Session PO.CT02.02 - Phase II Clinical Trials 2

CT224 / 14 - mRNA-4157, a personalized cancer vaccine, in combination with pembrolizumab, demonstrates trend for improved recurrence free survival compared to pembrolizumab alone in adjuvant melanoma patients across tumor mutational burden subgroups

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Abstract

Background: The open-label randomized Phase 2 mRNA-4157-P201/Keynote-942 trial met its primary endpoint of prolonged recurrence free survival (RFS) in patients with resected high-risk stage III/IV melanoma. Tumor immunogenicity provides a favorable landscape for inflammatory processes associated with clinical benefit to checkpoint inhibitors (ICI) and tumor mutational burden (TMB) has been shown to be an independent predictor of treatment outcomes in patients treated with ICI therapy. mRNA-4157 is a novel mRNA-based personalized cancer vaccine which encodes up to 34 patient-specific tumor neoantigens. Here we report analyses of baseline biopsies from the trial to explore the novel mechanism of action hypothesized to augment endogenous anti-tumor responses and generate immunity to additional tumor neoantigens.

Methods: Paraffin-embedded formalin-fixed baseline tumor core biopsies underwent whole exome sequencing (WES) and whole transcriptome sequencing. According to the established WES genomic score for pembrolizumab, the TMB high threshold utilized for analysis was 175/exome (10 mutations/megabase per F1CDx). The distribution of TMB expression in baseline tumor samples across study arms and their association with the primary RFS endpoint was evaluated. The association with RFS of other markers of inflamed tumors, including those established for pembrolizumab (e.g. gene expression profile (GEP) and PD-L1 expression) was also assessed.

Results: The RFS benefit of mRNA-4157 and pembrolizumab combination compared to pembrolizumab monotherapy observed in the intention-to-treat population was maintained with a similar treatment effect magnitude across both high (HR = 0.65; 95% CI: 0.3, 1.5) and low (HR = 0.59; 95% CI: 0.3,1.4) TMB subpopulations. In line with observations from historical data for pembrolizumab, improved RFS was observed in high TMB compared to low TMB patient subgroups in the pembrolizumab monotherapy arm. The trend for increased RFS benefit in the high TMB subpopulation was maintained in the mRNA-4157 and pembrolizumab study arm. Additional subgroup analyses (e.g. GEP and PD-L1) were assessed and will be discussed.

Conclusions: Our results indicate that mRNA-4157 demonstrates improvements in RFS irrespective of TMB status when administered in combination with pembrolizumab compared to pembrolizumab monotherapy in patients with resected high-risk cutaneous melanoma. The novel mechanism of action of mRNA-4157 may both deepen the activity of pembrolizumab and broaden the population of patients that can benefit from immune therapy. The association between TMB and mRNA-4157 treatment effect will be further explored in upcoming planned studies.