CT141

mRNA-4157 (V940) Individualized Neoantigen Therapy + Pembrolizumab in Advanced Unresectable HPV-negative Head and Neck Carcinoma: Clinical and Translational Analysis

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Background

- Patients with human papillomavirus negative (HPV-) head and neck squamous cell carcinoma (HNSCC) have poor prognosis with a 5-year survival rate <50%[1]; limited durable clinical responses to PD1/PD-L1 blockade may be due to diminished effector cytolytic activity and clonal diversity[2–5]
- mRNA-4157 (V940) is a novel mRNA-based individualized neoantigen therapy that encodes up to 34 neoantigens inducing specific antitumor T cell activation; durable clinical responses with pembrolizumab have been shown in melanoma[6]
- mRNA-4157-P101/KEYNOTE-603 (NCT03313778) is an ongoing phase 1 study evaluating mRNA-4157 alone or in combination with pembrolizumab in solid tumors

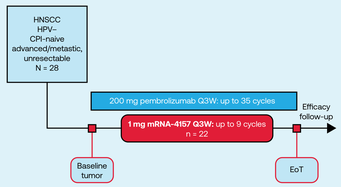
Objective

- To assess safety, tolerability, preliminary clinical activity, and translational biomarkers for mRNA-4157 + pembrolizumab in patients with HPV- HNSCC (Part C)

Methods

- Part C of this study enrolled patients ⩾18 years old with checkpoint inhibitor (CPI)-naive, recurrent/metastatic HPV- HNSCC
- Eligible patients received 200 mg pembrolizumab Q3W IV during a 6-week lead-in (during mRNA-4157 manufacture), then combined with 1 mg mRNA-4157 for up to 9 doses Q3W IM, followed by pembrolizumab, until disease progression, unacceptable toxicity, or 35 total cycles of pembrolizumab (**Figure 1**)
- Safety, tolerability, and preliminary clinical response were assessed per RECIST v1.1 criteria
- Longitudinal assessments of immunogenicity via IFN-γ ELISpot and ctDNA detection were performed using collected peripheral blood
- Next-generation sequencing was performed on baseline tumor biopsies

Figure 1. mRNA-4157-P101/KEYNOTE 603 Part C study design for patients with HPV- HNSCC



EoT, end of treatment.

Results

- Of 28 enrolled patients, 22 received mRNA-4157 + pembrolizumab (**Table 1**); six discontinued prior to receiving mRNA-4157 due to death or disease progression/deterioration and were not included in this analysis. All patients are off treatment as of the clinical cutoff date (May 4, 2023)

Table 1. Baseline characteristics

Baseline characteristics	mRNA-4157 + pembrolizumab N = 22
Sex, n (%)	
Male	14 (63.6)
Female	8 (36.4)
Age, median (range), years	62.5 (29–81)
⩾65 years, n (%)	9 (40.9)
ECOG PS score, n (%)	
0	9 (40.9)
1	13 (59.1)
Prior immuno-oncology therapy, n	0
Number of prior systemic therapies, n (%)	
0	3 (13.6)
1	15 (68.2)
⩾2	4 (18.2)
PD-L1, n	
Not evaluable	7
CPS ⩾1	15

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1.

- After the clinical cutoff date, the median (range) follow-up was 38.4 (11.7–194.9) weeks
- 8 (36.4%) patients completed 9 doses of mRNA-4157 (median 5.5 doses, range 1–9). Median (range) treatment duration of mRNA-4157 was 13.8 (0.1–26.1) weeks, and 20.1 (6.1–68.0) weeks for pembrolizumab. Most patients (n = 19/22, 86.4%) received 2 cycles of lead-in pembrolizumab (range, 2–4 cycles)

Table 2. Summary of TEAEs in ⩾2 patients

TEAE[a]	mRNA-4157 + pembrolizumab N = 22	
	Any grade	Grade 3
All TEAEs, n (%)	22 (100.0)	14 (63.6)
mRNA-4157-related TEAE	15 (68.2)	3[b] (13.6)
Influenza-like illness	9 (40.9)	0
Injection-site pain	8 (36.4)	0
Pyrexia	8 (36.4)	1 (4.5)
Fatigue	6 (27.3)	0
Vaccination-site pain	6 (27.3)	0
Chills	3 (13.6)	0
Nausea	3 (13.6)	0
Headache	2 (9.1)	0
Injection-site erythema	2 (9.1)	0
Lipase increased	2 (9.1)	1 (4.5)
Lymphocyte count decreased	2 (9.1)	1 (4.5)
Pain in extremity	2 (9.1)	0

[a]Defined as any event not present before exposure to mRNA-4157 or pembrolizumab, or any present event that worsens in intensity or frequency after exposure to study drug; [b]Grade 3 AEs were related to both mRNA-4157 and pembrolizumab; there were no grade 4 or 5 AEs related to mRNA-4157.

TEAE, treatment-emergent adverse event.

