Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): a randomised, phase 2b study

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Summary

Background Checkpoint inhibitors are standard adjuvant treatment for stage IIB–IV resected melanoma, but many patients recur. Our study aimed to evaluate whether mRNA-4157 (V940), a novel mRNA-based individualised neoantigen therapy, combined with pembrolizumab, improved recurrence-free survival and distant metastasis-free survival versus pembrolizumab monotherapy in resected high-risk melanoma.

Methods We did an open-label, randomised, phase 2b, adjuvant study of mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy in patients, enrolled from sites in the USA and Australia, with completely resected high-risk cutaneous melanoma. Patients with completely resected melanoma (stage IIIB–IV) were assigned 2:1 to receive open-label mRNA-4157 plus pembrolizumab or pembrolizumab monotherapy. mRNA-4157 was administered intramuscularly (maximum nine doses) and pembrolizumab intravenously (maximum 18 doses) in 3-week cycles. The primary endpoint was recurrence-free survival in the intention-to-treat population. This ongoing trial is registered at ClinicalTrials.gov, NCT03897881.

Findings From July 18, 2019, to Sept 30, 2021, 157 patients were assigned to mRNA-4157 plus pembrolizumab combination therapy (n=107) or pembrolizumab monotherapy (n=50); median follow-up was 23 months and 24 months, respectively. Recurrence-free survival was longer with combination versus monotherapy (hazard ratio [HR] for recurrence or death, 0·561 [95% CI 0·309–1·017]; two-sided p=0·053), with lower recurrence or death event rate (24 [22%] of 107 *vs* 20 [40%] of 50); 18-month recurrence-free survival was 79% (95% CI 69·0–85·6) versus 62% (46·9–74·3). Most treatment-related adverse events were grade 1–2. Grade ≥3 treatment-related adverse events occurred in 25% of patients in the combination group and 18% of patients in the monotherapy group, with no mRNA-4157-related grade 4–5 events. Immune-mediated adverse event frequency was similar for the combination (37 [36%]) and monotherapy (18 [36%]) groups.

Interpretation Adjuvant mRNA-4157 plus pembrolizumab prolonged recurrence-free survival versus pembrolizumab monotherapy in patients with resected high-risk melanoma and showed a manageable safety profile. These results provide evidence that an mRNA-based individualised neoantigen therapy might be beneficial in the adjuvant setting.

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Introduction

Neoantigens are immunogenic molecules generally arising from non-synonymous cancer-specific mutations in intracellular proteins that are processed and presented at the cell surface as peptides in association with major histocompatibility complex molecules. Neoantigens can stimulate robust antitumour T-cell responses.[1] Neoantigens are potential targets for cancer therapies, but tumour mutations and their antigen-presenting molecules (ie, human leukocyte antigens) are unique to each patient; no recurrent neoantigen peptide sequences have yet predicted responder patient populations.[2] Studies of tumour-associated antigen vaccines (eg, MAGE-A3, GM2-KLH) in resected melanoma and other cancers either did not show benefit or suggested a detrimental effect.[3,4] However, an individualised neoantigen therapy designed to target a patient's unique set of cancer neoantigens might overcome the limitations of previous approaches.[5,6] Treatment with an individualised neoantigen therapy can increase endogenous neoantigen T-cell responses, induce epitope spreading to new neoantigens (expansion of immune responses to other antigens), and expand immune recognition of neoantigen encoded epitopes on cancer cell surfaces.[1,5,7–9]

Research in context

Evidence before this study

Several adjuvant therapies have been approved and are now considered standard of care for patients with resected stage IIB–IV melanoma, including the checkpoint inhibitors ipilimumab, pembrolizumab, and nivolumab, and the *BRAF* V600-targeted drugs dabrafenib and trametinib. All have been found to prolong recurrence-free survival and distant metastasis-free survival in patients with resected high-risk melanoma. However, many patients still have disease recurrence and metastatic disease after adjuvant checkpoint inhibition, resulting in substantial morbidity and mortality.

