T-CELL RESPONSES TO INDIVIDUALIZED NEOANTIGEN THERAPY (INT) mRNA-4157 (V940) AS MONOTHERAPY OR IN COMBINATION WITH PEMBROLIZUMAB

Background T-cell targeting of tumor-specific non-synonymous mutations has been demonstrated to drive antitumor responses. Developing therapies against such neoantigens as monotherapy or in combination with a checkpoint inhibitor (CPI) may elicit antitumor immune responses, resulting in clinical benefit. The combination of the novel INT mRNA-4157 (V940) and pembrolizumab improved recurrence-free survival and demonstrated a manageable safety profile when compared with pembrolizumab monotherapy in patients with resected high-risk stage III/IV cutaneous melanoma in the randomized phase 2 mRNA-4157-P201/KEYNOTE-942 study (NCT03897881). Here, we report results from the first-in-human phase 1 study (NCT03313778) of mRNA-4157 ± pembrolizumab to characterize the mechanism of action in patients with resected cutaneous melanoma or non-small cell lung cancer (NSCLC).

Methods Baseline tumor core biopsies and matched whole blood from patients with resected NSCLC (cohort A, 1 mg mRNA-4157, n=4) and resected cutaneous melanoma (cohort D, 1 mg mRNA-4157 and 200 mg pembrolizumab, n=12) underwent whole exome sequencing (WES). The immune response to mRNA-4157 was assessed via antigen-specific T-cell assays in peripheral blood mononuclear cells (PBMCs). T-cell responses to INT neoantigen pools or to individual neoantigens were analyzed directly ex vivo using interferon-gamma enzyme-linked ImmunoSpot (ELISpot) assays at longitudinal study timepoints. Neoantigen-specific CD4 and/or CD8 T-cell responses were characterized through restimulation of expanded cells followed by intracellular cytokine staining. Direct ex vivo immunophenotyping was performed by flow cytometry.

Results T-cell immunogenicity analysis was assessed in available samples from cohorts A (n=3) and D (n=7) across multiple timepoints during the course of treatment. Neoantigen-specific T cells were induced in all patients tested. There was consistent induction of de novo T-cell responses in both cohorts and longitudinal immunogenicity analyses showed sustained T-cell responses to targeted neoantigens, including in blood samples collected at 30 weeks and beyond post start of treatment. Increases in pre-existing neoantigen responses that were present at baseline (endogenous) or after pembrolizumab run-in were observed following mRNA-4157 therapy. Combination of therapy drove expansion of effector CD4 and CD8 T cells with cytotoxic potential.

Conclusions In this phase 1 first-in-human study, mRNA-4157 as a monotherapy or in combination with pembrolizumab showed immunogenicity in patients with resected NSCLC or melanoma. These data demonstrate the ability of the algorithm to select neoantigens with tumor-infiltrating lymphocyte reactivities, support the mechanism of action hypothesized for mRNA-4157, and underscore the potential clinical benefit of an INT approach.