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Associations between circulating tumor DNA genomic profiles and serum thymidine kinase patterns in patients with advanced, hormone receptor-positive, HER2-negative (HR+/HER2-) breast cancer initiating treatment with a CDK4/6 inhibitor (CDK4/6i)

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BACKGROUND AND OBJECTIVES

- The identification of predictive biomarkers remains an unmet need in metastatic breast cancer (MBC)
- Thymidine kinase, an enzyme involved in DNA synthesis, has emerged as a promising biomarker in HR+/HER2- MBC; elevated baseline thymidine kinase activity (TKa) is associated with worse prognosis[1]
- Serial TKa assessment during cycle 1 of first-line CDK4/6i plus endocrine therapy (ET) has established three distinct response patterns -- suppressed, rebound, and unsuppressed -- the latter two are associated with inferior outcomes[2]
- This case series seeks to explore the relationship between TKa patterns and ctDNA profiles in patients with HR+/HER2- MBC initiating CDK4/6i-based therapy

METHODS

- Patients with HR+/HER2- MBC initiating a CDK4/6i + ET were identified at 2 cancer centers; a subset of patients are participants in the ongoing TK IMPACT study (NCT 049698964), patients with primary endocrine resistant disease and adjuvant CDK4/6i exposure were included
- Baseline ctDNA using either Guardant360 or Tempus xF was collected within 30 days of treatment initiation
- TKa was measured using the DiviTum® TKa assay (Biovica, USA) at baseline prior to initiation of a CDK4/6i, approximately cycle 1 day 15 (C1D15), and approximately cycle 2 day 1 (C2D1) of treatment; the lower limit of quantification of the assay is 50 DiviTum units of Acitivty (DuA)
- TKa response patterns were defined as follows:
  - Suppressed: <50 DuA at C1D15 and C2D1
  - Rebound: <50 DuA at C1D15 and >50 DuA at C2D1
  - Unsuppressed: >50 DuA at C1D15 and C2D1

REFERENCES

1. Paoletti et al. Evaluating serum thymidine kinase 1 in patients with hormone receptor-positive metastatic breast cancer receiving first-line endocrine therapy in the SWOG S0226 trial. *Clin Cancer Res.* 2021;27(22):6115-6123.

2. Maloney et al. Serum thymidine kinase activity in patients with HR-positive/HER2-negative advanced breast cancer treated with ribociclib plus letrozole: results from the prospective BioItaLEE trial. *Eur J Cancer.* 2023:186:1-11.

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RESULTS

Table 1 Patient and Tumor Characteristics: 25 patients (pts) were included, 8 met criteria for primary endocrine resistant disease

	Patients (n=25)
Age at primary diagnosis, median (years)	58
Menopausal status at primary diagnosis, number (%)	Pre: 9 (36) Post: 16 (64)
Neoadjuvant/adjuvant chemo, number (%)	11 (44)
Adjuvant ET, number (%)	15 (60)
Adjuvant CDK4/6i, number (%)	2 (8)
Years adjuvant ET, median (range)	5 (0-9)
De novo metastatic disease, number (%)	8 (32)
Lines of therapy in metastatic setting, median (range)	1 (1-4)
CDK4/6i used in metastatic setting, number (%)	
Palbociclib	3 (12)
Ribociclib	20 (80)
Abemaciclib	2 (8)
ET used in metastatic setting, number (%)	
Aromatase inhibitor	17 (68)
Fulvestrant	8 (32)

Figure 1 Early TKa Dynamics: Disease progression occurred in 3 suppressed pts after 3, 11, and 17 months (m) of treatment; 3 rebound pts progressed after 4, 9, and 19m; 3 unsuppressed pts progressed within 10m; among these, 2 suppressed, 2 rebound, and 2 unsuppressed pts were endocrine resistant

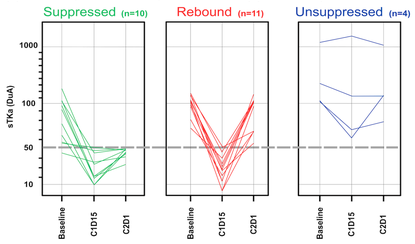


Figure 2 Co-Mutation Patterns: An average of 1 mutation (mut) per pt was seen in the suppressed group (range, 0-5), 5.7 muts per pt in the rebound group (range, 0-26), and 4.75 muts per pt in the unsuppressed group (range, 0-12); *TP53* muts were present in pts with all 3 TKa patterns; alterations in *AKT1*, *PTEN*, *ESR1*, *RB1*, *CCND1*, *CCNE1*, *BRAF*, and *ERBB2* were identified only in pts with rebound/unsuppressed TKa patterns; endocrine resistant pts denoted with an asterisk

