PS2-07-20 Ki-67-guided stratification and resistance mechanism analysis of CDK4/6 inhibitor therapy following adaptive-neoadjuvant endocrine treatment in HR+/HER2- breast cancer

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Abstract

Given the associated adverse events and economic implications, identifying patients who are most likely to benefit from CDK4/6i can help avoid under- or overtreatment. In this study, we performed a short-term adaptive neoadjuvant endocrine therapy (NET) to select patients who could benefit from CDK4/6i intensified therapy. We found that in patients initially nonresponsive to aromatase inhibitors therapy, the addition of CDK4/6i significantly reduced Ki-67 levels, indicating that these individuals may benefit from intensified CDK4/6i-based therapy. In addition, the single-cell transcriptome sequencing showed that malignant epithelial C2 cell cluster and FUT6 were identified as potential therapeutic targets associated with CDK4/6i resistance. Moreover, persistent or emerging *PIK3CA* and *TP53* mutations during adaptive therapy may serve as molecular indicators of resistance to sequential AI and CDK4/6i treatments.

Introduction

The absolute improvement of invasive disease-free survival (iDFS) with intensive adjuvant CDK4/6 inhibitor (CDK4/6i) therapy ranges from 4.9% to 7.6%[1-3]. Given the associated adverse events and economic implications, identifying patients who are most likely to benefit from CDK4/6i can help avoid under- or overtreatment. Short-term adaptive neoadjuvant endocrine therapy (NET) may facilitate the selection of patients who could benefit from intensified therapy[4].

This study aims to utilize adaptive NET to guide patient selection for combination endocrine therapy with CDK4/6i and to further explore molecular mechanisms underlying resistance to CDK4/6i.

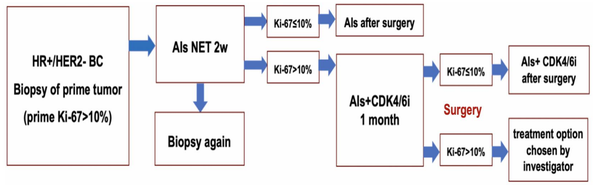


Figure 1. Study design.

Methods and Materials

Postmenopausal patients with stage II–III HR+/HER2- breast cancer and a baseline Ki-67 index >10% were prospectively enrolled in a multicenter clinical trial (Clinical trial.gov Identifier: NCT05809024). All patients received 2 weeks of NET with aromatase inhibitors (AIs), followed by a second tumor biopsy. Based on post-treatment Ki-67 levels (cut-off: 10%), patients were stratified into two groups: (A) AI-responsive (Ki-67 ≤10%), who proceeded directly to surgery; and (B) AI-nonresponsive (Ki-67 >10%), who received an additional cycle of AI combined with the CDK4/6i dalpiciclib prior to surgery (**Figure 1**).

Tumor samples were collected at three time points—prior to NET, after AI therapy, and after AI plus CDK4/6i—for single-cell transcriptome sequencing and next-generation sequencing (NGS).

Results

Between February 2023 and 2025, 120 patients were enrolled. After 2 weeks of AI therapy, 68.3% (82/120) achieved Ki-67 ≤10% (AI-responsive), while 31.7% (38/120) remained with Ki-67 >10% (AI-nonresponsive). Among the AI-nonresponsive patients, 50.0% (19/38) remained Ki-67>10% following one cycle of AI plus CDK4/6i (CDK4/6i-nonresponsive), while the remaining 50.0% achieved Ki-67 ≤10% (CDK4/6i-responsive, **Table 1**). No new drug-related AEs were observed.

Table 1. The Ki-67 characteristics of enrolled patients.

Ki-67	Patients No.（%）
Prime Ki-67	
Ki-67≤20%	23 (19.2%)
Ki-67>50%	10 (8.3%)
Ki-67>20% and ≤50%	87 (72.5%)
Ki-67 after AI	
Ki-67≤10%	82 (68.3%)
Ki-67>10%	38 (31.7%)
Ki-67 after CDK4/6i	
Ki-67≤10%	19 (50.0%)
Ki-67>10%	19 (50.0%)

Single-cell sequencing was conducted in 23 patients: AI-responsive (n=7), AI-nonresponsive (n=12), CDK4/6i-responsive (n=2), and CDK4/6i-nonresponsive (n=2). Seven distinct cell clusters were identified: B cells, CD8+T cells, endothelial cells, epithelial cells, fibroblasts, macrophages, and mast cells (**Figure 2a**). Mast cells was significantly more abundant in the AIs-nonresponsive group, and the malignant epithelial C2 cell cluster was notably enriched in the CDK4/6i-nonresponsive group **(Figure 2b-2c)**. Bulk transcriptomic sequencing of 52 tumor samples revealed upregulation of FUT6, APOF, and SERPINA6 in the CDK4/6i-nonresponsive group, with FUT6 showing the most significant differential expression (**Figure 2d**).

