LBA9515

Minimal Residual Disease by Circulating Tumor DNA as a Biomarker of Recurrence-free Survival in Resected High-risk Melanoma Patients Treated With mRNA-4157 (V940), a Personalized Cancer Vaccine, and Pembrolizumab

Matteo S. Carlino,[1,*] Adnan Khattak,[2,3] Jeffrey S. Weber,[4] Tarek Meniawy,[5] Ryan J. Sullivan,[6] Matthew H. Taylor,[7] Kevin B. Kim,[8] Meredith McKean,[9] Mark B. Faries,[10] C. Lance Cowey,[11] Geoffrey T. Gibney,[12] Jason J. Luke,[13] Sajeve S. Thomas,[14] Anjali Rao,[15] Vasudha Sehgal,[15] Igor Feldman,[15] Praveen Aanur,[15] Michelle Brown,[15] Robert S. Meehan,[15] Celine Robert-Tissot,[15] Georgina V. Long[16]

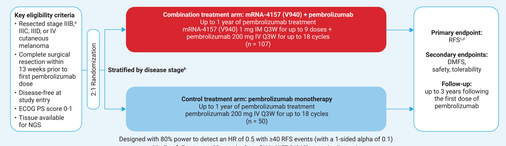
[1]Westmead and Blacktown Hospitals, The Melanoma Institute Australia and the University of Sydney, Sydney, Australia; [2]Hollywood Private Hospital, Nedlands, Australia; [3]Edith Cowan University, Perth, Australia; [4]NYU Langone Medical Center, New York, NY, USA; [5]Saint John of God Subiaco Hospital, Subiaco, Australia; [6]Massachusetts General Hospital, Boston, MA, USA; [7]Providence Cancer Institute, Franz Clinic, Portland, OR, USA; [8]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [9]Sarah Cannon Research Institute, Nashville, TN, USA; [10]The Angeles Clinic and Research Institute, Los Angeles, CA, USA; [11]Texas Oncology, Dallas, TX, USA; [12]Lombardi Cancer Center, Washington, DC, USA; [13]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [14]Orlando Health, Orlando, FL, USA; [15]Moderna, Inc., Cambridge, MA, USA; [16]Melanoma Institute Australia, The University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia.

*Presenting author.

Background

- The open-label, randomized, phase 2 mRNA-4157-P201/KEYNOTE-942 trial (**Figure 1**) met the primary endpoint of recurrence-free survival (RFS) with the combination of mRNA-4157 (V940) and pembrolizumab versus pembrolizumab monotherapy in patients with resected high-risk stage III/IV melanoma (hazard ratio [HR]: 0.561; 95% confidence interval [CI]: 0.309, 1.017; 1-sided *P* value = 0.0266)[1]

Figure 1. mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design



DMFS, distant metastasis-free survival, hierarchically tested per protocol; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; IM, intramuscular; ITT, intention-to-treat; IV, intravenous; NGS, next-generation sequencing; Q3W, every 3 weeks; RFS, recurrence-free survival.
[a]Patients with stage IIIB disease were eligible only if relapse occurred within 3 months of prior surgery of curative intent.
[b]According to the 8th edition of the *AJCC Cancer Staging Manual*.
[c]The primary endpoint was investigator-assessed RFS (defined as the time from first dose of pembrolizumab until the date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the ITT population.
[d]The primary analysis for RFS was specified to occur after all patients completed ≥12 months on study and ≥40 RFS events were observed. Descriptive analysis was specified to occur when ≥51 RFS events were observed.
*Time of database cutoff was November 14, 2022.

- mRNA-4157 (V940) is a novel mRNA-based individualized neoantigen therapy that encodes up to 34 patient-specific immunogenic tumor neoantigens and induces antigen-specific T-cell responses against those neoantigens.[2,3] Based on the novel immunotherapy mechanism of action, it was hypothesized that mRNA-4157 (V940) could synergize with the activity of checkpoint inhibitors, such as pembrolizumab, by increasing the antitumor activity of patients' T cells
- Analysis of biomarkers associated with clinical response to pembrolizumab, including tumor mutational burden (TMB), tumor inflammation signature (TIS; related to gene-expression profile), and programmed death ligand-1 (PD-L1), indicated that combination treatment with mRNA-4157 (V940) may deepen the clinical benefit in biomarker-high patients and broaden the effect to patients less likely to respond to pembrolizumab monotherapy[4-10]
- Analysis of circulating tumor DNA (ctDNA) in liquid biopsies at baseline may be used to predict clinical benefit from cancer therapy and identify patients at higher risk of relapse across multiple cancer types. In the adjuvant setting, personalized ctDNA assays are a highly sensitive approach that enables detection of minimal residual disease (MRD) post resection, which has been associated with higher risk across various indications[11,12]

