REWIRING TREATMENT PATHWAYS: HOW MOLECULAR PROFILING AFTER CDK4/6 INHIBITOR (CDK4/6I) FAILURE SHAPES FUTURE THERAPY IN LUMINAL HER2-NEGATIVE BREAST CANCER

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BACKGROUND

CDK4/6 inhibitors have improved outcomes in luminal HER2-negative metastatic breast cancer. However, resistance eventually develops, and the optimal post-progression strategy remains unclear. Molecular profiling can reveal resistance mechanisms and actionable alterations.

OBJECTIVES

- Investigate the molecular profile of patients with luminal metastatic breast cancer after progression on CDK4/6 inhibitors, aiming to identify endocrine resistance mechanisms and potential actionable targets.
- Evaluate progression-free and overall survival after CDK4/6i progression, and compare PFS between patients with PI3K/AKT/mTOR pathway mutations and those with other alterations.

METHODS

This retrospective study included patients with HR+/HER2− metastatic breast cancer treated with CDK4/6 inhibitors between 2016 and 2025 at AC Camargo Cancer Center. Clinical data were obtained from medical records. Tumor samples were collected from metastatic lesions at progression or from primary tumors prior to systemic therapy. After histopathologic review and manual microdissection, DNA was extracted from FFPE samples and analyzed using the Somatic GS Focus Panel, which evaluates clinically relevant mutations and copy number alterations. Variant interpretation followed a certified molecular diagnostics workflow.

REFERENCES

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RESULTS

A total of 85 patients with HR+/HER2− metastatic breast cancer treated with CDK4/6 inhibitors were identified. 18 cases were excluded due to technical failure or insufficient tissue, resulting in 67 patients included in the molecular analysis.
The most frequently used CDK4/6 inhibitor was ribociclib (50.7%), followed by abemaciclib (28.2%) and palbociclib (16.9%). Endocrine partners included aromatase inhibitors in 52.1% of patients, fulvestrant ± goserelin in 22.5%, AI combined with goserelin in 8.5%, tamoxifen in 4.2%, and non-assessed in 12.7%.
CDK4/6 inhibitors were administered mainly as first-line therapy (78.9%), followed by second line (12.7%) and third line (1.4%), with 7% not available.

Table 1. Clinical Characteristics of the Cohort

VARIABLE	PORCENTAGE (%)
SEX	
FEMALE	**98,6%**
MALE	1,4%
AGE (YEARS)	MEDIAN 58.3 (30-79)
MENOPAUSAL STATUS	
POSTMENOPAUSAL	**64,7%**
PREMENOPAUSAL	30%
HISTOLOGY	
IDC (INVASIVE DUCTAL CARCINOMA)	**78,1%**
ILC (INVASIVE LOBULAR CARCINOMA)	20,3%
HISTOLOGIC GRADE	
GRADE I	5,1%
GRADE II	**64,4%**
GRADE III	30,5%
IMUNOPHENOTYPE	
LUMINAL A	16,7%
LUMINAL B	**62,1%**
LUMINAL HER2 LOW	**21,2%**
ADJUVANTE ENDOCRINE THERAPY (ET)	59%
PREVIOUS CHEMOTHERAPY (CT)	29%

Median progression-free survival (PFS1) with CDK4/6 inhibitors was 25.0 months (95% CI: 18.0–31.0), and median overall survival (OS1) was not reached (95% CI: 85.0–NA). After disease progression on CDK4/6 inhibition, the median PFS2 was 7.0 months, while median OS2 was 13.0 months (95% CI: 7.0–19.0).
Molecular profiling revealed that 40% of the analyzed cases harbored at least one somatic alteration. Among the 34 positive samples, the most frequent mutations were PIK3CA (35.3%), followed by ESR1 (8.8%), ERBB2 (8.8%), TP53 (8.8%)PTEN (5.9%) and AKT1 (5.9%). Co-occurring alterations such as PIK3CA + ESR1, PIK3CA + PTEN, and ERBB2 + ATM were observed in 3.7% of cases each, and mutations in DNA repair genes (BRCA1/2 or ATM) were present in approximately 7% of patients.
When survival was stratified by molecular subgroup, patients harboring alterations in the PI3K/AKT/PTEN pathway showed a numerically shorter PFS compared to those with other mutations (median ≈ 20 vs. 30 months, log-rank p = 0.1385), with a steeper decline within the first 24 months, although without statistical significance.

Figure 1. Distribution of Somatic Mutations

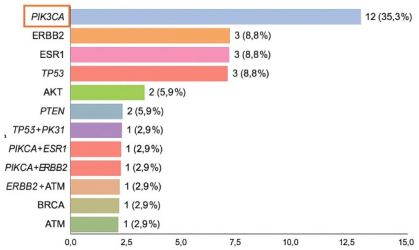
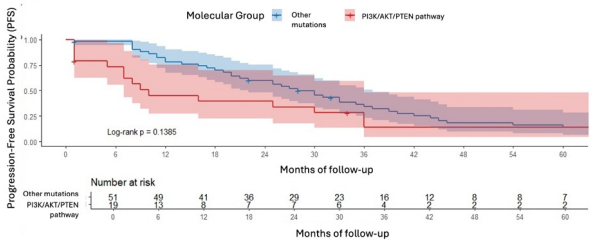


Figure 2. Kaplan–Meier Curve – PFS by Molecular Group (PI3K/AKT/PTEN vs. Other Mutations)



CONCLUSION

Molecular profiling after CDK4/6 inhibitor failure revealed actionable alterations in 40% of patients. Frequent PIK3CAand ESR1 mutations confirm key resistance pathways, while alterations in BRCA1/2 and ATM suggest sensitivity to PARP inhibitors. The presence of HER2-low tumors highlights the potential of antibody–drug conjugates (ADCs). These findings support integrating genomic profiling into post-CDK4/6 treatment strategies to advance precision oncology.

Authors declare no conflict of interest.
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