remaining 16 were premenopausal. ECOG performance status was 1 in 42, was 2 in 24, and 3 in one patient at the start of treatment. The breast primary tumor was on the left side in 31 cases, right side in 35 cases, and one patient had bilateral breast cancer. Baseline metastatic disease involved one organ/site in 23 (34%), two organs/sites in 32 (48%), three in 11, and one patient had

involvement of five organs. Bony metastasis alone was seen in 17 (25%) patients, visceral alone in 30 (45%), and the remaining 20 had both bony and visceral metastases. Details of previous cancer directed systemic therapy are shown in [Table 1]. Median duration of hormone therapy was 6 months. Previous hormone therapy included anastrozole (five in adjuvant setting and four in metastatic setting), letrozole (six in adjuvant setting and two in metastatic setting), exemestane (nine in adjuvant setting and five in metastatic setting), tamoxifen (eight in adjuvant setting and one in metastatic disease), and fulvestrant (one in metastatic setting).

For these 67 patients, palbociclib was commenced as 1<sup>st</sup> line systemic therapy in 24 (36%) cases. Amongst the remaining 43 cases, it was 2<sup>nd</sup> line in 21 (31%); 3<sup>rd</sup> line in 16 (24%); and 4<sup>th</sup> line in 6 (9%). Median PFS for palbociclib use in first line was 18.7 months (95% CI: 4.6–32.9) while in subsequent lines, it was 13.8 months (95% CI: 9.8–17.9; log-rank *P* = 0.228). Median OS in patients who received palbociclib in first line was 23.2 months (95% CI 20.1–26.3) and for those who received it in subsequent lines was 16.3 months (95% CI: 12.5–20.1; *P* = 0.069).

Duration of treatment with palbociclib ranged from 1 to 44 months [median 9 months; Table 2]. Of these, 15 patients received it for 4 months or less, 10 due to progressive disease (PD), and 5 due to adverse drug reactions (ADR). In the first-line setting, four patients received it for 4 months or less, two each due to PD and ADR. At last follow-up, palbociclib treatment was ongoing in 25 cases (11/25 were receiving palbociclib in 1<sup>st</sup> line setting). Best response on imaging was CR in 11 cases (6 in 1<sup>st</sup> line setting and 5 in subsequent line setting); PR in 33; SD in 03; and PD in 20.

While on palbociclib, additional treatment received by the patients included injection zoledronic acid in 41 patients; inj. fulvestrant in 31 cases; tab. letrozole in 35 patients; tab. exemestane in 1 case; inj. leuprolide in 1 patient; and inj. denosumab in 1 case.

The overall survival (OS) and PFS are shown in [Figure 1]. Median PFS was 16.1 months (95% CI: 9.6–22.8) and median OS was 20.7 months (95% CI: 14.1–27.3).

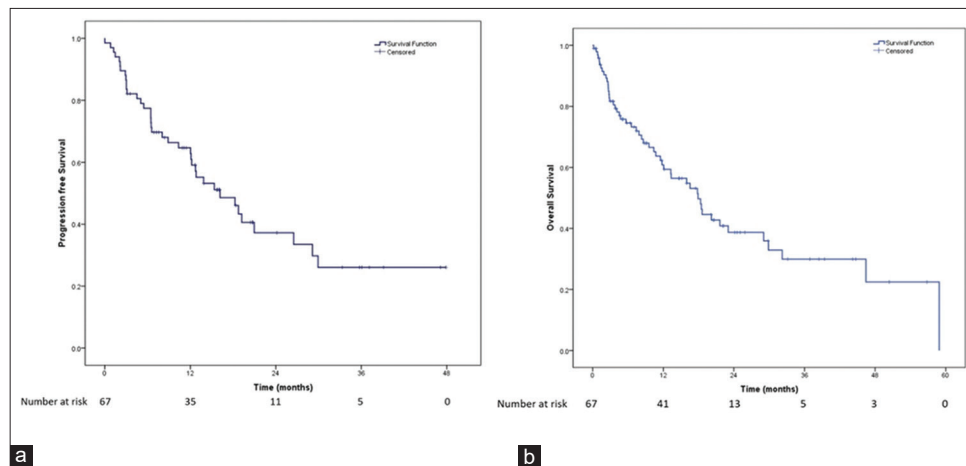
Median PFS with bone only metastasis: 20.9 months (95% CI: 5.9–36.0), while with visceral metastasis 16.1 months (95% CI: 9.8–22.5; *P* = 0.537). Median OS with bone only metastasis: 22.7 months (95% CI: 17.8–27.5), while with visceral metastasis, it was 18.5 months (95% CI: 13.6–23.4; *P* = 0.314).