Objectives

- To assess the distribution of patients with MRD at baseline across study arms
- To assess RFS (the primary study endpoint) in patient subgroups that are ctDNA-positive or ctDNA-negative at baseline
- To assess the prognostic value of ctDNA status at baseline

Methods

- ctDNA was assessed on baseline plasma samples using the personalized amplicon-based next-generation sequencing NeoGenomics (RaDaR®) assay. Tumor core biopsies and matched whole blood samples were subjected to whole exome sequencing (WES) to identify up to 48 patient-specific somatic variants most suitable for MRD detection
  - ctDNA was not evaluable at baseline for 20.4% (32/157) of patients from this study due to unavailability of plasma sample at baseline (mRNA-4157 (V940) + pembrolizumab: n = 15; pembrolizumab monotherapy: n = 14) or insufficient number of RaDaR® variants identified in WES data (quality-control flag; mRNA-4157 (V940) + pembrolizumab: n = 2; pembrolizumab monotherapy: n = 1)
- Tumor biomarker assessments were conducted on formalin-fixed paraffin-embedded tumor core biopsies provided as previously described[13]
- Data are reported for biomarker-evaluable patients and were analyzed by assigned treatment arms
- Biomarker associations with the primary mRNA-4157-P201/KEYNOTE-942 study endpoint, RFS, were evaluated with Kaplan-Meier (KM) analyses and assessed with HRs (95% CIs) based on an unstratified Cox proportional hazards model that included treatment as a covariate within each biomarker subgroup
  - RFS was defined as the time from first dose of pembrolizumab until the date of first recurrence (local, regional, or distant metastasis), a new primary melanoma, or death from any cause
- The prognostic value of ctDNA and tumor biomarkers with respect to RFS was assessed by HRs (95% CIs) comparing ctDNA and biomarker subgroups, pooled from both treatment arms, and obtained from an unstratified Cox proportional hazards model that included biomarker group as a covariate

Results

- The majority of ctDNA-evaluable patients were ctDNA-negative at baseline (88.0% [110/125]; **Table 1**)
- The proportion of ctDNA-positive patients at baseline was slightly higher in the mRNA-4157 (V940) + pembrolizumab arm (14.4%) than in the pembrolizumab monotherapy arm (5.7%)

Table 1. Distribution of ctDNA-positive and ctDNA-negative patients across study arms

ctDNA, n (%)	mRNA-4157 (V940) + pembrolizumab (n = 90)	Pembrolizumab (n = 35)	Total (n = 125)
Positive	13 (14.4)	2 (5.7)	**15 (12.0)**
Negative	77 (85.6)	33 (94.3)	**110 (88.0)**

ctDNA, circulating tumor DNA.

- Baseline disease characteristics and tumor biomarker levels (TMB, TIS, and PD-L1) were generally similar between the ctDNA-evaluable population (n = 125) and the overall intention-to-treat (ITT) population (N = 157; **Table 2**)
- The ctDNA-non-evaluable population (n = 32) had baseline disease characteristics, TIS, and PD-L1 expression similar to those of the total ITT population (N = 157)
  - The mean TMB was lower in the ctDNA-non-evaluable subgroup (mean = 561) than in the overall ITT population (mean = 818)
- Within ctDNA-negative patients, baseline disease characteristics, as well as TIS and PD-L1, were generally balanced between both study arms (**Table 2**)
  - There was a larger subgroup of TMB-high patients in the mRNA-4157 (V940) + pembrolizumab arm (80.0% [72/90]) compared to the pembrolizumab monotherapy arm (62.9% [22/35])
  - In ctDNA-negative patients (n = 110), the RFS HR was 0.254 (95% CI: 0.106, 0.607) with adjustment by TMB versus 0.225 (95% CI: 0.095, 0.531) without adjustment by TMB, suggesting that the RFS treatment effect was robust and not driven by TMB

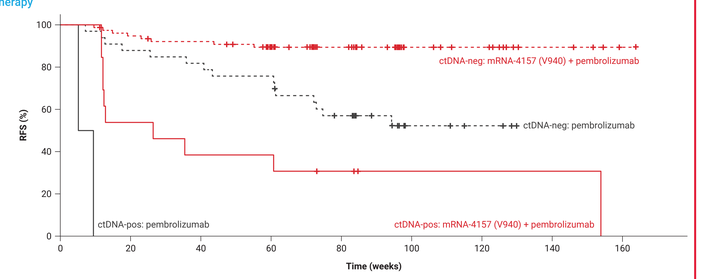
Table 2. Baseline characteristics across ctDNA-evaluable, ctDNA-non-evaluable, and ITT populations; baseline characteristics by treatment arm and ctDNA status

