TPS3183 **Poster Session**

A phase I/Ib study of olaparib and ASTX727 in BRCA 1/2- and HRD-mutated tumors.

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Background: Patients with germline or somatic HRR pathway mutations often develop resistance despite initial response. Overlapping toxicities hinder combination strategies in breast, ovarian, prostate, and pancreatic cancers, creating a need for safer and more effective approaches. Preclinical studies have shown that DNMT inhibition enhances PARP inhibitor efficacy by promoting PARP trapping on DNA. This phase I study aims to assess the safety and tolerability of olaparib and AST727 in HRR-mutated patients and establish the RP2D for a phase II trial, to be supported by the NCI ComboMatch program. Correlative studies include the creation of PDX and organoid models for ex vivo analysis of therapy response. **Methods:** Further studies include cfDNA and tumor tissue assessment to elucidate mechanisms of resistance (reversion mutations, epigenetic markers) and PD markers of HR pathway modulation. Rad51 foci will be measured to determine DNA repair function and CHIP assays (clonal hematopoiesis of indeterminate potential) to study the differential rate of CHIP as an early event in the evolution of AML/MDS. Trial Design: This is a single center phase I/Ib clinical trial evaluating the combination of olaparib and ASTX727 (an oral formulation of decitabine with cedazuridine, a cytidine deaminase inhibitor that allows for oral administration). All participant enrollment and study participation will be conducted at UCSF as single site trial with collaboration from other centers for correlative/exploratory objectives. The phase I dose escalation portion will follow a standard 3+3 design for enrollment and will include adults with advanced/metastatic solid tumor malignancies with germline or somatic mutations in the HRR pathway (i.e., BRCA1/2, PALB2, ATM, and/or CHEK2 mutations). Patients will be treated in 2 escalating cohorts with a 12 patient phase Ib dose expansion in the same population. At least 6 of 12 expansion patients must have germline HRD mutations. Key Eligibility: The participant must have histologically confirmed advanced solid tumors with a germline and/or somatic mutation in one or more of the following genes: BRCA1/2, PALB2, ATM, and/or CHEK2. Patients must have adequate organ function and recovered from prior treatment associated toxicities. Prior treatment with PARP inhibitors is allowed if the participant has not required dose reductions or delays due to toxicity. Participants with treated brain metastases are eligible if follow-up brain imaging shows no evidence of progression for at least 4 weeks. Individuals with a prior or concurrent malignancy are eligible, however participants diagnosed with MDS or AML are excluded from the study. Trial Status: The study is ongoing and 4 patients have been enrolled to date. Clinical trial information: NCT06177171. Research Sponsor: National Cancer Institute/U.S. National Institutes of Health.