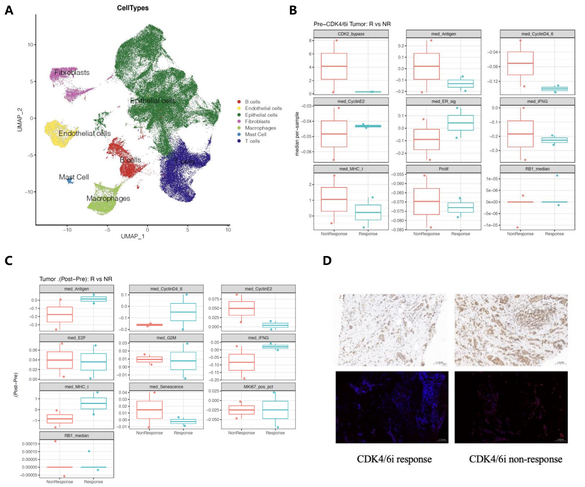


Figure 2. A. Single-cell sequencing was used to screen out cell subpopulations; B. Tumors with baseline ER-high/Prolif-low/CDK2-bypass low (type R) belong to the endocrine-driven subtype, and patients of this type are sensitive to CDK4/6i; Tumors with CDK2-bypass high/Prolif-high (NR type) are relatively resistant to CDK4/6i. C. In the sensitive group, CDK4/6i treatment significantly upregulated Antigen Processing and MHC-I molecular pathways in tumor cells. D.FUT6 can be used as a biomarker for predicting CDK4/6i resistance.

NGS was performed on 61 patients **(Figure 3a-3c)**. *PIK3CA* mutations were detected in 54.5% of patients before AI therapy, rising to 60.6% after AI therapy (72.7% in the AI-nonresponsive group; 53.8% in the AI-responsive group), and declining 42.8% following AI plus CDK4/6i treatment (62.5% in the CDK4/6i-nonresponsive group; 16.6% in the CDK4/6i-responsive group). TP53 mutations were observed in 36.3% of patients before AI therapy, 42.6% after AI therapy, and 57.1% following AI plus CDK4/6i treatment (75.0% in the CDK4/6i-nonresponsive group; 33.3% in the CDK4/6i-responsive group, **Figure 3d**).

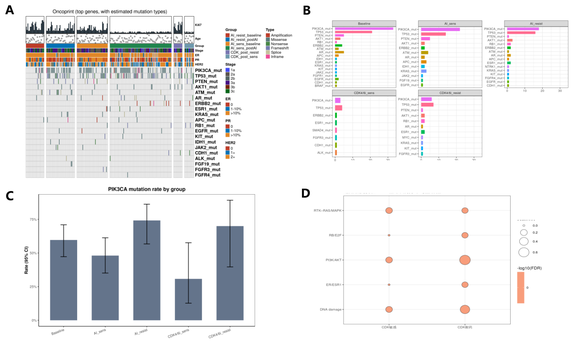


Figure 3. A. Mutation analysis landscape map; B. ESr1 is enriched in AI resistance, and RB1 is enriched in CDK resistance. The PI3K pathway (PIK3CA/AKT1/PTEN) is visible at multiple stages and is continuously background driven. C. PIk3CA is one of the most common mutations in this cohort and remains at a high frequency in the CDK-resistant population, suggesting that the PI3K/AKT signaling is a long-term "safety net" survival pathway. In the CDK-resistant population, the proportion of pathway mutations in RB/E2F, PI3K/AKT, ER/ESR1, and DNA damage is higher and more significant.

Conclusions

In patients initially nonresponsive to AI therapy, the addition of CDK4/6i significantly reduced Ki-67 levels, indicating that these individuals may benefit from intensified CDK4/6i-based therapy. FUT6 were identified as potential therapeutic target associated with CDK4/6i resistance. Moreover, persistent or emerging *PIK3CA* and *TP53* mutations during adaptive therapy may serve as molecular indicators of resistance to sequential AI and CDK4/6i treatments.

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