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Original Article

Clinical Benefit and Safety of Palbociclib in Hormone Positive Breast Cancer with Visceral Metastasis: Real-World Experience from a Tertiary Cancer Center

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Abstract

Introduction Palbociclib, the first CDK4/6 inhibitor, has shown promising results in phase III clinical studies by enhancing the efficacy of endocrine therapy (ET) in HR +/ HER2– advanced breast cancer. However, real-world data on its use in patients with visceral metastatic disease are limited. We aimed to assess the effectiveness and tolerability of palbociclib in this high-risk population across different lines of treatment.

Materials and Methods Patients with hormone-positive metastatic breast cancer who received palbociclib with ET between 2015 and 2021 were grouped into skeletal and visceral metastatic disease. Visceral metastatic diseases were subclassified into lung, liver, and brain metastatic diseases. All subgroups were analyzed for progression-free survival (PFS), toxicity, and prognostic factors. Subgroups were compared using the chi-square test, and survival analyses were done using the Kaplan–Meier test.

Results Among 100 patients who received palbociclib, 70 had progressed on previous ET. The common metastatic site was bone (56%), followed by lung (24%), liver (18%), and brain (2%). With a median follow-up of 37 months, the median PFS of the overall population was 24 months: bone metastasis 27 months, lung 25 months, liver 12 months, and brain 4 months. Weak hormone positivity, ET-resistant metastatic patients, and high grade were associated with poorer responses. The common side effects were neutropenia (40%), anemia (35%), thrombocytopenia (15%), and hepatotoxicity (10%). Three percent of patients discontinued treatment due to toxicity.

Conclusion Palbociclib with ET showed improved PFS and safety in visceral metastatic disease, comparable to randomized controlled trials. However, further studies are required to evaluate its efficacy in extensive visceral metastatic disease and previously heavily treated patients.

Keywords
- CDK4/6 inhibitors
- palbociclib
- visceral metastatic breast cancer
- metastatic hormone-positive breast cancer

Introduction

Breast cancer is the most commonly observed cancer (13.5% of total cases) and the leading cause of cancer death (10.6% of total cases) in India, contributing significantly to the cancer burden.[1] Hormone receptor-positive subtypes are the most common, both in India and worldwide, with an incidence in India ranging from 25 to 60%.[2–4]

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The pathogenesis in the hormone receptor-positive subgroup is driven by estradiol through the estrogen receptor/progesterone receptor (ER/PR) pathway.[5] These subgroups are considered prognostically better; hence, hormonal agents are the treatment of choice in metastatic breast cancer (MBC) unless the patient has a visceral crisis or progressive visceral metastasis.[6,7]

Six years have elapsed since the first cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitor was approved for use in ER+ breast cancer. Its effectiveness and safety when paired with endocrine therapy (ET) have been established through numerous randomized trials, making it the preferred first-line treatment for the majority of patients[8]

Palbociclib, a first-in-class, selective inhibitor of CDK4/6, when combined with ET, results in synergistic effects. These findings led to the design of clinical studies in which the addition of palbociclib to ET resulted in significantly improved progression-free survival (PFS) in both previously treated (PALOMA-3)[9] and treatment-naive (PALOMA-1 and -2)[8,10] women with HR +/HER2– advanced breast cancer.

The real-world experience of patients with visceral metastatic disease, prognostic factors, and tolerance of this drug in the first, second, and subsequent lines is limited. It is crucial to consider the potential outcomes and risks for patients with visceral organ metastases, who are at high risk, when exploring new treatment options.

In our study, we analyzed the real-world efficacy and tolerance of palbociclib across different subgroups and treatment lines among HR+ patients with MBC affecting visceral organs.

Materials and Methods

Objectives

Evaluate real-world data for PFS and objective response rate palbociclib in HR + ve MBC with visceral metastatic disease. Tolerance and toxicity of palbociclib in visceral metastatic disease. Compare with the randomized controlled trial (RCT) and other real-world evidence.

Methods

In our present retrospective single-institutional observational study, after obtaining ethical committee approval, we documented clinical, demographic, and tumor-related information, as well as treatment-related toxicity details of patients with hormone-positive HER2 negative MBC who received palbociclib in combination with ET between 2015 and 2021. Patients with a minimum of 2 years of follow-up were analyzed for PFS. Patients were grouped into skeletal and visceral metastatic disease. Visceral metastatic diseases were subclassified into lung, liver, and brain metastatic diseases, while all subgroups were assessed for PFS, toxicity, and prognostic factors.