	ctDNA status			ctDNA-positive		ctDNA-negative	
	Evaluable (n = 125)	Non-evaluable (n = 32)	ITT (N = 157)	mRNA-4157 (V940) + pembrolizumab (n = 13)	Pembrolizumab (n = 2)	mRNA-4157 (V940) + pembrolizumab (n = 77)	Pembrolizumab (n = 33)
Sex, n (%)							
Female	40 (32.0)	16 (50.0)	56 (35.7)	4 (30.8)	0	26 (33.8)	10 (30.3)
Male	85 (68.0)	16 (50.0)	101 (64.3)	9 (69.2)	2 (100)	51 (66.2)	23 (69.7)
Age, years							
Mean (SD)	60.9 (13.3)	60.2 (15.5)	60.7 (13.7)	65.0 (11.4)	67.5 (10.6)	61.2 (13.9)	58.0 (12.4)
Median (range)	63.0 (26.0, 83.0)	60.5 (24.0, 89.0)	62.0 (24.0, 89.0)	67.0 (46.0, 81.0)	67.5 (60.0, 75.0)	63.0 (26.0, 83.0)	61.0 (26.0, 76.0)
Age group, n (%)							
<65 years	68 (54.4)	19 (59.4)	87 (55.4)	6 (46.2)	1 (50.0)	42 (54.5)	19 (57.6)
≥65 years	57 (45.6)	13 (40.6)	70 (44.6)	7 (53.8)	1 (50.0)	35 (45.5)	14 (42.4)
Race, n (%)							
White	119 (95.2)	32 (100)	151 (96.2)	13 (100)	2 (100)	73 (94.8)	31 (93.9)
Not reported	6 (4.8)	0	6 (3.8)	0	0	4 (5.2)	2 (6.1)
ECOG PS score, n (%)							
0	105 (84.0)	25 (78.1)	130 (82.8)	9 (69.2)	1 (50.0)	67 (87.0)	28 (84.8)
1	20 (16.0)	4 (12.5)	24 (15.3)	4 (30.8)	1 (50.0)	10 (13.0)	5 (15.2)
Missing	0	3 (9.4)	3 (1.9)	0	0	0	0
Disease stage at randomization, n (%)							
IIIC	103 (82.4)	28 (87.5)	131 (83.4)	11 (84.6)	2 (100)	63 (81.8)	27 (81.8)
IIID	4 (3.2)	0	4 (2.5)	1 (7.7)	0	1 (1.3)	2 (6.1)
IV	18 (14.4)	4 (12.5)	22 (14.0)	1 (7.7)	0	13 (16.9)	4 (12.1)
TMB[a]							
Mean (SD)	878 (1210)	561 (634)	818 (1130)	608 (727)	79.0 (83.4)	1060 (1340)	619 (963)
Median (range)	400 (4.00, 7600)	361 (2.00, 2020)	400 (2.00, 7600)	235 (70.0, 2210)	79.0 (20.0, 138)	563 (17.0, 7600)	264 (4.00, 4700)
Missing, n (%)	0	3 (9.4)	3 (1.9)	0	0	0	0
TIS							
Mean (SD)	4.44 (1.23)	4.69 (1.22)	4.49 (1.23)	4.08 (1.21)	4.34 (2.67)	4.48 (1.25)	4.49 (1.16)
Median (range)	4.54 (0.77, 7.14)	4.95 (1.83, 6.56)	4.56 (0.77, 7.14)	4.02 (2.07, 6.71)	4.34 (2.45, 6.23)	4.59 (0.77, 7.14)	4.57 (2.13, 6.88)
Missing, n (%)	0	3 (9.4)	3 (1.9)	0	0	0	0
PD-L1 CPS ≥1, n (%)							
Positive	79 (63.2)	17 (53.1)	96 (61.1)	9 (69.2)	2 (100)	49 (63.6)	19 (57.6)
Negative	15 (12.0)	3 (9.4)	18 (11.5)	2 (15.4)	0	9 (11.7)	4 (12.1)
Missing	31 (24.8)	12 (37.5)	43 (27.4)	2 (15.4)	0	19 (24.7)	10 (30.3)

CPS, combined positivity score; ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; ITT, intention-to-treat; PD-L1, programmed death ligand-1; SD, standard deviation; TIS, tumor inflammation signature; TMB, tumor mutational burden.
[a]TMB = the number of nonsynonymous tumor mutations with an allele frequency ≥5%.