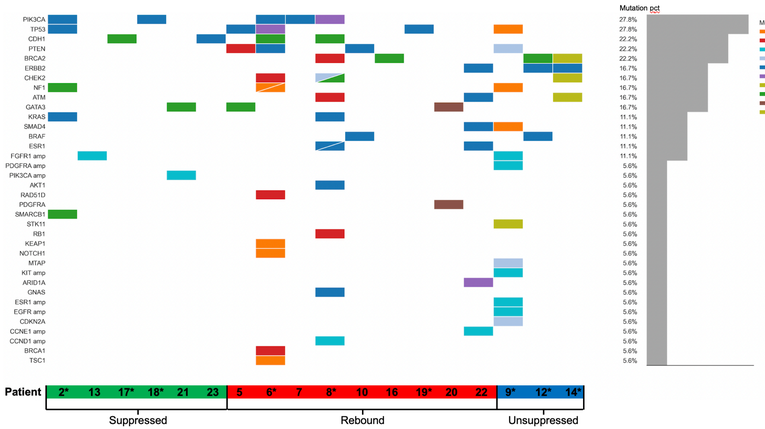


Figure 3 Frequency of Genomic Alterations: The most commonly occurring alterations in this cohort included *TP53*, *PIK3CA*, and *PTEN*

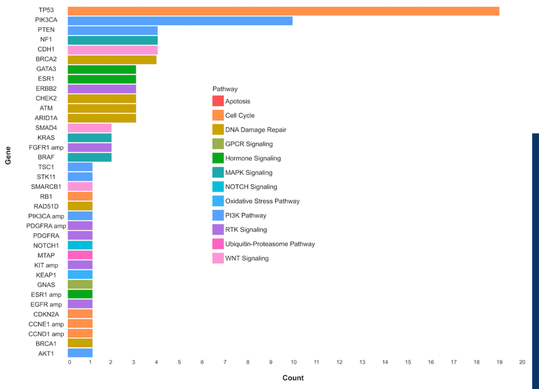
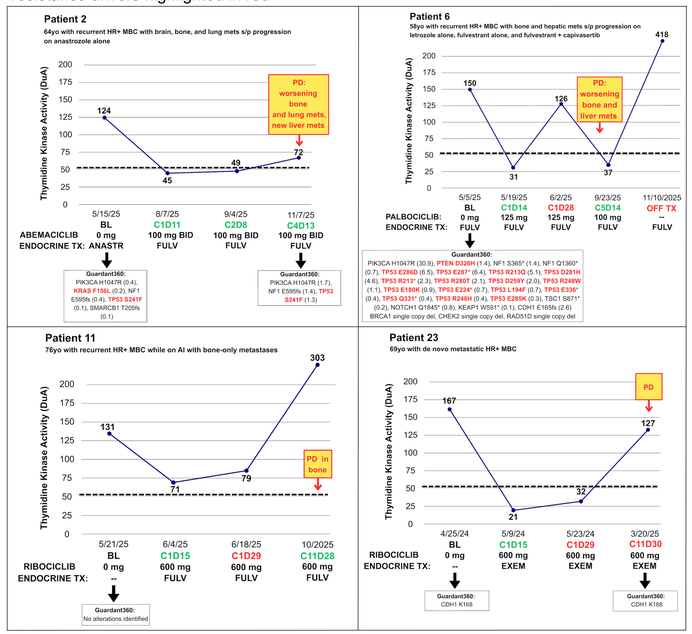


Figure 4 Notable Progressors on CDK4/6i Therapy: TKa levels and baseline ctDNA from 4 pts who progressed on treatment, green = on CDK4/6i, red = off CDK4/6i, potential resistance drivers highlighted in red



OBSERVATIONS AND DISCUSSION

- Patients with rebound or unsuppressed TKa patterns had a higher average mutation burden compared to those with suppressed TKa
- Baseline ctDNA revealed multiple ET and CDK4/6i resistance mediators, which occurred more frequently in patients with rebound and unsuppressed TKa patterns
- These results support TKa as a clinically relevant pharmacodynamic biomarker with prognostic and predictive value in patients with HR+, HER2- MBC enabling non-invasive treatment monitoring
- The findings presented are exploratory and hypothesis-generating. Additional patients will be tested for baseline ctDNA and early TKa dynamics. Longitudinal TKa monitoring will continue, including evaluation at progression for acquired genomic changes.

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