Primary outcome: Median PFS of HR+ MBC patients treated with palbociclib and ET, stratified by metastatic site (skeletal vs. visceral) and further subclassified into lung, liver, and brain metastases.

Secondary outcomes: Prognostic factors influencing treatment response, including hormone receptor status, ET menopausal status, different lines of palbociclib use, and tumor grade. Evaluation of the safety profile of palbociclib in real-world clinical practice, focusing on the incidence of toxicities, dose reduction, and treatment discontinuation due to toxicity.

Comparison of PFS between different subgroups using the chi-square test and survival analysis with the Kaplan–Meier method.

Assessment of the overall clinical benefit and safety of palbociclib in HR+ MBC with visceral metastasis, including its comparability to results from RCTs.

Inclusion criteria: Hormone receptor-positive MBC patients who have been treated with palbociclib in combination with ET between 2015 and 2021.

Exclusion criteria: Patients with severe comorbidities, those lost to follow-up, individuals who discontinued palbociclib for reasons other than disease progression or intolerance, those with multiple malignancies, and individuals experiencing visceral crisis.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20. All subgroups were analyzed for PFS, toxicity, and prognostic factors. Subgroups were compared using the chi-square test. Survival times and rates were evaluated with the Kaplan–Meier method. Median overall survival (OS) was calculated from the day of starting palbociclib. Factors affecting the treatment results were evaluated using log-rank and Cox regression tests. A *p*-value of less than 0.05 was considered statistically significant.

Ethics

In accordance with the ethical principles outlined in the Declaration of Helsinki, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Institutional Ethical Committee Sri Shankara Cancer Hospital and Research Centre IEC approval no: SSRHRC/IEC16/131; Date of approval: 12-11-2022.

Results

Patient Demographic Details

A total of 100 patients who received palbociclib between 2016 and 2021 were analyzed, with a median follow-up duration of 37 months. The median age of the population was 56 years. Among these patients, 24% were premenopausal, 30% had progressed on previous hormonal therapy, and 70% had metastatic disease without prior hormonal therapy at presentation. Fifty-six percent of the patients had only skeletal metastasis, while 44% had visceral metastasis, with no patients experiencing a visceral crisis. Specifically, 24% had lung metastasis, 18% had liver metastasis, and 2% had brain metastasis (►**Table 1**).

Table 1 Patients' demographic details

CDK4/6 inhibitors	Palbociclib	Percentage
Age group		
> 60	43	43
50–59	33	33
40–49	15	15
< 40	9	9
Menstruation		
Premenopause	24	24
Postmenopause	76	76
Presentation		
ET resistant	30	30
De novo metastasis	70	70
Metastatic sites		
Skeletal	56	56
Visceral metastasis	44	44

Abbreviation: ET, endocrine therapy.

Table 2 Tumor-related factors

CDK4/6 inhibitors	Palbociclib
Histopathology	
Intraductal	86
Lobular	8
Other	6
Grade	
1	8
2	56
3	36
Hormone status	
Strong positive	67
Weak positive	33
HER 2NEU	
Negative	89
Low expression	10
Positive	1
KI-67%	
< 15%	26
15–29%	22
> 30	52

Tumor-Related Factors

The most common histology was intraductal carcinoma (86%), with grade 2 being the most common grade. Sixty-seven percent of patients had strong hormone receptor positivity, and 10% had low HER2 positivity. Based on Ki-67% expression, 52% of patients had > 30% expression, 22% had 15 to 29% expression, and 26% had < 15% expression. One patient had triple-positive disease with HER2 positivity confirmed by fluorescence in situ hybridization testing in a repeat biopsy after progression, but clinically behaved like hormone receptor-positive disease. After discussion in the tumor board, this patient received treatment with palbociclib (►**Table 2**).

Treatment-Related Factors

Fifty-one percent of patients received CDK4/6 inhibitors in the first line, 37% in the second line, and 12% in the third line or subsequent lines. Fifty-eight percent of patients received CDK4/6 inhibitors with aromatase inhibitors, while 42% received them with fulvestrant. Twenty-five percent of patients required a first dose reduction, 8% required a second dose modification, and 3% discontinued CDK4/6 inhibitors due to toxicities. The most common grade 1 and 2 toxicities included neutropenia (40%), followed by anemia (35%). Twenty-two percent of patients experienced non-hematological toxicities such as fatigue, nausea, mucositis, and elevation of liver enzymes (►**Table 3**).

