Ethics Approval The study was approved by participating study sites' Institutional Review Boards and the Sponsor has conducted the trial in full compliance with all GCP and FDA regulations.

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Clinical trials in-progress

798 SAFETY, TOLERABILITY, AND IMMUNOGENICITY OF MRNA-4157 IN COMBINATION WITH PEMBROLIZUMAB IN SUBJECTS WITH UNRESECTABLE SOLID TUMORS (KEYNOTE-603): AN UPDATE

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Background T-cell targeting of mutation-derived epitopes (neoantigens) has shown to drive anti-tumor responses. Immunizing patients against such neoantigens in combination with a checkpoint inhibitor (CPI) may elicit greater anti-tumor responses than CPI alone. Mutations are rarely shared between patients, thus requiring a personalized approach to vaccine design. mRNA-4157 is a lipid encapsulated mRNA based personalized cancer vaccine encoding neoantigens selected using a proprietary algorithm to induce neoantigen specific T cells and associated anti-tumor responses. This report includes updates from the mRNA-4157 Phase1(P1) study. The initial data was presented at ASCO2019.[1]

Methods This study evaluates the safety and efficacy of mRNA-4157 as monotherapy in patients with resected solid tumors (Part A) and in combination with pembrolizumab in patients with advanced/metastatic solid tumors (Parts B). The selected solid tumors in Part A-B includes melanoma, bladder carcinoma, HPV-negative (HPV-neg) HNSCC, NSCLC, SCLC, MSI-High (MSI-h), or TMB-High cancers. Expansion cohorts includes patients with CPI-naïve MSS-CRC and HPV-neg HNSCC (Part C) and with resected melanoma (Part D). Patients receive up to 9 cycles (Q3W) of mRNA-4157 by intramuscular injection at up to 1 mg alone (Part A) or in combination with pembrolizumab (200 mg IV Q3W, Parts B-D). Pembrolizumab is administered for two cycles before the first dose of mRNA-4157 and may continue after 9 cycles of combination. Endpoints include safety, tolerability, efficacy and biomarker assessments.

Results 79 patients received mRNA-4157; 16 as monotherapy and 63 in combination with pembrolizumab. Only low grade and reversible treatment related AEs were reported. 14/16 Part A patients (3 melanoma, 11 NSCLC, 2 MSI-h CRC) remained disease free on study. 28 patients in Parts B (6 bladder, 2 HNSCC, 3 melanoma, 10 NSCLC, 2 SCLC, 4 MSI-h tumor, 1 TMB-h tumor), 27 patients in Part C (10 HNSCC and 17 MSS-CRC), and 8 patients with resected melanoma (Part D) received combination. 3 CR (1 HNSCC, 1 MSI-h CRC and 1 MSI-h prostate), and 8 PR (1 bladder, 4 HNSCC, 2 SCLC and 1 MSI-h endometrial) were observed with combination. Of 10 CPI-naïve HPV-neg HNSCC patients, the response rate was 50% (1CR, 4PR, 4SD) mPFS 9.8months, which compared favorably to published rates of ~14.6% mPFS 2.0months for pembrolizumab monotherapy.[2 3] Biomarker assessments including immune gene expression profiling will be presented.

Conclusions mRNA-4157 has an acceptable safety profile along with observed clinical responses in combination with pembrolizumab. Preliminary efficacy analysis from CPI-naïve relapsed/refractory HPV-neg HNSCC cohort suggests activity of this combination. Study is ongoing.

Trial Registration NCT03313778

Ethics Approval The study was approved by each participating sites' local IRB.

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799 DURABLE RESPONSES AND IMMUNE ACTIVATION WITH INTRATUMORAL ELECTROPORATION OF PIL-12 PLUS PEMBROLIZUMAB IN ACTIVELY PROGRESSING ANTI-PD-1 REFRACTORY ADVANCED MELANOMA: KEYNOTE 695 INTERIM DATA

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Background Electroporated plasmid IL-12 (TAVO or tavokinogene telseplasmid) is a novel pro-inflammatory intratumoral therapy with substantial single agent activity in melanoma, which has been shown to synergize with anti-PD-1 antibodies in patients predicted as non-responders to anti-PD-1.[1 2] Interim data from patients with stage III/IV melanoma actively progressing on anti-PD-1 antibody are presented herein.

Methods Patients with confirmed disease progression by RECIST v1.1 after at least 12 weeks of treatment on pembrolizumab or nivolumab (or combination checkpoint blockade) and within 12 weeks of last dose (with no intervening

therapies) were enrolled. There was no limit on the number of prior lines of therapy. At least one accessible lesion was electroporated with plasmid IL-12 (pIL-12-EP) on days 1, 5 and 8 every 6 weeks and pembrolizumab was administered every 3 weeks. Tumor response in treated and untreated lesions was assessed by RECIST v1.1 every 12 weeks. Endpoints include ORR, safety, PFS, OS, and DOR.