Advances in cancer immunology have shown that successes seen with checkpoint inhibitors are linked in part to enhanced immune recognition of neoantigens following immune-checkpoint blockade. Therefore, increasing neoantigen presentation, recognition, and immune activation could augment the effects of immune-checkpoint inhibitors, producing clinically superior outcomes compared with checkpoint blockade alone. Tumour mutations and their antigen-presenting molecules (ie, human leukocyte antigens) are unique to each patient, and no recurrent neoantigen peptide sequences have yet predicted responder patient populations; therefore, a completely individualised strategy might be needed to capture the full benefit of neoantigen therapy.

Added value of this study

To our knowledge, this study is the first randomised trial to show a clinically significant benefit of an individualised neoantigen therapy approach. Treatment with mRNA-4157 in combination with pembrolizumab showed a clinically meaningful improvement in both recurrence-free survival and distant metastasis-free survival compared with pembrolizumab monotherapy. Most adverse events related to either treatment were grade 1–2, and no grade 4–5 events were related to mRNA-4157 in the combination group. Further, the percentage of patients with any grade or grade 3–4 immune-mediated adverse events and serious adverse events was similar between treatment groups.

Implications of all the available evidence

The results of KEYNOTE-942 add to the growing body of evidence showing the clinical utility of individualised neoantigen therapy for the adjuvant treatment of patients with resected high-risk melanoma and show the viability of the individualised neoantigen therapy approach for oncology patients. On the basis of the trial results, a phase 3 registrational study has been initiated (NCT05933577).

Despite standard-of-care adjuvant therapy, including checkpoint inhibitors and combination BRAF–MEK inhibitors, disease recurrence can result in substantial morbidity and mortality. The KEYNOTE-054, Checkmate 238, and COMBI A/D trials showed approximately 50% recurrence rate within 5 years in stage III melanoma following complete resection.[10–12] Several biomarkers might be predictive of outcomes to adjuvant treatment, including tumour mutational burden (TMB), programmed death-ligand 1 (PD-L1) tumour and immune cell expression, and circulating tumour DNA (ctDNA). TMB is associated with neoantigen load and might be a predictive biomarker for response to checkpoint inhibitor therapy.[13] On the basis of its novel mechanism of action, we hypothesised that the individualised neoantigen therapy mRNA-4157 (V940) enhances the activity of checkpoint inhibitors by increasing endogenous T-cell responses and inducing de-novo T-cell responses, resulting in improved clinical benefit with minimal additional adverse events.

mRNA-4157 is an mRNA-based individualised neoantigen therapy encoding up to 34 neoantigens in a lipid nanoparticle formulation and is tailored specifically to an individual's tumour mutanome and human leukocyte antigen type. Neoantigens derived via the internal neoantigen selection algorithm (appendix p 13) and encoded in mRNA-4157 can be endogenously translated to enter the natural cellular antigen processing and presentation pathways. Subsequently, mRNA-4157 can stimulate reactive T cells targeting patient-specific tumour neoantigens, representing a novel modality for the treatment of cancer. Moderna's modified mRNA platform was implemented for the SARS-CoV-2 (COVID-19) vaccine (mRNA-1273), showing its utility and rapid adaptability.[14] Preclinical studies initially characterised the immunogenicity and safety profile of mRNA-4157, indicating that mRNA-4157 induces robust antigen-specific T-cell responses to neoantigens encoded by the mRNA sequence.[6,15] These observations provided biological evidence of the novel mechanism of action of mRNA-4157 and formed the rationale for the randomised phase 2b assessment of mRNA-4157 in combination with pembrolizumab described herein. Therefore, in patients with completely resected high-risk cutaneous melanoma, we aimed to assess whether the combination therapy could improve recurrence-free survival and distant metastasis-free survival with a tolerable toxicity profile in line with current treatments.

