539 **PHASE 1 STUDY OF MRNA-2752, A LIPID NANOPARTICLE ENCAPSULATING MRNAS ENCODING HUMAN OX40L/IL-23/IL-36γ, FOR INTRATUMORAL (ITU) INJECTION +/- DURVALUMAB IN ADVANCED SOLID TUMORS AND LYMPHOMA**

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Background mRNA-2752 is a novel mRNA-based therapeutic agent encoding OX40L T cell co-stimulator, IL-23 and IL-36γ pro-inflammatory cytokines. Preclinical data demonstrate synergy in combination with PD-L1 blockade.

Methods This study evaluated the safety and efficacy of ITu mRNA-2752 administered Q2W up to 7 doses as monotherapy (Arm A) or in combination with the PD-L1 inhibitor durvalumab (Arm B) in patients (pts) with palpable tumors or tumors accessible with image guidance. Biomarker analyses included IHC of immune markers, whole transcriptome assessments, and protein evaluations of IL-23, IL-36γ and pro-inflammatory cytokines in pre- and post-treatment tumor biopsies and plasma. A PK/PD model was built to capture the IL-23 serum concentrations at the Q2W regimen to predict the exposure at the QW regimen to support an exploratory cohort.

Results As of 08April 2021, 49 pts were treated: Arm A (n=19) and Arm B (n=30) at doses ranging from 0.25 to 8mg Q2W. Treatment emergent adverse events (TEAEs) occurring in ≥ 10% of pts included Gr 1/2 injection site erythema/pain/swelling, fever, chills, fatigue, AST/ALT increase, lumbar myalgia, and maculopapular rash. One DLT of cytokine release syndrome was seen at the 8mg dose in Arm B. A squamous-cell bladder cancer and DLBCL have achieved confirmed PRs on Arm B, ongoing for 23 and 16 cycles, respectively. Biomarker analyses show increased IL-23 and IL-36γ protein expression, and their respective downstream cytokines IL-22 and IL-6, in tumor and plasma 6–24h after dosing; most cytokines assessed were elevated after treatment. Increased IFNγ and TNFα in tumor and plasma, sustained increases in interferon response genes including PD-L1 and markers of T cell infiltration, and activation in the TME (particularly in pts achieving a PR) indicate pro-inflammatory treatment effects with mRNA-2752 +/- durvalumab. PK/PD modeling showed the Cmax of IL-23 serum concentration of mRNA-2752 at 8mg approached a plateau, and simulations showed increasing the dosing frequency from Q2W to QW vs. dose increase may have a greater effect on increasing drug exposure.

Conclusions ITu mRNA-2752 is safe and tolerable when combined with durvalumab. The recommended dose for expansion is 8mg mRNA-2752. Analyses of tumor and plasma biomarkers suggest a sustained treatment effect that includes elevated IFNγ, TNFα, and PD-L1 levels, providing rationale for combination therapy. Enrollment is ongoing in expansion cohorts of TNBC, urothelial cancer, lymphoma, immune-checkpoint refractory melanoma and NSCLC. PK/PD modeling supports QW dosing which is being explored in cutaneous melanoma in the neoadjuvant setting.

Trial Registration NCT03739931

REFERENCES

1. Hewitt SL, Bai A, Bailey D et al. Durable anticancer immunity from intratumoral administration of IL-23, IL-36γ, and OX40L mRNAs. Sci Transl Med. 2019;11 (477):1–15.

Ethics Approval The study was approved by the respective participating Institution's Ethics Board and conducted in accordance with the International Council for Harmonisation harmonised tripartite guideline E6(R1): Good Clinical Practice and all applicable government regulations.

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 by the Editor of this journal.

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