Real-World Outcomes with First-Line CDK4/6 Inhibitors in HR+/HER2− Metastatic Breast Cancer

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Abstract

Background: CDK4/6 inhibitor plus endocrine therapy (ET) is standard first-line therapy for HR+/HER2− metastatic breast cancer (mBC). Real-world effectiveness and the comparative performance of abemaciclib vs palbociclib remain uncertain

Methods: Retrospective, single-institution cohort (King Fahad Medical City, Riyadh). Adults with HR+/HER2−/low mBC initiating first-line ET+CDK4/6 (Jan 2021–Dec 2023) were included; patients receiving first-line chemotherapy/ADC or ET alone were excluded. Primary endpoint: progression-free survival (PFS); secondary: overall survival (OS). Kaplan–Meier with log-rank tests were used. Multivariable Cox models adjusted for agent (abemaciclib vs palbociclib), age, ECOG, presentation (de novo vs recurrent), metastatic burden, and liver involvement. Ribociclib (n=1) was excluded from agent comparisons. Median follow-up ≈23.9 months.

Results:

- Eighty-one patients were eligible; median age mid-50s; most ECOG 0–1. Presentation was mainly de novo; visceral disease predominated. ET backbones: aromatase inhibitor 62, tamoxifen 16, fulvestrant 3; ovarian function suppression in 34/81 (42%). CDK4/6 agent: palbociclib 43 (53%), abemaciclib 37 (46%).
- Whole-cohort PFS: median 28.7 months (37 events, ~46%).

Agent comparison (abemaciclib vs palbociclib): HR 0.76 (95% CI 0.46–1.25; p=0.51), i.e., numerically longer with abemaciclib but not significant.

- Subgroups (univariate): de novo > recurrent (p=0.044); bone-only > visceral (p=0.044).
- Multivariable predictors of PFS:
  - Liver metastasis independently predicted shorter PFS (adjusted HR 4.62, 95% CI 1.94–11.01, p=0.001).
  - De novo presentation predicted longer PFS vs recurrent (HR 0.34, 95% CI 0.13–0.87, p=0.024).
  - Agent, age, ECOG, and overall site count were not significant after adjustment.

OS: 21 deaths (25.9%) at cutoff; median OS not reached.

Conclusion: First-line ET+CDK4/6 achieved a ~29-month median PFS. No statistically significant PFS difference was observed between abemaciclib and palbociclib. Outcomes were driven by disease biology and burden: liver involvement conferred markedly worse PFS, while de novo presentation was favorable. Continued follow-up and genomic validation (e.g., PIK3CA/ESR1) are ongoing.

Primary Objective

Real-world PFS with first-line ET+CDK4/6 in HR+/HER2− mBC.

Secondary Objectives

Comparisons: abemaciclib vs palbociclib , de novo vs recurrent, bone-only vs visceral.

Predictors of PFS: multivariable Cox (agent, age, ECOG, presentation, burden/sites, liver).

Overall survival: time to death; censored at last follow-up.

Methods

Design & Setting

Retrospective, single-institution (KFMC, Riyadh)

Study period: Jan 2021 – Dec 2023

Population

Adults with HR+/HER2− metastatic breast cancer initiating first-line ET+CDK4/6 (n=103)

Eligible HR+/HER2−/low mBC treated first-line with ET+CDK4/6. (n=81)

Exclusions:

- Prior systemic therapy for metastatic disease or prior CDK4/6 exposure. (n=20)
- Received first-line chemotherapy/ADC, endocrine therapy alone, or best supportive care (n=2)
- Records insufficient for outcome assessment.

Descriptives: medians (IQR) and proportions.

Group tests: χ^2/Fisher for categorical; Mann–Whitney U for continuous.

Time-to-event: PFS primary, OS secondary; Kaplan–Meier curves with medians (95% CI); log-rank for comparisons.

Multivariable Cox (PFS): covariates = agent, age, ECOG, presentation (de novo/recurrent), metastatic burden (# sites) and liver/visceral; report adjusted HRs (95% CI).

Censoring & alpha: censored at last follow-up; two-sided p<0.05.

Results

Baseline Characteristics: Among 81 patients with HR+/HER2− metastatic breast cancer treated with first-line ET+CDK4/6 inhibitor, median age was 54 years (range 34-80). Most patients were female (96.3%), postmenopausal (54.3%), and had ECOG 0-1 (66.7%). De novo metastatic disease was present in 86.4%, while 13.6% had recurrent disease. Visceral metastases were present in 65.4% and bone-only disease in 34.6%. Visceral crisis occurred in 3.7% of patients.

Treatment Distribution: CDK4/6 inhibitors included palbociclib (53.1%), abemaciclib (45.7%), and ribociclib (1.2%). Aromatase inhibitors were the most common endocrine backbone (70.4%), followed by tamoxifen (22.2%) and fulvestrant (7.4%).

Progression-Free Survival: At median follow-up of 23.9 months, median PFS for the overall cohort was 28.7 months (95% CI: 22.1-35.3), with 37 progression events (45.7%). No significant PFS difference was observed between abemaciclib and palbociclib (33.1 vs 26.8 months; HR 0.76, 95%CI 0.46-1.25, p=0.51).