- In ctDNA-negative patients at baseline, a substantial RFS benefit with mRNA-4157 (V940) + pembrolizumab versus pembrolizumab monotherapy was observed (HR: 0.225; 95% CI: 0.095, 0.531; **Figure 2**)
  - RFS KM curves started to separate within 24 weeks, as compared to 40 weeks observed in the overall ITT population[1]
- A trend towards RFS benefit of mRNA-4157 (V940) + pembrolizumab versus pembrolizumab monotherapy was also observed for ctDNA-positive patients at baseline; however, the small sample size limits the interpretation of these results

Figure 2. Improved RFS in ctDNA-negative patients at baseline treated with a combination of mRNA-4157 (V940) + pembrolizumab compared to pembrolizumab monotherapy



Number at risk

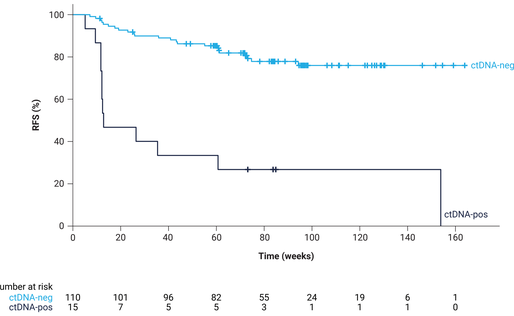
ctDNA-neg: mRNA-4157 (V940) + pembrolizumab	77	72	69	57	38	18	15	6	1
ctDNA-neg: pembrolizumab	33	29	27	25	17	6	4	0	0
ctDNA-pos: mRNA-4157 (V940) + pembrolizumab	13	7	5	5	3	1	1	1	0
ctDNA-pos: pembrolizumab	2	0	0	0	0	0	0	0	0

	mRNA-4157 (V940) + pembrolizumab vs pembrolizumab HR (95% CI)	mRNA-4157 (V940) + pembrolizumab Events, n/N (%)	Pembrolizumab Events, n/N (%)
ctDNA-pos	NE	10/13 (76.9)	2/2 (100)
ctDNA-neg	0.225 (0.095, 0.531)	8/77 (10.4)	15/33 (45.5)

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; NE, not evaluable; neg, negative; pos, positive; RFS, recurrence-free survival.

- Assessments of the association of various biomarkers with RFS across study arms suggested that ctDNA status at baseline had negative prognostic value (RFS HR comparing ctDNA status: 0.149; 95% CI: 0.073, 0.306) in patients with resected high-risk melanoma (**Figure 3**; **Table 3**)

Figure 3. ctDNA status at baseline has prognostic value in patients with resected high-risk melanoma



Number at risk

ctDNA-neg	110	101	96	82	55	24	19	6	1
ctDNA-pos	15	7	5	5	3	1	1	1	0

ctDNA, circulating tumor DNA; neg, negative; pos, positive; RFS, recurrence-free survival.

Table 3. Prognostic value of baseline ctDNA and other tumor biomarkers in patients with resected high-risk melanoma

RFS HR (95% CI) Comparing Biomarker Subgroups in the Biomarker-evaluable Population			
ctDNA-neg vs ctDNA-pos	TMB-high vs TMB–non-high	TIS-high vs TIS-low	PD-L1–pos vs PD-L1–neg
0.149 (0.073, 0.306) n (110 vs 15)	0.476 (0.263, 0.862) n (109 vs 45)	0.452 (0.242, 0.844) n (77 vs 77)	0.661 (0.299, 1.46) n (96 vs 18)

CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; neg, negative; PD-L1, programmed death ligand-1; pos, positive; RFS, recurrence-free survival; TIS, tumor inflammation signature; TMB, tumor mutational burden.

Conclusions

- MRD detection by plasma ctDNA assay at the start of adjuvant melanoma treatment was observed in only 12% of patients in mRNA-4157-P201/KEYNOTE-942 but was associated with shorter RFS in those patients
- In ctDNA-negative patients, the combination treatment of mRNA-4157 (V940) + pembrolizumab improved RFS compared to pembrolizumab monotherapy
- Data in the mRNA-4157-P201/KEYNOTE-942 study suggest that MRD detection by ctDNA has prognostic value that may be comparable, or potentially stronger than tissue-based biomarkers in patients with resected high-risk melanoma and should be further explored
- The reduced sample size and low number of events in the ctDNA-evaluable group limit comparison of these results with those of the ITT population, and the association between MRD and mRNA-4157 (V940) treatment effect will be further explored in upcoming planned studies. Additional analyses, including assessment of longitudinal ctDNA patterns, are ongoing

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Acknowledgments

This study (ClinicalTrials.gov Identifier: NCT03897881) was sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme, LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Editorial and medical writing support were provided by Austin Horton, PhD, of Lumanity Communications Inc., and were funded by Moderna, Inc.

Author contact: Celine Robert-Tissot, Celine.Robert-Tissot@modernatx.com

Poster presented at the American Society of Clinical Oncology (ASCO®) Annual Meeting; June 2-6, 2023; Chicago, IL, USA.