Personalized Acquired CDK4/6i Resistance: Associations with Baseline Characteristics Like Obesity in Real-World (RW) Clinical-Multiomics Data

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Introduction

- CDK4/6 inhibition combined with endocrine therapy (ET) has become a cornerstone in the treatment (tx) of patients (pts) with HR+/HER2- advanced breast cancer (advBC)
- However resistance remains a major challenge
- To more precisely optimize tx, there is a need for improved understanding of differences in acquired resistance mechanisms depending on baseline characteristics
- Historically, a lack of robust RW clinical-multiomic data, including highly complete baseline clinical details, has limited research in this space
- **Study Objective**: This study aimed to use a novel RW clinical-multiomics database with deep clinical data to assess differences in CDK4/6 inhibitor (CDK4/6i)-based tx resistance mechanisms depending on baseline characteristics

Methods and Materials

- **Data Source:** This study used the US-based, deidentified Flatiron Health-Caris Life Sciences Breast Cancer (BC) Clinical-Molecular Database (CMDB), with electronic health record (EHR)-derived data from the Flatiron Health Research Database[1] linked to whole exome sequencing (WES), whole transcriptome sequencing (WTS), immunohistochemistry, and digital pathology data from Caris (data cutoff December 31, 2024)
- **Inclusion Criteria and Cohort Selection:**

Figure 1. Cohort Selection

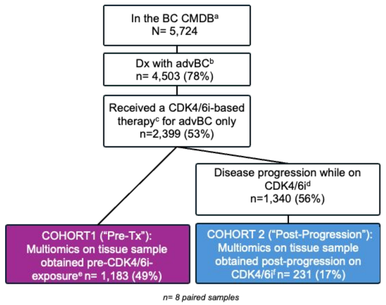
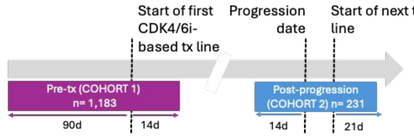


Figure 2. Schematic Depiction of Cohorts 1 and 2



[a]BC CMDB inclusion criteria: 1) Dx with BC with confirmation based on clinical notes in the EHR. 2) ≥2 documented clinical visits in the Flatiron Health network on or after January 01, 2011. 3) Had Caris WES and WTS testing on a sample with histology consistent with BC and collected no earlier than 60 days (d) before, on, or any time after the chart-confirmed date of initial dx of BC. [b]AdvBC: Stage IV/metastatic disease at dx or initial dx with stage I-III disease and subsequent locoregional recurrence after primary BC surgery or distant metastatic disease. [c]Including palbociclib, ribociclib, and/or abemaciclib ± ET. [d]Recorded progression event must have occurred no earlier than 14d after first CDK4/6i tx start date but no later than 14d after starting the next line of therapy. [e]Sample collection date within 90d before or 14d after start date of first CDK4/6i tx received for advBC. [f]Sample collection date between 14d prior to progression date and 21d after start date of first subsequent tx after first CDK4/6i tx

- **Variables:** Demographic and clinical characteristics, treatment information, real-world progression, genomic alterations (via WES), gene expression (via WTS)
- **Statistical Methods:**
  - Characteristics were summarized with descriptive statistics
  - Differential mutational prevalence and differential gene expression + associated gene ontology (GO) enrichment was evaluated in post-progression vs. pre-tx samples for the full study population and among cohorts defined by baseline obesity status collected between -6m and +7d of CDK4/6i start
    - Differential expression leveraged a quasi-likelihood negative binomial model for analysis of log-transformed counts per million and using multiple testing correction adjustment via the false discovery rate [FDR] method

Results

- **Participants:** A total of 1,406 pts ("Pre-tx" Cohort 1, n = 1,183; "Post-progression" Cohort 2, n = 231) who received a CDK4/6i-based treatment for advBC met study criteria (**Figure 1**)
- Key baseline characteristics were generally similar between cohorts, with the exception that a higher proportion of patients in Cohort 1 (27%) had liver metastasis than did Cohort 2 (16%) (**Table 1**)
- Genomic alterations in *ESR1* and *RB1* were enriched in the post-progression vs. pre-tx setting overall, but *RB1* was not significantly enriched in post-progression samples of patients with obesity (data not shown)
- A total of 232 genes were differentially expressed in the post-progression vs. pre-tx samples ($P < 0.01$, log fold-change of 0.5), including *MUC5AC*, *ACAN*, *IGHV4-39*, *MEGF10*, *FAT3*, and *MMP9* (**Figure 3**)
- GO enrichment analyses revealed distinctions in molecular processes associated with CDK4/6i-based tx resistance depending on baseline BMI status (obese vs. not obese) (**Figure 4**)
  - For example, for pts with obesity, the top molecular processes with differential gene expression enriched in post-progression samples included endopeptidase activity, FGF binding, and MHC class II receptor activity. Alternatively, for pts who were not obese at baseline, extracellular matrix, glycosaminoglycan binding, metabolic processes, collagen binding, and *ERBB2* class receptor binding represented the top unique GOs enriched in post-progression samples (**Figure 4**)