Methods

Study design and participants

We did an open-label, randomised, phase 2b, adjuvant study of mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy in patients with completely resected high-risk cutaneous melanoma from sites in the USA and Australia. Eligible patients were aged at least

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See **Online** for appendix

18 years with resectable stage IIIB–IV (per American Joint Committee on Cancer, 8th edn) cutaneous melanoma. Patients with stage IIIB disease were only eligible if relapse occurred within 3 months of previous surgery; acral, mucosal, and uveal melanomas were excluded. Patients had to have had a complete surgical resection no more than 13 weeks before the first pembrolizumab dose and be clinically and radiologically disease-free at study entry. Patients were required to have an Eastern Cooperative Oncology Group performance status score of 0 or 1 and acceptable haematological and chemistry parameters, and to provide tumour and blood samples suitable for next-generation sequencing. Key exclusion criteria included a history of haematological or primary solid tumour malignancy (other than cutaneous melanoma) unless disease-free for at least 5 years, previous treatment with select agents (including investigational agents, checkpoint inhibitors, or live vaccines) immediately before trial enrolment, and presence of certain comorbidities (including active immune diseases, immunodeficiency, and infections). The full inclusion–exclusion criteria are described in the appendix (p 2).

The trial protocol (see appendix) and amendments were approved by relevant independent review or ethics committees at each institution. The trial was done in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonisation. All patients provided written informed consent. The trial was sponsored and overseen by Moderna, in collaboration with Merck Sharp & Dohme, a subsidiary of Merck & Co, Rahway, NJ, USA.

Randomisation and masking

In this open-label, phase 2b study, patients with completely resected high-risk (stage IIIB–IV) cutaneous melanoma were randomly assigned 2:1 to receive mRNA-4157 plus pembrolizumab (combination therapy) or pembrolizumab alone (monotherapy). Randomisation was stratified according to stage, done centrally at enrolment via an interactive web response system on the basis of a block randomisation technique, and done before treatment initiation with pembrolizumab. Some manual allocation was permitted in the protocol to account for manufacturing availability and was used between February and April, 2021 owing to the manufacturing and testing required for the mRNA-1273 COVID-19 vaccine for the COVID-19 pandemic, limiting resources. Manual reallocation was done before tissue collection, next-generation sequencing, and treatment initiation.

Procedures

Each mRNA-4157 individualised neoantigen therapy was produced by use of a proprietary, automated in-house bioinformatics system for neoantigen prediction and therapy design in an integrated manufacturing process (appendix p 13).[15] Patient tumour and blood samples were analysed by use of next-generation sequencing via the Illumina Novaseq Platform (San Diego, CA, USA). Whole-exome sequencing (Personalis, Menlo Park, CA, USA) data were used to assess each patient's mutanome, the entirety of the somatic cancer mutations of a tumour. Additionally, whole-exome sequencing of blood samples was used to establish the patient's human leukocyte antigen type by use of a next-generation sequencing approach (in adherence to the guidelines of the American Society for Histocompatibility and Immunogenetics). The transcriptome was established by RNA sequencing. Patient-specific data (from whole-exome sequencing, RNA sequencing, and human leukocyte antigen typing; appendix p 13) were provided as inputs to the internal automated mRNA-4157 bioinformatics system, which established the amino acid sequences of up to 34 selected neoantigens. The top amino acid candidates were incorporated into an optimised concatemeric mRNA-4157 sequence (long, continuous mRNA molecule), which was transferred electronically for manufacturing of each patient-specific mRNA-4157.

