Optimal sequencing after progression with CDK4/6 inhibitors in hormone receptor-positive metastatic breast cancer: a real-worldanalysis

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Introduction

- CDK4/6 inhibitors (CDKi) combined with endocrine therapy (ET) are the standard of care for HR+/HER2- metastatic breast cancer in first-line.
- Significant knowledge gap exists regarding optimal sequencing after progression.
- This study evaluates optimal second-line strategies after CDK4/6i progression and identify prognostic factors impacting treatment outcomes

Methods and Materials

- Retrospective cohort analysis;
- Single-institution, referral cancer center;
- Period: 2016-2025;
- 377 patients with HR+/HER2- MBC;
- Treated with CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib);

OUTCOMES

- PFS2: Progression-free survival after CDK4/6i therapy
- OS: Overall survival

STATISTICAL ANALYSIS

- Kaplan-Meier survival curves
- Cox proportional hazards models
- Multiple imputation for missing data

Results

Figure 1. Study Cohort Flowchart.

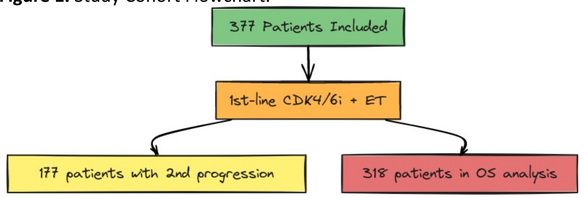


Table 1. Baseline Characteristics of the Cohort (N=377)

Characteristic	N / Mean (SD) / n (%)
Demographics	
Sex	
Female	374 (98.9%)
Male	4 (1.1%)
Clinical/Disease Characteristics	
Menopausal Status at Metastasis (n = 373)	
Pre-menopausal	143 (38.3%)
Post-menopausal	230 (61.7%)
Visceral Metastasis at CDKi Start (n= 377)	
Yes	187 (49.6%)
No	190 (50.4%)
Line of CDKi Initiation (n= 377)	1.79 (± 0.93)
Pathological / Treatment Characteristics	
Type of CDK4/6 Inhibitor (n= 377)	
Palbociclib	138 (36.5%)
Ribociclib	129 (34.1%)
Abemaciclib	111 (29.4%)
Hormonal Therapy Combined with iCDK (n = 376)	
Yes	230 (61.2%)
No	146 (38.8%)
Dose Reduction during iCDK (n = 372)	
Yes	132 (35.5%)
No	240 (64.5%)

Results

- Strategies based on endocrine therapy demonstrated superior outcomes compared to chemotherapy and CDK4/6i rechallenge.

Table 2. Median PFS2 according to second-line treatment strategy

Second-Line Strategy	Median PFS2 (months)	Comparison
Fulvestrant or Everolimus Combination	**12.1**	Best PFS2 rates
Fulvestrant	11.3	Superior to CDK4/6i rechallenge (HR 0.41, p=0.004; CI 0.23-0.75)
Capecitabine-based Regimens	6.9	Inferior performance
CDK4/6i rechallenge	5.4	Poorest outcome

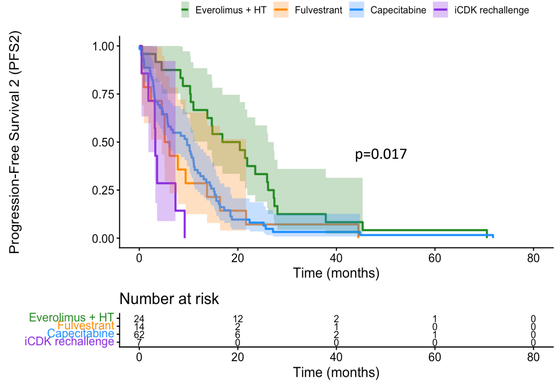


Chart 1. Progression-Free Survival 2 (PFS2) by Second-Line Treatment Strategy

Results

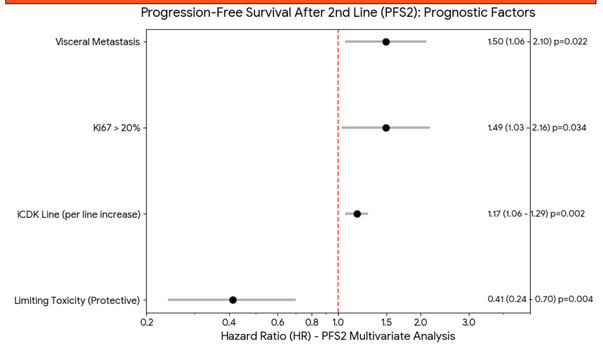


Chart 2. Progression-free survival after second line (PFS2): Multivariate Analysis of Prognostic Factors

- **Limiting Toxicity** appears as a **strong protective factor**, suggesting a biologically distinct subgroup of patients with better outcomes.

Conclusions

Second-line therapeutic choices significantly impact post-progression outcomes.

CLINICAL IMPLICATIONS:

- Prioritize endocrine combinations after CDK4/6i progression;
- Consider fulvestrant-based regimens as preferred second-line option;
- Individualize treatment based on prognostic factors (like visceral metastasis, Ki-67 and others) and molecular profiling is the key.

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