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 08 April 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. 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.

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

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.