Patients assigned to the combination group received 200-mg pembrolizumab intravenously every 3 weeks during mRNA-4157 manufacturing. Combination treatment began on availability of mRNA-4157, which was administered intramuscularly in alternating limbs at a 1-mg dose with the next scheduled dose of pembrolizumab for synchronous dosing in 3-week cycles for up to nine doses. Dose modification of either treatment was not permitted; however, patients who could not receive their scheduled dose of treatment because of adverse events could, at the discretion of the investigator, omit or delay a dose or stop treatment. Patients received pembrolizumab until disease recurrence, unmanageable toxicity, or completion of 18 cycles, whichever occurred first. After study treatment completion, patients were followed-up until death, withdrawal of consent, loss to follow-up, or 3 years after their first dose of pembrolizumab, whichever occurred earlier.

All patients were assessed by physical examination, blood tests, and radiological imaging (CT or MRI) at baseline, on study (every 12 weeks from first dose of pembrolizumab for 12 months), and during follow-up (every 12 weeks for months 12–24; every 26 weeks for months 24–36). Recurrence was histologically confirmed whenever possible, based on availability of tumour sample. For patients without any event, follow-up was censored at the latest disease evaluation.

Adverse events were collected and categorised by severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 5.0. Immune-mediated adverse events were programmatically established from a list of Medical Dictionary for Regulatory Activities (MedDRA) terms, which was updated in accordance with each new version of MedDRA. In the combination therapy group, adverse

events and serious adverse events were followed-up for 100 days after the last dose of mRNA-4157 or until the start of new anticancer therapy, whichever was earlier. In both treatment groups, adverse events were followed for 30 days (90 days for serious adverse events) after the last dose of pembrolizumab. Relatedness to treatment was established by the investigator.

TMB and PD-L1 assessments were done on patient tumour samples used for individualised neoantigen therapy design. TMB was established by whole-exome sequencing of tumour and matched normal whole blood samples from all patients by use of the Illumina Novaseq platform (Illumina, San Diego, CA, USA). The threshold for high TMB was 175 mutations per exome (corresponding to ≥10 mutations per megabase with the US Food and Drug Administration [FDA]-approved FoundationOne CDx, Cambridge, MA, USA).[13] PD-L1 expression in melanoma tissue was assessed by use of immunohistochemical staining (22C3 PharmDx SK006, Agilent/Dako, Santa Clara, CA, USA). The combined positive score of membranous PD-L1 on tumour cells and tumour-associated immune cells was analysed and tumours with a combined positive score ≥1 were considered PD-L1-positive. PD-L1 status was only assessed for patients with sufficient tissue remaining from baseline biopsy samples.

We established minimal residual disease using ctDNA and assessed it using pretreatment plasma samples via the personalised amplicon-based next-generation sequencing NeoGenomics RaDaR assay (Fort Myers, FL, USA). Tumour core biopsies, which were used for individualised neoantigen therapy design and matched whole blood samples were subjected to whole-exome sequencing to identify up to 48 patient-specific somatic variants most suitable for minimal residual disease detection. To establish presence or absence of ctDNA at study timepoints, each variant call was weighted on the basis of noise established by the RaDaR algorithm. Per-variant weighted information was aggregated into a cumulative ctDNA detected or not detected call. We assessed ctDNA and its association with recurrence-free survival and distant metastasis-free survival and its prognostic biomarker value using the Kaplan-Meier method (see Statistical analysis).

Outcomes

The primary endpoint was recurrence-free survival (time from first dose of pembrolizumab until date of first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause) in the intention-to-treat population. For patients without any events, recurrence-free survival was censored at the latest disease evaluation before new anticancer therapy (including surgery) initiation or new primary cancer diagnosis (non-melanoma), if any. Secondary endpoints included distant metastasis-free survival (time from first dose of pembrolizumab until the date of first distant recurrence or death from any cause), safety, and tolerability. Exploratory endpoints included assessment of TMB, PD-L1 status in baseline tumours, and ctDNA status at start of treatment, as potential predictive biomarkers.

Statistical analysis

The trial design called for assignment of approximately 150 patients to the combination therapy or monotherapy groups in a 2:1 ratio. Forty recurrence-free survival events (recurrence or death) were required to provide approximately 80% power to detect a hazard ratio (HR) of 0·5 with an overall one-sided α of 0·10.

