TPS3181 **Poster Session**

Trial in progress: First-in-human study of ATX-559, an oral inhibitor of DHX9, in patients with advanced or metastatic solid tumors, and molecularly defined cancers.

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Background: DHX9 is a multifunctional RNA helicase that is involved in the maintenance of genomic stability by resolving DNA/RNA secondary structures that may lead to DNA replication stress and DNA damage. High expression of DHX9 is evident in multiple cancer types. ATX-559, an oral inhibitor of DHX9, has been shown preclinically to induce robust anti-tumor activity of a variety of different solid tumors with genomic instability, including models with BReast CAncer gene 1 and/or 2 alterations or deficiency (BRCA deficient) and microsatellite instability-high (MSI-H) and/or deficient mismatch repair (dMMR). **Methods:** This is a first-in-human, Phase 1, open-label, single-arm, dose-escalation and expansion study to evaluate the safety profile of ATX-559 and to determine the recommended phase 2 dose (RP2D). In dose-escalation, patients with locally-advanced or metastatic solid tumors, and molecularly-defined cancers will be enrolled for safety assessment, guided by a model-assisted dose escalation design (Yuan, 2019) to identify an acceptable dose. To assess evidence of preliminary antitumor activity in the expansion study, participants with (1) BRCA deficient, HER2-negative, metastatic breast cancer, and (2) dMMR/MSI-H solid tumors will be enrolled using a Simon 2-stage design (Simon, 1989). Primary endpoints include identification of the RP2D dose that is deemed acceptable per the model-assisted dose escalation design and to evaluate safety and tolerability as noted by the frequency and severity of adverse events (AEs). Secondary endpoints will evaluate pharmacokinetics (PK), pharmacodynamics (PD) peripherally and in a biopsy sub-study, and preliminary anti-tumor activity per RECIST v1.1. Exploratory objectives will explore potential biomarkers in relationship to ATX-559 exposure, as well as those that may correlate with treatment outcomes. A randomized cohort has also been included during dose expansion in recognition of Project Optimus. The study is open and enrollment is ongoing. Clinical trial information: NCT06625515. Research Sponsor: Accent Therapeutics.