Treatment Outcomes

Among the patients treated with palbociclib, 5% exhibited a complete response, 41% showed a partial response, and 47% experienced disease progression. Additionally, 7 patients died during treatment. The median PFS of palbociclib when used in the first line was 32 months, compared to 23 months in the second line, and 13 months in the third line or subsequent lines. Premenopausal women had a PFS of 21 months compared to 25 months for postmenopausal women.

Weak hormone positivity, ET-resistant metastatic patients, and high grade were identified as poor responders. With a median follow-up of 37 months, the median PFS of the overall population was 24 months. Specifically, bone metastasis had a median PFS of 27 months, lung metastasis 25 months, liver metastasis 12 months, and brain metastasis 4 months (►**Table 4**; (►**Graphs 1** and **2**).

Discussion

The present study examined palbociclib's efficacy and safety in 100 HR-positive MBC patients with visceral metastases, finding a median PFS of 24 months. Bone metastasis had the longest PFS (27 months), followed by lung (25 months), liver (12 months), and brain (4 months). Common side effects included neutropenia (40%), anemia (35%), thrombocytopenia (15%), and hepatotoxicity (10%), with 3% discontinuing treatment due to toxicity. Among these, two patients had prolonged neutropenia, and one patient had persistent liver enzyme elevation as well as generalized weakness due to the drug. Among the patients who progressed on palbociclib and underwent biopsy followed by molecular testing, 12% started

Table 3 Treatment-related factors

Sequence	No. of patients
First line	51
Second line	37
Third and subsequent	12
CDKi + Endo	
CDKi + AI	55
CDKi + Fulvestrant	42
CDKi + Exemestane	3
Toxicities	
No AE	30
Anemia (grade I II)	35
Neutropenia (I II)	40
Thrombocytopenia (grade I II)	15
Nonhematological	22
Hematological (grade III IV)	3
Nonhematological (grade III IV)	2
Dose modification	
No modification	64
First dose	25
Second dose	8
Discontinue	3
Response to treatment	
Complete	5
Partial	41
Progress	47
Death	7

Abbreviations: AE, adverse event; AI, aromatase inhibitor.

on PiK3 inhibitors (alpelisib), 46% started on everolimus and exemestane, 32% started on chemotherapy, and the remaining patients opted for best supportive care.

This is the only study evaluating the efficacy of palbociclib in different lines of metastatic hormone receptor-positive breast cancer.

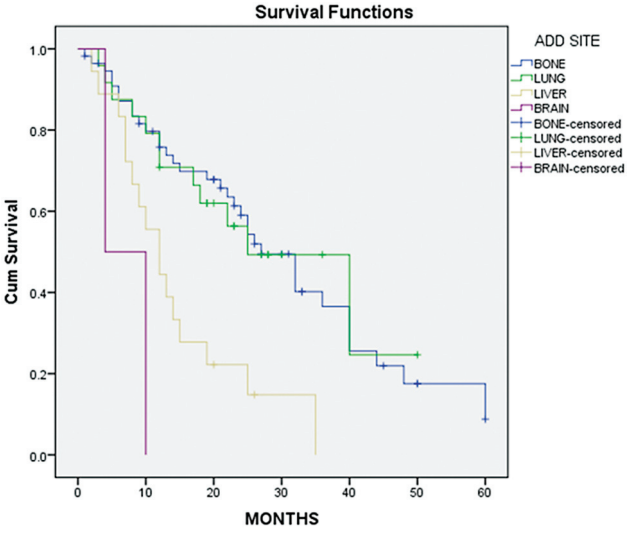
In the landmark PALOMA-2 study,[10] which included 444 metastatic patients treated with palbociclib plus letrozole, the median PFS was 24.8 months, compared to 14.5 months with letrozole alone. Our study, with a median PFS of 24 months, despite 70% of patients having prior ET, showed comparable outcomes. Notably, de novo metastatic disease in our cohort exhibited a median PFS of 40 months, significantly surpassing the PALOMA-2 trial. This divergence may be attributed to the selective use of palbociclib upfront in metastatic disease during the evolving era of CDK inhibitors. Common toxicities in the PALOMA-2 trial included neutropenia (66.4%), leukopenia (24.8%), anemia (5.4%), and fatigue (1.8%), with 1.8% experiencing febrile neutropenia and 9.7% discontinuing treatment, aligning with findings in our study.

