A Phase 1 Study of mRNA-2752, a Lipid Nanoparticle Encapsulating mRNAs Encoding Human OX40L, IL-23, and IL-36γ, for Intratumoral (ITU) Injection Alone and in Combination with Immune Checkpoint Blockade

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Background

The intratumoral injection of mRNA expressing IL-23 (ITU-iTu) arms is permissive for therapies of disease of the urinary bladder. In phase I study, ITU-IL-23 demonstrated objective responses and sustained improvements in urinary symptoms. To examine ITU-Ill-23 kinetics and immune modulatory effects at higher doses, we conducted a phase I dose escalation study in patients with advanced solid tumors. Materials and Methods: ITU-IL-23 was administered at doses of 2 mg (Arm A), 2 mg + 10 μg nivolumab (Arm B), and 4 mg + 10 μg nivolumab (Arm C) in a 4:1:1 ratio to 3 patients in each cohort. Patients were evaluated at baseline, and drug and biomarker levels were measured. Results: ITU-IL-23 was associated with dose-dependent elevation and sustained expression of INFγ, IL-23, and IL-22 in both tumor and plasma, with increased levels of downstream cytokines in Arm C (IL-12, IL-23, and IL-22). Two patients had cytokine release syndrome (CRS) during Arm A (1 PR in a PD-injected bladder tumor, 1 CR in a PD-injected bladder tumor). For Arm B (3 PRs), one patient died of cardiac arrest during treatment. Safety and immunogenicity were favorable across all arms. Conclusions: ITU-IL-23 was well-tolerated across doses and in combination with nivolumab. Biomarker analyses suggest potential mechanisms to improve clinical responses in future studies.