TPS4218 **Poster Session**

A first-in-human study of MT-303, an innovative in vivo mRNA chimeric antigen receptor (CAR) therapy targeting GPC3, in adults with hepatocellular carcinoma.

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Background: Hepatocellular carcinoma (HCC) remains a leading cause of cancer mortality worldwide, with advanced cases posing significant treatment challenges. GPC3, a cell surface protein highly expressed in HCC, represents a promising therapeutic target. MT-303 is an in vivo chimeric antigen receptor (CAR) therapy, leveraging mRNA-lipid nanoparticle (LNP) technology to reprogram myeloid cells directly within the body. This novel platform eliminates the logistical and technical barriers of ex vivo CAR therapies while retaining the ability to activate targeted immune responses. MT-303's mRNA encodes a GPC3-targeted CAR receptor incorporating a single-chain variable fragment (scFv) linked to the transmembrane domain and cytoplasmic tail of CD89. Crucially, functional CAR expression is restricted to Fc receptor common gamma chain-expressing cells, predominantly myeloid cells, ensuring precise immune activation. Preclinical studies demonstrated that MT-303 effectively infiltrates tumors, triggers tumor cell killing, produces chemokines and cytokines, eliciting an adaptive antitumor immunity. Rodent models of "cold" tumors and nonhuman primate studies have highlighted MT-303's safety, pharmacodynamic effects, and dose-dependent activity, supporting its clinical development (Argueta, SITC 2024, #1125). **Methods:** This first-in-human, multicenter, open-label, Phase 1 dose-escalation trial evaluates the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of MT-303 in participants with GPC3-expressing tumors, with a primary focus on Hepatocellular Carcinoma. MT-303 is administered intravenously every 14 days using a Bayesian Optimal Interval design, with backfill cohorts for dose refinement. The primary endpoints are safety, maximum tolerated dose (MTD), and recommended Phase 2 dose (RP2D). Secondary endpoints include detailed PK profiling and assessment of immune-related adverse events (e.g., ICANs, CRS). Exploratory endpoints encompass efficacy measures (e.g., objective response rate [ORR], duration of response [DOR]), immune reprogramming (e.g., peripheral CAR expression, cytokine profiles), and intratumoral immune changes, including T-cell receptor clonality and GPC3 modulation. Enrollment is ongoing, with safety and preliminary efficacy data expected to inform future development. Clinical trial information: NCT06478693. Research Sponsor: None.