Efficacy analyses were done in the intention-to-treat population, which included all enrolled patients. A supportive per-protocol population excluded patients never treated, patients who received treatment different from their final assignment, and ineligible patients with metastasis at baseline. All safety analyses were done by use of the safety population (all randomly assigned patients who received at least 1 dose of study treatment).

The study was powered for hypothesis testing of recurrence-free survival and subsequent hierarchical testing of distant metastasis-free survival between the two groups by use of the stratified log-rank test in the intention-to-treat population. Primary analysis of recurrence-free survival was done by the assigned treatment by use of the log-rank test stratified by disease stage at randomisation. If the result was positive in the intention-to-treat population as per the protocol definition (recurrence-free survival one-sided p value <0·099 [adjusting for an administrative α of 0·001], corresponding to a two-sided p value <0·198 [=2*0·099]), a hierarchical testing approach was applied to the secondary endpoint of distant metastasis-free survival, and the stratified log-rank test was used for comparison. The distant metastasis-free survival result was considered to be positive with a two-sided p value <0·198 (=2*0·099). All other p values for statistical comparisons were two-sided and considered descriptive. HRs and 95% CIs in the intention-to-treat and per-protocol populations were estimated by use of a stratified Cox proportional hazards model with the Efron method of tie handling and treatment group as a covariate; medians with 95% CIs and rates at 12 months and 18 months were estimated by use of the non-parametric Kaplan-Meier method. Proportional hazards assumption of the treatment effect on recurrence-free survival and distant metastasis-free survival was assessed by use of a stratified Cox proportional model with treatment and treatment by logarithm of time interaction as covariates (appendix p 7). Safety was summarised with descriptive statistics. For exploratory purposes, predictors of recurrence-free survival were investigated. Prespecified subgroup analyses were done by use of HRs and 95% CIs calculated on the basis of an unstratified Cox proportional hazards model within each subgroup and with treatment group as a covariate, unless otherwise specified, and the

