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-36γ. 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-36γ and other pro-inflammatory cytokines were performed in pts 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 ≥ 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-36γ, IFNγ, and TNFα. 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.