Subgroup Analysis: De novo presentation demonstrated significantly longer PFS compared to recurrent disease (30.5 vs 17.8 months; HR 0.32, 95% CI 0.10- 0.97, p=0.044). Bone-only metastases showed longer PFS than visceral disease (34.5 vs 27.6 months; HR 1.97, 95% CI 1.02-3.80, p=0.044).

Overall Survival: At median follow-up of 24 months, n= 21 (25.9%) of patients had died and median OS was not reached, precluding meaningful survival analysis.

Characteristic	n (%)	Characteristic	n (%)
Age, median (range)	54y (34–80)	Presentation	
Female	78 (96.3)	De novo	70 (86.4)
Postmenopausal	44 (54.3)	Recurrent	11 (13.6)
ECOG 0–1	54 (66.7)	Metastatic pattern	
ECOG ≥2	27 (33.3)	Bone-only	28 (34.6)
Visceral crisis	3 (3.7)	Visceral	53 (65.4)

Table .1 Baseline Characteristics: Disease Burden & Biology

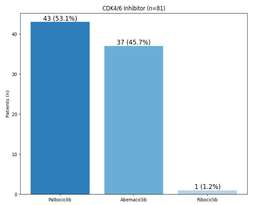


Chart 1. Endocrine Therapy Backbone (first line)

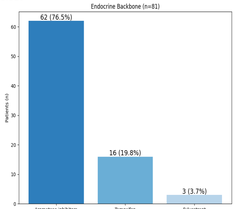


Chart 2. CDK4/6 inhibitors in First line

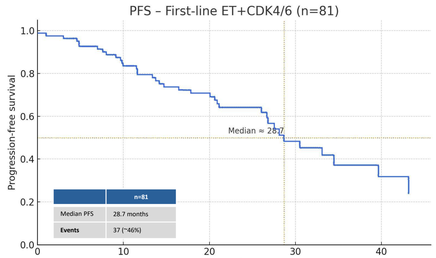


Chart 3. Progression Free Survival (Whole Cohort)

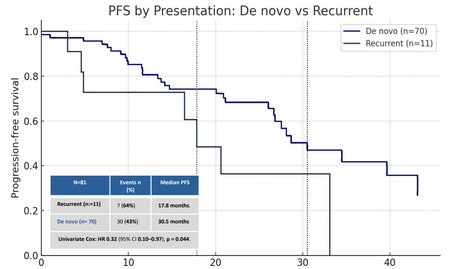


Chart 5. Progression Free Survival: De Novo vs Recurrent

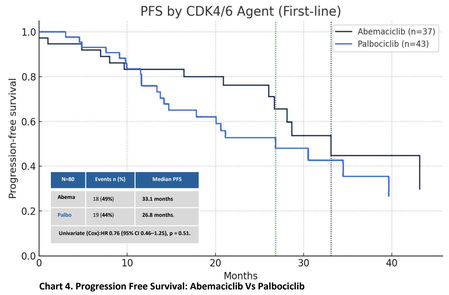


Chart 4. Progression Free Survival: Abemaciclib Vs Palbociclib

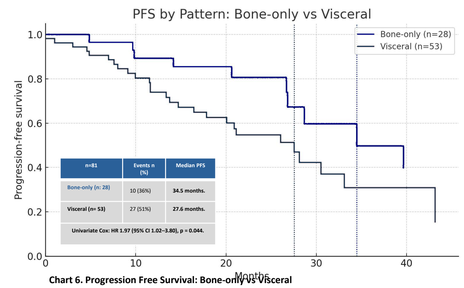


Chart 6. Progression Free Survival: Bone-only Vs Visceral

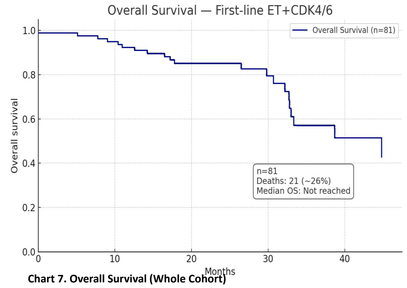


Chart 7. Overall Survival (Whole Cohort)

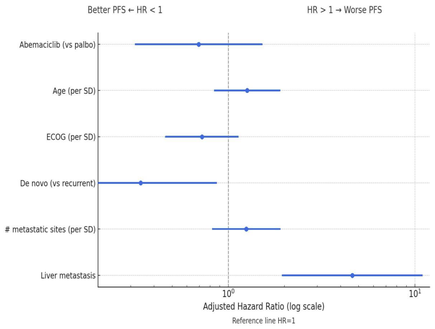


Chart 8. Multivariable Predictors of PFS

Conclusions

- Real-world median PFS ~29 months with first-line ET+CDK4/6.
- No statistically significant PFS difference between abemaciclib and palbociclib.
- Biology/burden drive outcomes: bone-only & de novo do better; liver metastasis independently predicts shorter PFS.
- OS not reached at ~24-month follow-up (~26% deaths)

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