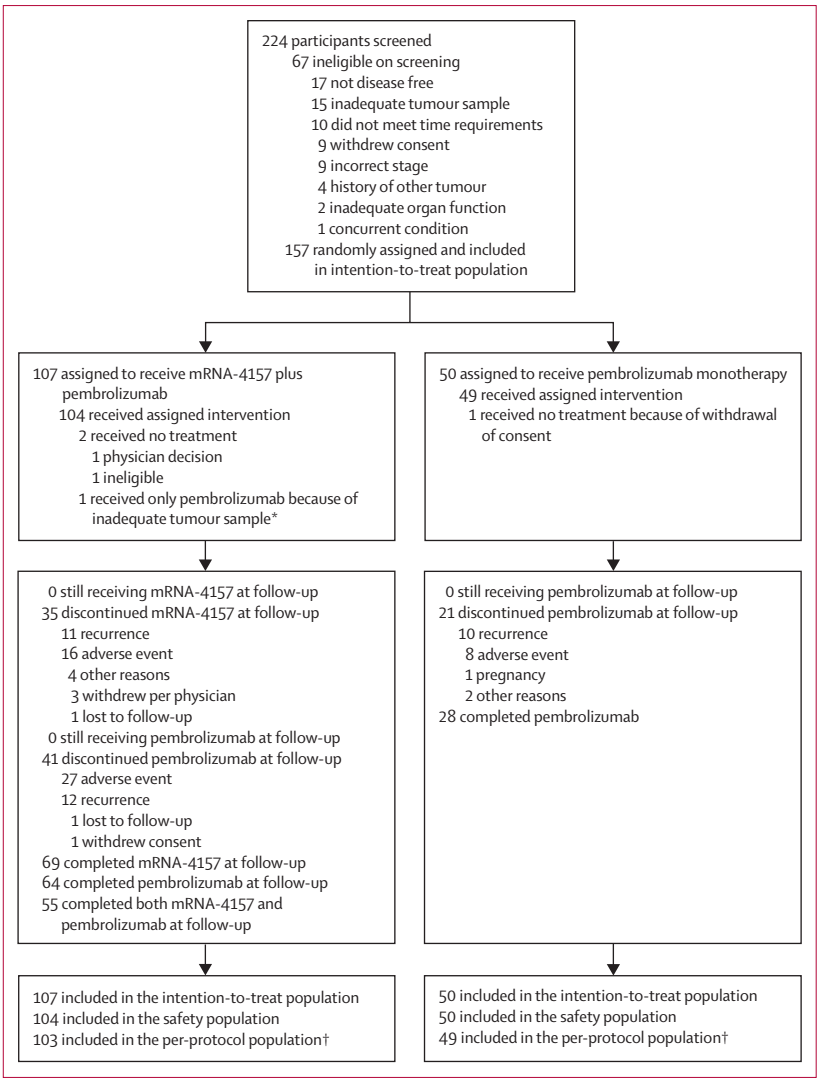


Figure 1: **Enrolment, randomisation, and follow-up**
*One patient was randomly assigned to the combination group but only received pembrolizumab; the patient was summarised in the monotherapy group in the safety population. †Four patients assigned to receive mRNA-4157 plus pembrolizumab and one patient assigned to receive pembrolizumab monotherapy were excluded from the per-protocol population due to protocol deviations. One patient in the mRNA-4157 plus pembrolizumab group was excluded due to the presence of metastatic disease at baseline (deviation in inclusion or exclusion criteria); all others were excluded as they did not receive the planned study drug.

descriptive p values within each subgroup were obtained by use of an unstratified log-rank test. The interaction between each subgroup variable and the treatment groups was evaluated in a Cox model including treatment group, subgroup variable, and treatment by subgroup variable interaction. SAS (version 9.4) and R (version 4.2.2) were used for statistical analysis. This trial is registered at ClinicalTrials.gov, NCT03897881.

Role of the funding source

The funder was responsible for the study design and had a role in data collection, data analysis, data interpretation, and writing of the report.

Results

From July 18, 2019, to Sept 30, 2021, 157 patients were enrolled (combination therapy, n=107; monotherapy, n=50; figure 1). Three patients did not receive study treatment (combination n=2; monotherapy n=1); one patient assigned to the combination group received pembrolizumab monotherapy because their mRNA-4157 individualised neoantigen therapy could not be produced owing to insufficient tumour tissue. mRNA-4157 was successfully prepared for all other patients enrolled in the combination group (>99%); 91% of patients received mRNA-4157 with 34 neoantigens (range 9–34 neoantigens; appendix p 3).

During the conduct of this study, which coincided with the COVID-19 pandemic, the majority of patients had a protocol deviation classified either as minor or major. Protocol deviations that occurred in more than 10% of patients included deviations in visit scheduling, study procedure or assessment (including COVID-19-related missed visits), informed consent process or timing, and study treatment administration. As prespecified in the statistical analysis plan, the per-protocol population excluded patients who had protocol deviations that might have affected the safety or efficacy assessments, and patients who were never treated. One such patient was included in the primary intention-to-treat population but was excluded from the per-protocol population owing to the presence of metastatic disease at baseline (deviation in inclusion or exclusion criteria). Four additional patients (combination group, n=3; monotherapy group, n=1) were excluded from the per-protocol population because they did not receive the planned study drug.

Nine patients randomly assigned to the combination therapy group were manually reallocated to the monotherapy group because of COVID-19-related manufacturing limitations. Once manufacturing resumed in April, 2021, the monotherapy group was fully enrolled (n=50), and all remaining patients (n=37) were therefore assigned to the combination therapy group. Baseline characteristics were generally balanced between treatment groups in both the overall population and the subpopulations enrolled before and after February, 2021, and the study population was representative of patients with high-risk resected melanoma (table 1, appendix pp 4–5).

