

SAFETY AND PRELIMINARY EFFICACY OF MRNA-2752, A LIPID NANOPARTICLE ENCAPSULATING MRNAS ENCODING HUMAN OX40L/IL-23/IL-36 γ FOR INTRATUMORAL (ITU) INJECTION, AND DURVALUMAB (IV) IN TNBC, HNSCC, AND MELANOMA

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Background mRNA-2752 is a first-in-class mRNA-based therapeutic agent encoding T cell co-stimulator OX40L, and pro-inflammatory cytokines IL-23 and IL-36 γ . Preclinical data demonstrated activity in a range of tumor microenvironments (TMEs), including immune checkpoint inhibitor (CPI)- refractory cancer models, and synergy when combined with α -PD-L1 antibodies. Data from the dose escalation phase of the study was previously reported and the recommended mRNA-2752 dose for expansion (RDE) was up to 8mg ITu.

Methods We evaluated the safety and efficacy of ITu mRNA-2752 administered as monotherapy (Arm A; previously reported ASCO 2020) and in combination with the PD-L1 inhibitor durvalumab (Arm B) in patients (pts) with tumors that were palpable or accessible with image guidance. Here we report preliminary data for the expansion cohorts in TNBC, CPI-refractory melanoma, and HNSCC. Biomarker analyses included IHC/F-IHC of immune status markers and whole transcriptome assessments of paired tumor biopsies. Protein quantification of IL-23, IL-36 γ and other pro-inflammatory cytokines were performed in plasma and tumors.

Results As of 01JUL 2022, 88 pts were treated, 69 in Arm B with mRNA-2752 dosed by tumor size ranging from 0.25-8 mg. The most common treatment related adverse events occurring in \geq 10% of pts in Arm B included grade 1/2 injection site erythema/pain/swelling, fever, chills, fatigue, nausea, and flushing. Grade 3 events included injection site pain/erythema, and fever. There were no grade 4/5 related events. Objective responses were observed in immune refractory tumors by RECIST and iRECIST, including a confirmed PR in a PD-L1 low TNBC and confirmed iCR in an immune checkpoint-refractory melanoma pt, respectively. Biomarker analyses of plasma and tumor show mRNA-2752 treatment was associated with elevated pro-inflammatory cytokines, including IL-23, IL-36 γ , IFN γ , and TNF α . F-IHC of paired tumor biopsies showed increase in proliferating CD8+ T cells. Transcriptional profiling of the TME demonstrates a pronounced immune response including dendritic cell recruitment and T cell activation, which remained elevated in longitudinal samples. The greatest increases in immune response and markers of cytolytic activity were observed in pts deriving clinical benefit.

Conclusions ITu mRNA-2752 + IV durvalumab is safe, tolerable, and shows preliminary efficacy in immune refractory tumors, including TNBC and melanoma. Biomarker analyses indicate mRNA-2752 drives cytokine responses. Consistent with the expected mechanism of action, a productive and sustained inflammatory response is observed in the TME in response to treatment, including signatures of increased innate and adaptive immune cell abundance and effector response.

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Trial Registration NCT03739931

Ethics Approval This study was approved by participating Institutions' Ethics Board and conducted according to the principles of ICH GCP. Participants gave informed consent before taking part.

Consent Written informed consent was obtained from the patient for publication of this abstract and any accompanying images. A copy of the written consent is available for review upon request.

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