Table 4 Treatment outcomes

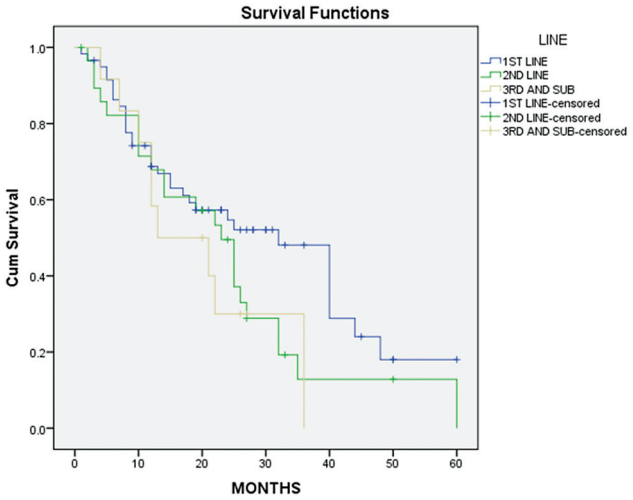
Median PFS in subgroups	Months	*p*-Value
Sequence of palbociclib		
First line	32	
Second line	23	0.170
Third and more	13	
Menstrual status		
Premenopausal	21	
Postmenopausal	25	0.218
Site of metastasis		
Skeletal	27	
Visceral	15	0.054
Hormonal status		
Strong positive	32	0.127
Weak positive	14	
KI-67		
< 15	40	0.189
15–30	19	
> 30	22	
Presentation		
ET resistant	22	
De novo	40	0.113

Abbreviations: ET, endocrine therapy; PFS, progression-free survival.

In contrast, the initial PALOMA-3 trial[9] evaluated the efficacy of palbociclib plus fulvestrant in MBC patients who had progressed on previous ET, involving 345 patients with a median follow-up of 8.9 months. The median PFS was 9.5 months in those with visceral metastatic disease, whereas in patients with nonvisceral metastases, the median PFS was 16.6 months. In our study, PFS in visceral metastatic disease was 15 months compared to 27 months in skeletal



Graph 1 Progression-free survival (PFS) based on metastatic sites.



Graph 2 Progression-free survival (PFS) based on different lines CDK4/6 used.

metastasis, with acceptable toxicities, the most common being neutropenia, anemia, and thrombocytopenia. This disparity is due to the selection of patients with low visceral metastatic disease in our study during the initial days of CDK4/6i approval.

In the MONARCH 2 phase III RCT,[11] which evaluated abemaciclib plus fulvestrant in subgroup patients having visceral metastasis at presentation, results were more favorable than palbociclib plus ET with an hazard ratio of 0.48.

There are not many studies comparing CDK4/6 inhibitors head-on with chemotherapy drugs, especially in extensive visceral metastasis cases before CDK4/6 inhibitors were available. However, CDK4/6 inhibitors provide a chemotherapy-free regimen for HR-positive MBC without a visceral crisis.

In the RIGHT Choice trial, an open-label phase II study[12] conducted in 13 countries, a head-to-head comparison between a CDK4/6 inhibitor (ribociclib) plus ET and combination chemotherapy was evaluated. The study involved 112 patients receiving ribociclib plus ET, while in our current study, 100 patients received palbociclib plus ET. The percentage of patients with de novo metastatic disease was similar between the two studies (64.4% in RIGHT Choice vs. 70% in our study). However, there were notable differences in the patient populations: 67.6% of patients in the RIGHT Choice trial had visceral metastasis compared to 44% in our study, and 47% of patients in the RIGHT Choice trial had a visceral crisis, while none in our study did. The median PFS in the ribociclib arm of the RIGHT Choice trial was 21.8 months, compared to 12.8 months in the chemotherapy arm. In our study, the median PFS in the palbociclib arm was 24 months. Regarding safety, grade 3 or 4 hematological toxicity occurred in 59.8% of patients in the RIGHT Choice trial, whereas in our study, severe hematological toxicity was only 4%. Severe nonhematological toxicity was 3% in the RIGHT Choice trial compared to 4% in our study. There were five deaths in the ribociclib arm of the RIGHT Choice trial, compared to seven deaths in our study. The trial showed improved PFS, similar response rates, and lower rates of symptomatic adverse events with ribociclib plus ET compared to chemotherapy. In summary, the efficacy and safety results of our study are similar to those observed in the ribociclib arm of the RIGHT Choice trial.

In the FALCON study,[13] which compared fulvestrant with anastrozole, PFS was 22.3 versus 13.8 months in skeletal metastatic disease compared to 40 months in our study, with a comparable toxicity profile.

