First-in-Human Dose Escalation Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Initial Efficacy of mRNA-LNP MT-302 in vivo CAR therapy in Solid Tumors

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Background

In vivo CAR therapy holds the promise of rapid delivery, expanded access, and ease of repeat dosing. MT-302 is an mRNA-lipid nanoparticle (mRNA-LNP) encoding a TROP2-targeted scFv and the transmembrane domain and cytoplasmic tail of CD89 which requires the myeloid specific Fc receptor common gamma chain for activity. MT-302 programmed myeloid cells phagocytosed and killed TROP2+ cancer cells with anti-tumor efficacy in multiple in vivo models

Method

MYE Symphony, a Phase 1 multicenter clinical trial (NCT05969041), evaluated the safety, dosing, pharmacokinetics (PK), and immunologic activity of MT-302 in advanced solid tumors with high rates of TROP2 expression. MT-302 was delivered off the shelf with intravenous administration (antihistamine and antipyretic premeds) weekly or every two weeks. Primary endpoints were safety and establish an MTD and RP2D. Secondary endpoints were PK and rates of immune effector cell-associated neurotoxicity syndrome (ICANS) and Grade 3-5 cytokine release syndrome (CRS). Exploratory endpoints included response (RECIST v1.1) and immune analyses. TROP2 expression was retrospectively assessed by immunohistochemistry.

Results

The MT-302 component of MYE Symphony enrolled 27 participants treated across 7 cohorts. Participants were heavily pretreated (median 3 prior metastatic regimens) with high disease burdens across 11 tumor subtypes. The median number of administered doses was 3 (min 1, max 20) with a median cumulative mRNA dose of 9 mg (min 0.9, max 46). Treatment-related adverse events in ≥20% of participants included CRS (52%), pyrexia (37%), neutropenia (33%), and headache (22%), which were transient and manageable. There were no Grade ≥3 CRS events. One Grade 4 ICANS was experienced at the highest dose. The MTD, without steroids, was 0.1 mg/kg. The best overall response was a confirmed PR in HR+ breast cancer lasting 16 months. PK analyses showed pegylated and ionizable lipid terminal half-lives of 45-50 hours. Translational studies revealed CAR+ cells penetrating tumors, with increased T-cell infiltration and enhanced antigen presentation. CAR-specific-dose-dependent IFNγ, CXCL9/10 induction was observed, and the CXCL9:SPP1 ratio correlated with changes in tumor burden, underscoring pro-inflammatory TME remodeling.

Conclusion

MT-302 demonstrated tolerable repeat dosing, robust biological activity, and direct tumor penetration by CAR+ myeloid cells. Although clinical responses were limited, clear proof-of-mechanism was established, with CAR+ cells driving cytokine induction, immune infiltration, and tumor microenvironment remodeling. .

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