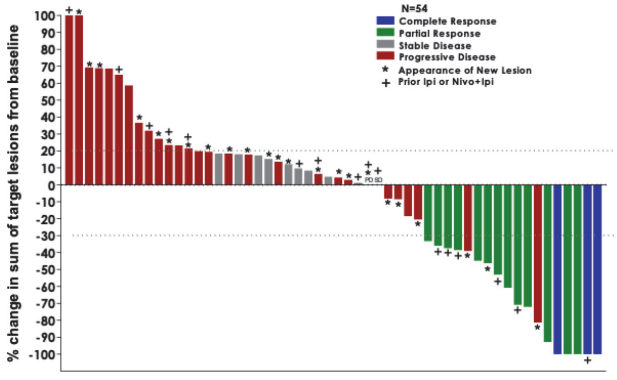
Results The first 56 patients treated of 100 planned were included in this interim analysis. Of these, 84% had Stage IV disease, 30% had M1c or M1d disease, and 27% had prior exposure to ipilimumab. In 54 efficacy evaluable patients the investigator-assessed ORR was 30% (3 CR/13 PR), 5 patients had 100% reduction of target lesions. All responses have been confirmed, only two responding patient progressed while on study, 2 patients completed the study with ongoing responses (figures 1 and 2). In patients with M1c/M1d disease, the ORR was 35.2% (n=6/17). Tumor reduction was observed in untreated lesions in 12 of 12 patients who had unaccessible lesions or accessible untreated lesions. The median overall survival (mOS) and duration of response (mDOR) has not been reached, with a median follow-up time of 13 months. Grade 3 treatment-related adverse events (TRAEs) were seen in 5.4% of patients, and there were no grade 4/5 TRAEs. The rate of grade 3 treatment-emergent (TEAEs) regardless of cause was 23.2%. The median time for pIL-12-EP treatment was 10 minutes (range 2,46). Consistent with prior studies of single-agent pIL-12-EP, tumor IHC, and transcriptomic assessments revealed hallmarks of antigen-specific antitumor immunity in this study. Additional analyses including microbiome, TCR clonality, and peripheral blood biomarker assays will be presented.

Conclusions In this rigorously defined PD-1 antibody refractory patient population, the addition of pIL-12-EP to PD-1 antibody therapy induced deep, durable, systemic response in local treated and distant visceral metastatic untreated lesions with nominal systemic toxicity.

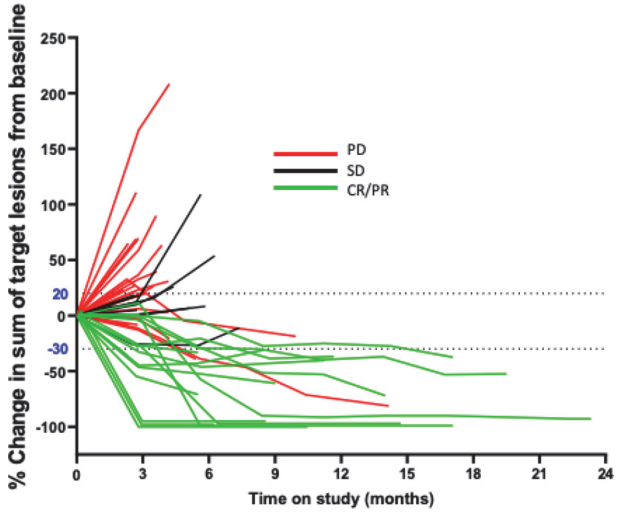
Trial Registration Trial Registration: NCT#03132675

Ethics Approval The study was approved by a central IRB and/or local institutional IRBs/Ethics Committees as required for each participating institution.

Consent Written informed consent was obtained from the patients participating within the trial, the current abstract does not contain sensitive or identifiable information requiring an additional consent from patients.



Abstract 799 Figure 1
Best confirmed overall response by RECIST v1.1 after confirmed progression on anti PD-1



Abstract 799 Figure 2
Percent change in sum of target lesions over time

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800 A PHASE I DOSE ESCALATION AND EXPANSION STUDY OF INTRATUMORALLY ADMINISTERED CV8102 AS A SINGLE-AGENT OR IN COMBINATION WITH ANTI-PD-1 ANTIBODIES IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background CV8102 is a non-coding, non-capped RNA complexed with a carrier peptide activating the innate (via TLR7/8, RIG-I) and adaptive immune system.[1 2] An ongoing phase I trial is investigating i.t. CV8102 either as a single agent or in combination with systemic anti-PD-1 antibodies in patients with advanced melanoma (MEL), squamous cell carcinoma of the skin (cSCC) or head and neck (hnSCC) and adenoid cystic carcinoma (ACC).

Methods An open-label, cohort-based, dose escalation and expansion study in patients with advanced cutaneous melanoma (cMEL), cutaneous squamous cell carcinoma (cSCC), head and neck squamous cell carcinoma (hnSCC) or adenoid cystic carcinoma (ACC) is ongoing investigating i.t. CV8102 as single agent and in combination with anti-PD-1 antibodies.