Table 1. Summary of Key Baseline Patient Characteristics

Characteristics	Cohort 1 (Pre-tx) (n = 1183)	Cohort 2 (Post- Progression) (n = 231)
Age at start of CDK4/6i tx, median (IQR), y	65 (55-73)	64 (54-71)
Race, No. (%)		
White	686 (58)	143 (62)
Non-White (group Black, Asian, other)	315 (27)	66 (29)
Unknown	182 (15)	22 (10)
Socioeconomic status, No. (%)[a]		
1-3 (Lower SES)	668 (58)	119 (52)
4-5 (Higher SES)	441 (37)	96 (42)
Unknown	74 (6)	16 (7)
Baseline BMI, No. (%)[b]		
≤18.5-29.9 (Not Obese)	678 (57)	131 (57)
≥30 (Obese)	436 (37)	86 (37)
Unknown	69 (6)	14 (6)
Baseline ECOG PS, No. (%)[c]		
0/1	823 (70)	169 (73)
2+	137 (12)	14 (6)
Unknown	223 (19)	48 (21)
Bone metastasis at baseline, No. (%)[d]	821 (69)	177 (77)
Liver metastasis at baseline, No. (%)[d]	320 (27)	37 (16)
Lung metastasis at baseline, No. (%)[d]	239 (20)	53 (23)
Brain metastasis at baseline, No. (%)[d]	43 (4)	9 (4)

Abbreviations: BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; SES, socioeconomic status; y, year

[a]Area level composite approach (based on the Yost Index) including median household income, median home value, median gross rent, % of individuals living below 150% of poverty line, % of individuals considered working class, % of individuals who are unemployed, and education index. This approach leveraged a 5-year estimate of the variables listed above from the US Census Bureau's American Community Survey (ACS, 2015-2019).[2] [b]Based on height and weight measurements taken within 6 months prior to and up to 7d post first CDK4/6i start date. [c]Defined as ECOG PS captured closest to the first CDK4/6i start date within window of 14d prior to earliest of first local recurrence or metastatic diagnosis date and 60d post first CDK4/6i start date. [d]Any time prior to and up to 7d post first CDK4/6i start date

Figure 3. Volcano Plot of Differentially Expressed Genes in Post-progression vs. Pre-tx Samples

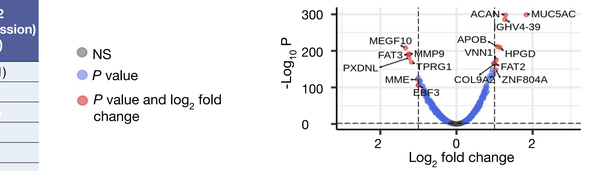
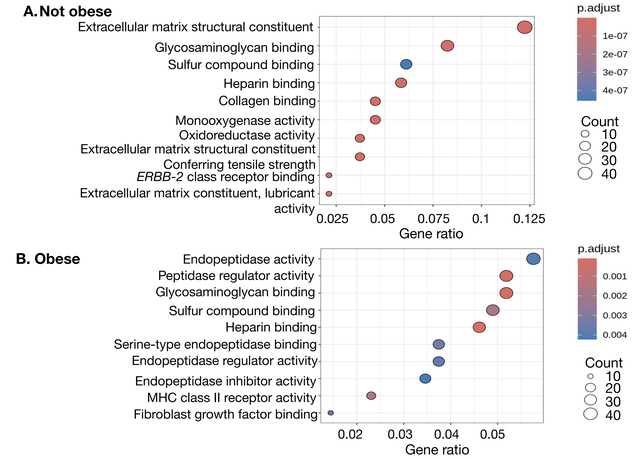


Figure 4. Gene Ontology Enrichment (Molecular Processes) in Post-progression vs. Pre-tx Samples Based on Differentially Expressed Genes



ClusterProfiler was used for functional annotation (molecular processes) of differentially expressed genes in post-progression vs. pre-tx samples based on Entrez gene map

Discussion and Conclusions

- Using a novel RW clinical-multiomics database with deep clinical and molecular data, this study confirmed known biological associations related to CDK4/6i-based tx resistance and uncovered new ones
- Critically, we identified distinctions in acquired resistance processes linked to baseline obesity, with potential tx implications. Further validation of these findings in independent cohorts is warranted. Future research should explore additional differences in resistance mechanisms depending on other clinical or demographic characteristics

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