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Activity: Abstract
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Blood tumor mutational burden (bTMB) and blood copy number burden (bCNB) by genome-wide circulating tumor DNA (ctDNA) assessment predict outcome and resistance in hormone-receptor positive (HR+), HER2 negative (HER2-) metastatic breast cancer (MBC) patients (pts) treated with CDK4/6 inhibitor (CDK4/6*i*)

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Abstract:

Background: CDK4/6*i* combined with ET improves survival for pts with HR+, HER2- MBC. However, biomarkers to predict efficacy and resistance are needed. We hypothesized that a comprehensive next-generation sequencing (NGS)-based liquid biopsy assessment of ctDNA mutation and copy number analysis may identify novel prognostic and predictive biomarkers. **Methods:** We collected serial blood for ctDNA testing from the 51 pts with HR+, HER2- MBC enrolled in the Alt Dose Palbo trial (NCT03007979), a single-arm phase II study of palbociclib plus letrozole or fulvestrant at 5 days on/2 days off weekly schedule as the first- or second-line ET. The median follow up was 38.2 months at data cutoff for this analysis. Plasma collected at baseline (BL) from all 51 pts, at progression (PD) from all 20 pts who have progressed, and at additional interim timepoints from 2 pts to explore longitutinal changes, with paired germline DNA, were subjected to the PredicineWES$^+$ assay and low-pass whole-genome sequencing (lpWGS). The PredicineWES$^+$ assay provides deep sequencing of 600 genes in the PredicineATLAS panel combined with whole-exome sequencing (WES) of all exonic regions of 20,000 genes enabling genome-wide detection of somatic single nucleotide variation (SNV), indels, copy number variation (CNV) and determination of bTMB. LpWGS offers an unbiased and high-throughput assessment of CNVs and tumor fraction in cell free DNA to derive bCNB. Statistical associations of bTMB, bCNB, and individual alterations with clinical benefit (CB), defined as no PD at 24 weeks by RECIST 1.1, and progression-free survival (PFS) were examined by Fisher's exact test, Kaplan-Meier analysis, and Cox model. P values were adjusted to control false discovery rate (FDR). **Results**: The BL median bTMB was 1.6 mutations per megabase pair [IQR 0.6-3.5]. Pts with CB (N=41, 80%) had significantly lower bTMB scores (median [IQR] 1.2 [0.6-2.6] vs. 8.3 [2.4-21.4], (P<0.01) and significantly lower bCNB (P=0.03). bTMB and bCNB were highly correlated (Spearman correlation ρ =0.77, P=6.2E-11). bTMB above the predefined cutoff of 16 identified pts with significantly shorter PFS (4.7 vs 18.2 months, HR 3.73, CI 1.24-11.27, P=0.01). In contrast, BL clinical features including ET sensitivity, bone only vs. visceral, or de novo vs. recurrent MBC, were not associated with CB. BL alterations (SNV or CNV) in 91 genes, occurring in at least 3 pts each, were significantly associated with worse PFS (adjusted P<0.05), 61 of which were outside of the 600-gene panel. The 91 genes included both novel and previously reported alterations implicated in CDK4/6i and ET resistance. Examples include AR, ATM, AURKA, BRCA2, CCND1, DDR2, ESR1, FAT1, FGFR4, FOXP1, MYC, RB1, and RUNX1T1, some of which were also enriched at PD. Additional novel variants were enriched at PD, including ABCC12, ABCA13, SHANK1, and TET1. Serial analysis at BL, cycle 1 day 15 (C1D15), C2D1, the last Q3-month staging scan without PD, and at imaging detection of PD from 2 pts revealed a decline in bCNB at C1D15, then plateau, followed by an increase in bCNB that preceded imaging detection of PD. **Conclusion**: The comprehensive ctDNA profiling approach with PredicineWES$^+$ and lpWGS identified high BL bTMB and bCNB as poor prognostic biomarkers in pts on CDK4/6*i* and ET. Our study also discovered novel candidate genes involved in cell cycle and DNA damage repair pathways in association with poor outcome. Results from this study highlight the genomic heterogeneity of HR+, HER2- MBC and provide important insights in the understanding of CDK4/6*i* and ET resistance mechanisms to guide therapeutic development in pts with resistant disease.

Author Disclosure Information:

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