Session CTPL01 - Harnessing the Immune System in the Clinic

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CT001 - A personalized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma: Efficacy and safety results from the randomized, open-label Phase 2 mRNA-4157-P201/Keynote-942 trial

April 16, 2023, 12:45 PM - 1:00 PM | Chapin Theater - Convention Center

Presenter/Authors

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Disclosures

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Abstract

Background: Targeting of mutation-derived epitopes (neoantigens) by T cells has been demonstrated to drive anti-tumor immune responses. mRNA-4157 is a novel mRNA-based personalized cancer vaccine, which encodes up to 34 patient-specific tumor neoantigens. It was hypothesized mRNA-4157 could synergize with adjuvant pembrolizumab to improve recurrence free survival (RFS) in patients with resected stages IIIB/IIIC/IIID and IV melanoma.

Methods: Eligible patients with completely resected, high-risk cutaneous melanoma were randomly assigned 2:1 (stratified by stage) to receive mRNA-4157 in combination with pembrolizumab or pembrolizumab alone. mRNA-4157 (1mg) was administered intramuscularly every 3 weeks for a total of 9 doses and pembrolizumab (200mg) intravenously was given every 3 weeks for up to 18 cycles. Safety was evaluated as a secondary endpoint. RFS in the overall intention-to-treat population was the primary end point. The study was designed with 80% power to detect a hazard ratio (HR) of 0.5 with an overall 1-sided type I error of 0.1 when a total of 40 RFS events were observed. The primary analysis for RFS was specified to occur after all patients completed a minimum of 12 months on study and at least 40 RFS events were observed.

Results: 107 patients received the combination of mRNA-4157 with pembrolizumab and 50 patients were treated with pembrolizumab monotherapy. Recurrence or death was reported in 24 of 107 patients (22.4%) in the combination arm and in 20 of 50 patients (40%) in the monotherapy arm, at a median follow-up of 101 and 105 weeks respectively. 18-month RFS rates (95% CI) were 78.6% (69.0%, 85.6%) vs 62.2% (46.9%, 74.3%) in the combination and monotherapy arm respectively. The combination showed protocol defined statistical significance and a clinically meaningful improvement in RFS compared to pembrolizumab, with a reduction in the risk of recurrence or death by 44% (HR = 0.561; 95% CI: (0.309, 1.017); stratified log-rank test 1-sided p-value of 0.0266. The majority of treatment related adverse events were Grade 1/2. The number of patients reporting treatment related Grade ≥ 3 adverse events was generally similar between the arms (25% vs 18%, respectively). The most common mRNA-4157 related Grade 3 event was fatigue. No Grade 4 or Grade 5 events related to mRNA-4157 were reported. No potentiation of immune-mediated adverse events were observed with the addition of mRNA-4157 to pembrolizumab.

Conclusions: mRNA-4157 in combination with pembrolizumab as adjuvant therapy for resected high-risk melanoma significantly prolonged RFS compared to pembrolizumab without an increase in clinically meaningful adverse events. These results are the first to demonstrate improvement of RFS over adjuvant standard of care PD-1 blockade in resected high-risk melanoma and provide the first randomized evidence that a personalized neoantigen approach is potentially beneficial for cancer patients. A phase 3 study will be initiated in patients with melanoma.