TPS1121 Poster Session

IND.241: A Canadian Cancer Trials Group liquid-biopsy informed platform trial to evaluate treatment in CDK4/6-inhibitor resistant ER+/HER2- metastatic breast.

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Background: The combination of a CDK4/6 inhibitor + endocrine therapy (CDK4/6i+ET) is standard first-line systemic treatment for patients with ER+/HER2-negative metastatic breast cancer (MBC). Beyond this initial therapy, there are numerous therapeutic agents available/ in development for subsequent lines of treatment. Circulating tumor DNA (ctDNA) via liquid biopsy is a promising, non-invasive approach for blood-based tumor genotyping, patient stratification and response assessment with the potential to enhance biomarker-driven strategies and aid in development of new therapeutics. **Methods:** IND.241 is a master protocol platform design consisting of independent substudies monitoring patients with ER+/HER2- MBC prior to progression (PD) on CDK4/6i+ET and investigating novel agents or drug combinations in $2^{nd}/3^{rd}$ lines after progression on CDK4/6i+ET. The primary objective of the novel drug/combination substudies is to centrally interrogate ctDNA (Tempus xF+, a 523-gene liquid biopsy panel) and evaluate whether biomarker selection improves ORR or CBR as assessed by RECIST 1.1. Secondary objectives include safety and toxicity profile for each drug/combination, PFS, and OS. The monitoring substudy (Substudy A) enrolls patients currently on CDK4/6i+ET treatment and aims to characterize the molecular profile, clinical features, and ctDNA dynamics of acquired resistance. This platform trial enables creation and maintenance of a tissue and data bank including clinical data, genomics, and radiomics from all substudies to evaluate surrogates of treatment outcomes and potential biomarkers of response, resistance, and disease progression. Patients with specific biomarkers detected in ctDNA will be enrolled into corresponding biomarker positive cohorts of substudies. Patients with no substudy-specific biomarkers are randomized to biomarker negative cohorts of available substudies. Treatment substudies follow a 2-stage design. Currently, the monitoring substudy A is actively accruing. Substudy B is evaluating lunresertib (PKMYT1 inhibitor) + gemcitabine in patients +/-CCNE1 overexpression / amplification. Substudy C is evaluating niraparib (PARP inhibitor) + fulvestrant (ET) in patients +/- alterations in BRCA1/2 (germline/somatic) or PALB2 (germline). These latter two substudies have now closed to accrual, with efficacy and safety evaluation ongoing. Substudy D, which has recently been added, is evaluating lunresertib + camonsertib (ATR inhibitor) in patients +/- CCNE1 overexpression/amplification, FBXW7 or PPP2R1A alterations. Additional substudies are in development for inclusion in this platform trial. Clinical trial information: NCT05601440. Research Sponsor: Repare Therapeutics; GSK.