The KENDO randomized phase II trial[14] is the only study that compared the efficacy and safety of chemotherapy plus ET versus CDK4/6 inhibitors (CDK4/6i) plus ET in hormone receptor-positive (HR+)/HER2-negative MBC. The study found that CDK4/6i plus ET showed clinically meaningful improvements in PFS and OS compared to chemotherapy plus ET, although the difference was not statistically significant. Basal-like tumors under CDK4/6i plus ET had worse PFS and OS compared to other subtypes, while luminal A tumors performed worse with chemotherapy. The PAM50 intrinsic subtypes were found to have prognostic and predictive value, with luminal A associated with the best prognosis and basal-like with the worst prognosis. Genes and pathways involved in breast cancer cell survival and proliferation were associated with worse outcomes, while immune-related genes and signatures showed favorable survival trends, especially in the CDK4/6i arm. Tumor-infiltrating lymphocytes and the presence of tertiary lymphoid structures were associated with better outcomes in the CDK4/6i arm. CD24 was identified as a potential therapeutic target, and messenger ribonucleic acid-based CD19 and CXCL13 were found to be predictors of tertiary lymphoid structure presence. Overall, the results suggest that CDK4/6i plus ET is a viable treatment option for aggressive HR+/HER2-negative MBC instead of chemotherapy, and PAM50 intrinsic subtypes, genomic, and immunological features are promising biomarkers for personalized therapeutic choices.

Our study findings of palbociclib with ET in real-world data suggest that palbociclib plus ET, which is a widely used CDK4/6 inhibitor with ET, showed similar efficacy and safety comparable with RCTs in visceral metastatic disease without visceral crisis. This is the only study that evaluated the efficacy of palbociclib in multiple lines.

Conclusion

Based on real-world evidence, palbociclib demonstrates similar responses and better tolerance in visceral metastatic hormone positive breast cancer. However, further studies are required to identify additional predictive markers and factors related to CDK4/6 inhibitors resistance. Moreover, the efficacy of palbociclib inhibitors should be evaluated, particularly in patients with a high disease burden and extensive visceral metastatic disease.

Patient Consent

Informed patient consent was obtained to conduct this study.

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None.

Conflict of Interest
None declared.

References

1 Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2020;70(04): 313–336
2 Jonnada PK, Sushma C, Karyampudi M, Dharanikota A. Prevalence of molecular subtypes of breast cancer in India: a systematic review and meta-analysis. Indian J Surg Oncol 2021;12 (Suppl 1):152–163
3 Kumar RV, Panwar D, Amirtham U, et al. Estrogen receptor, progesterone receptor, and human epidermal growth factor receptor-2 status in breast cancer: a retrospective study of 5436 women from a regional cancer center in South India. South Asian J Cancer 2018;7(01):7–10
4 Pandit P, Patil R, Palwe V, Gandhe S, Patil R, Nagarkar R. Prevalence of molecular subtypes of breast cancer: a single institutional experience of 2062 patients. Eur J Breast Health 2019;16(01): 39–43
5 Belachew EB, Sewasew DT. Corrigendum: molecular mechanisms of endocrine resistance in estrogen-receptor-positive breast cancer. Front Endocrinol (Lausanne) 2021;12:689705
6 Cardoso F, Paluch-Shimon S, Senkus E, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31(12):1623–1649
7 Gennari A, André F, Barrios CH, et al; ESMO Guidelines Committee. Electronic address: clinicalguidelines@esmo.org. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol 2021;32(12): 1475–1495
8 Finn RS, Crown JP, Lang I, 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(01):25–35
9 Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. Lancet Oncol 2016;17(04): 425–439
10 Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med 2016;375(20):1925–1936
11 Sledge GW Jr, Toi M, Neven P, et al. MONARCH 2: abemaciclib in combination with fulvestrant in women with HR+/HER2- advanced breast cancer who had progressed while receiving endocrine therapy. J Clin Oncol 2017;35(25):2875–2884
12 Lu YS, Bin Mohd Mahidin EI, Azim H, et al. Final results of RIGHT Choice: Ribociclib plus endocrine therapy vs combination chemotherapy in premenopausal women with clinically aggressive HR+/HER2− advanced breast cancer. J Clin Oncol 2024;42(23): 2812–2821
13 Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet 2016;388(10063):2997–3005
14 Schettini F, Palleschi M, Mannozzi F, et al. CDK4/6-inhibitors versus chemotherapy in advanced HR+/HER2-negative breast cancer: results and correlative biomarker analyses of the KENDO randomized phase II trial. Oncologist 2024;29(05):e622–e634

