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INDIVIDUALIZED NEOANTIGEN THERAPY mRNA-4157 (V940) PLUS PEMBROLIZUMAB IN RESECTED MELANOMA: 3-YEAR UPDATE FROM THE mRNA-4157-P201 (KEYNOTE-942) TRIAL

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Background: mRNA-4157 is a novel, mRNA-based individualized neoantigen therapy designed to increase endogenous antitumor T-cell responses by targeting unique patient (pt) tumor mutations. In the primary analysis of the Ph 2 mRNA-4157-P201 (KEYNOTE-942) trial (median planned follow-up, 23 mo), pts with completely resected high-risk stage IIIB–IV cutaneous melanoma receiving mRNA-4157 + pembrolizumab (pembro; combo) had prolonged recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs pembro alone (Weber JS, et al. *Lancet.* 2024).

Methods: Pts were assigned 2:1 to mRNA-4157 (1 mg IM, max 9 doses) + pembro (200 mg IV, max 18 cycles) or pembro alone. The primary endpoint was investigator-assessed RFS; secondary endpoints were DMFS and safety. This planned supportive analysis was triggered when the last randomized pt had ≥2 y follow-up. Translational subgroup analyses were also reported. HLA genotypes were analyzed by exome sequencing of DNA from PBMC. RFS and DMFS were not formally tested; nominal 2-sided p-values are descriptive.

Results: With an additional year follow-up (data cutoff, 03 Nov 2023; median [range], 34.9 [25.1–51.0] mo) after primary analysis, minimal new events occurred. RFS benefit in the combo vs pembro arm was maintained with 49% risk reduction in recurrence and/or death (HR [95% CI], 0.510 [0.288–0.906]; 2-sided nominal p-value 0.019). The 2.5-yr RFS rate of combo treatment (tx) vs pembro alone was 74.8% vs 55.6%. Combo tx also produced clinically meaningful, sustained improvement in DMFS vs pembro alone (HR [95% CI], 0.384 [0.172–0.858], 2-sided nominal p-value 0.0154). OS favored combo vs pembro alone; 2.5-y OS rate was 96.0% vs 90.2% (HR [95% CI], 0.425 [0.114–1.584]). RFS benefit of combo vs pembro was maintained in TMB high (HR [95% CI], 0.564 [0.253–1.258]), TMB non-high (0.571 [0.245–1.331]), PD-L1 positive (0.471 [0.226–0.979]), PD-L1 negative (0.147 [0.034–0.630]), and ctDNA negative (0.207 [0.091–0.470]) subgroups; ctDNA positive HR was not estimable.
No significant associations between individual HLA alleles and RFS were observed in either tx arm. Maximal heterozygosity at HLA class I genotype loci (A, B, C) improved RFS vs homozygosity for ≥1 locus in the pembro arm (HR [95% CI], 0.425 [0.179–1.01]) but not combo arm (1.252 [0.498–3.146]).
mRNA-4157 was well tolerated and combo tx had a safety profile consistent with previous analysis with no potentiation of immune-related AEs.

Conclusions: The current analysis with ~3 y median follow-up showed durable and meaningful long-term RFS and DMFS benefit with mRNA-4157 + pembro vs pembro alone. A trend for improved OS with combo tx was also observed. HLA and translational subgroup results suggest mRNA-4157 + pembro may benefit a broader pt population vs pembro alone.