**Table 1:** Previous systemic therapy (before commencement of palbociclib).

Previous adjuvant systemic therapy		Previous systemic therapy for metastatic disease	
Hormonal therapy	Chemotherapy	Hormonal therapy	Chemotherapy
28/67 (42%)	31/67 (46%)	13/67 (19%)	14/67 (21%)

**Table 2:** Palbociclib treatment and outcome.

	All cases	1 <sup>st</sup> line use	Subsequent line use
<i>n</i>	67	24 (36%)	43 (64%)
Duration of Rx in months– range (Median)	1–44 (9) months	1–44 (13) months	1–42 (8) months
Rx for <4 months	15 (22%)	04 (17%)	11 (26%)
Rx ongoing at last follow-up	25	11	14
Best response (imaging – RECIST criteria)			
CR	11	06	05
PR	33	12	21
SD	03	02	01
PD	20	04	16
ADRs			
Total (all neutropenia)	10	05	05
Grade 2	02	02	00
Grade 3	07	03	04
Grade 4	01	00	01
Treatment interruption (1 month in all cases)	10	04	06
Restarting dose			
75 mg	02	00	02
100 mg	01	01	00
125 mg	06	03	03
Not restarted (due to PD)	01	00	01



**Figure 1:** Survival of breast cancer patients treated with palbociclib. (a) Progression-free survival of the patients receiving palbociclib. (b) Overall survival of the patients receiving palbociclib.

Median PFS in patients with PS 1 was 18.7 months (95% CI 11.9–25.5) while it was 12.7 months (95% CI 7.1–18.2) in patients with PS 2 ( $P = 0.324$ ). Median OS in patients with PS 1 was 22.1 months (95% CI 15.7–28.4) while it was 16.4 months (95% CI 9.4–23.4) in patients with PS 2 ( $P = 0.256$ ).

The only ADR documented was neutropenia. It was self-limiting and recovered in all patients. Its grade is mentioned in the table. As a result of these ADRs, 10 patients required interruption of treatment with palbociclib for 1 month. The drug was reintroduced at lower doses in five patients,

as shown in [Table 2]. In one patient, palbociclib was not restarted because she developed PD.

## DISCUSSION

The selective CDK 4/6 inhibitor, palbociclib was approved for use in India since October 2016.<sup>[4]</sup> It is commonly used in combination with letrozole (now aromatase inhibitors) or fulvestrant as first or subsequent lines of therapy in hormone receptor-positive and Her 2-negative metastatic breast cancer. Our medical audit of 67 consecutive patients treated with palbociclib at a single center from November 2016 to

May 2020 represents robust real-world data from India. For the whole group, the median PFS was 16.1 months and median OS was 20.7 months. It was used as 1<sup>st</sup> line therapy amongst 24 of our patients, in whom the median PFS was 18.7 months and median OS was 23.2 months. Interestingly, the best response on imaging was CR in 11 cases, of which five patients had received palbociclib as subsequent line of therapy. Median duration of treatment was 9 months (range 1–44 months). Our median PFS was 16.1 months and median OS was 20.7 months. This translates into better quality of life and postponement of need for chemotherapy.<sup>[5]</sup>

The PFS and toxicity analysis results are consistent with other reports of routine clinical practice, that is, real-world evidence from India and other countries and the global clinical trials.<sup>[6-17]</sup> The observed OS is lower than reported in real-world studies and clinical trials. Our analysis suggests that patients who were less heavily pre-treated had better outcomes. Our population was mainly in second or later lines (64%), probably contributing to the low OS.

Palbociclib was tolerated well in our patient population with neutropenia as the major adverse event. About 15% of patients required drug interruption, 7.5% dose reduction, but no patient required drug discontinuation. The safety profile of palbociclib was consistent with that seen in clinical practice and trials in India and other countries.<sup>[6,10-12,15,16]</sup>

The major limitation of our study is its retrospective nature as that introduces a potential bias in patient selection, also it being a single-institutional single-arm study with a small sample size.

Use of palbociclib in second or later lines is associated with shorter duration of use, and hence, lower cost compared to use in first line, if the patients are not covered by health insurance and have to spend money for treatment. However, the global guidelines recommend use of palbociclib and other CDK 4/6 inhibitors as initial line of therapy for optimum benefit. To aid this, organizations like Pfizer have introduced patient assistance programs to lessen the economic impact for patients receiving these drugs in approved indications.

There is a further need to evaluate the quality of life of patients being treated with palbociclib in clinical practice, impact of biomarkers on the patient prognosis, and the mechanisms of resistance to CDK 4/6 inhibitors, requiring further studies in Indian population.

## CONCLUSION

Palbociclib has a place in the management of HR +ve/ Her2 – ve breast cancer patients.<sup>[18]</sup> Subsets of patients that can potentially benefit have been confirmed in our real-world setting, both in the first and subsequent lines of therapy.<sup>[19,20]</sup> Adverse events seen in our patients are similar to those reported in literature and we did not see any new safety red flags.

## Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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