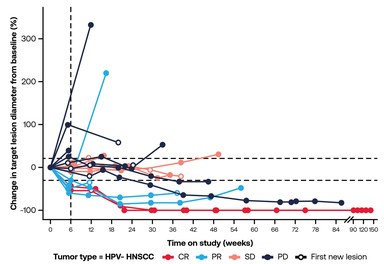
Safety

- Most mRNA-4157–related TEAEs were grade 1–2; the most common being influenza-like illness, injection-site pain, and pyrexia (**Table 2**)
- The safety profile was consistent with mRNA-4157 monotherapy and the well-characterized safety profile of pembrolizumab, with AEs being managed with established management guidelines

Clinical Response

- The objective response rate was 27.3% (6/22, 95% CI 10.7–50.2) and disease control rate was 63.6% (14/22, 95% CI 40.7–82.8), with best overall responses of 2 (9.1%) complete and 4 (18.2%) partial responses, and 8 (36.4%) stable disease at data cutoff (**Figure 2**)

Figure 2. Percent change of target lesion from baseline over time



The vertical reference line marks the scheduled start of mRNA-4157 + pembrolizumab dosing Q3W that followed the pembrolizumab Q3W lead-in dose. The horizontal reference lines are plotted at y = 20 for PD (⩾20% increase in the sum of diameters of target lesions) and y = −30 for PR (⩾30% decrease in the sum of diameters of target lesions).

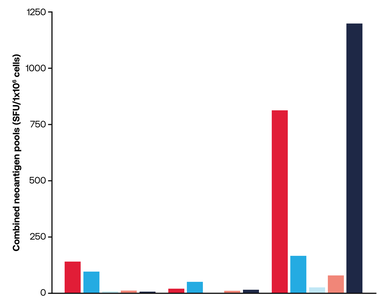
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

- Kaplan–Meier estimated median (95% CI) progression-free survival and overall survival were 15.0 (11.6–38.6) weeks and 107.1 (42.7–NE) weeks, respectively

Biomarkers

- Sustained de novo T cell induction to targeted neoantigens was seen in 5/5 available patient samples (**Figure 3**); IFN-γ responses were higher post mRNA-4157 + pembrolizumab compared with baseline
- Decrease in ctDNA levels post-baseline were observed in 3/4 patients with disease control and in 0/3 patients with progressive disease (**Figure 4**)

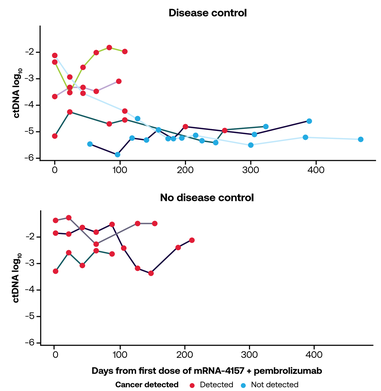
Figure 3. Neoantigen-reactive T cell response to neoantigen peptide pools



Immunogenicity was evaluable in 5/22 (22.7%) patients with all 3 timepoints; 7 patients had insufficient sample quantity or quality. Data are plotted as sum of responses to mRNA-4157–specific neoantigen peptide pools (mix of individualized neoantigen peptides) at indicated timepoints during treatment. Patients with CR, PR, or SD were classified as 'disease control' and patients with PD were classified as 'no disease control'.

DC, disease control; NDC, no disease control; SFU, spot forming unit.

Figure 4. ctDNA dynamics



There were 8 (36.4%) patients with evaluable samples; 14 patients had insufficient sample quantity or quality.

- Differential gene expression from pre-treatment tumor samples suggests increased baseline inflamed T cell-associated gene expression in patients with disease control (**Figure 5A**)
- Hallmark IL-2/STAT5 signaling and hallmark inflammatory response at baseline were found to be significantly enriched in patients with disease control by de novo Gene Set Enrichment Analysis (Benjamini–Hochberg-adjusted descriptive $P < 0.05$; **Figure 5B**)

Figure 5. (A) Heatmap of transcript expression by disease control status and (B) gene set enrichment analyses from baseline tumor samples

(A) Box indicates upregulated genes associated with inflamed T cell expression. (B) Gene set enrichment analysis categorized as hallmark pathways; blue indicates statistical significance and red indicates no statistical significance with multiplicity adjusted by Benjamini–Hochberg procedure.

TMB, tumor mutational burden.

Conclusions

- mRNA-4157 + pembrolizumab was associated with preliminary positive clinical responses and disease control in patients with HPV- HNSCC, including two complete responses
- mRNA-4157 + pembrolizumab was well tolerated, with an mRNA-4157 safety profile consistent with mRNA-4157 monotherapy
- mRNA-4157 + pembrolizumab showed evidence of activation of immune responses
  - Patients within the disease control subgroup demonstrated baseline inflamed T cell gene expression with decreased ctDNA levels post baseline
- Randomized assessment of the mRNA-4157 + pembrolizumab treatment effect in the advanced disease setting may be warranted

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