The median (IQR) number of mRNA-4157 doses was nine (5–9); the median (IQR) number of pembrolizumab doses was 18 (11–18) in the combination group and 18 (6–18) in the monotherapy group. In the combination therapy group, 84 patients (81%) initiated mRNA-4157 treatment at pembrolizumab cycle three, eleven (11%) at pembrolizumab cycle four, and nine (9%) at pembrolizumab cycle five. At the clinical database cutoff (Nov 14, 2022), median (IQR [range]) duration of follow-up was 23 months (17–30 [14–39]) in the combination therapy group and 24 months (21–31 [19–39]) in the monotherapy group.

In the combination therapy group, the most common reason for discontinuation of either mRNA-4157 or pembrolizumab was adverse events (15% [n=16] and 25% [n=26], respectively; appendix p 10). In the monotherapy group, the most common reason for discontinuation of pembrolizumab was disease recurrence (20% [n=10]). All scheduled mRNA-4157 treatments were completed by 69 patients (64%) in the combination group; 64 patients (60%) in the combination group and 28 (56%) in the monotherapy group completed all scheduled pembrolizumab treatments. At database cutoff, 122 patients (78%) were in follow-up (combination, n=84; monotherapy, n=38).

At database cutoff, 44 events (recurrences or deaths) were reported in the intention-to-treat population, with a minimum follow-up of 14 months. Recurrence or death occurred in 24 patients (22%) in the combination therapy group and 20 (40%) in the monotherapy group (appendix p 7). In the combination therapy group, recurrence events were local or regional in 14 (13%) patients, distant in seven (7%), and other (new melanoma or death) in three (3%); in the monotherapy group, these were local or regional in nine (18%) patients, distant in ten (20%), and other in one (2%). In the intention-to-treat population, recurrence-free survival was longer in the combination than the monotherapy group (HR for recurrence or death 0·561 [95% CI 0·309–1·017]; p=0·053; figure 2A). An increased separation of the recurrence-free survival curves was observed over time; supportive analysis indicated a trend for an improved piecewise HR after 40 weeks (appendix p 7). The 12-month rate of recurrence-free survival was 83% (95% CI 74·7–89·3) in the combination group and 77% (95% CI 62·5–86·6) in the monotherapy group; at 18 months, the rates were 79% (95% CI 69·0–85·6) and 62% (95% CI 46·9–74·3), respectively (figure 2A, appendix p 6).

Results in the per-protocol population were consistent with the intention-to-treat population (HR, 0·542 [95% CI 0·297–0·990]; descriptive p=0·043; appendix p 14). The recurrence-free survival benefit was consistent across most subgroups (appendix p 15). TMB data were available for 154 patients (98%; combination therapy n=104; monotherapy n=50). In the intention-to-treat population, 79 (74%) patients in the combination therapy group and 30 (60%) in the monotherapy group had high TMB. When TMB-high was compared with non-TMB-high, HRs were 0·536 (95% CI 0·234–1·225) in the combination group and 0·482 (95% CI 0·199–1·166) in the monotherapy group (appendix p 6). The recurrence-free survival HR in the TMB-high subgroup was 0·652 (95% CI 0·284–1·494; figure 2B, appendix p 6) and in the non-TMB-high subgroup was 0·586 (95% CI 0·243–1·415; figure 2C, appendix p 6) for combination therapy versus monotherapy. Multivariate analysis adjusting for TMB in the TMB-evaluable population provided a recurrence-free survival HR (95% CI) of 0·620 (0·339–1·131) for the combination therapy versus monotherapy group, similar to the HR observed in the intention-to-treat population. PD-L1 status could be established for 114 (73%) of 157 patients

	mRNA-4157 plus pembrolizumab (n=107)	Pembrolizumab (n=50)
Sex*		
Male	70 (65%)	31 (62%)
Female	37 (35%)	19 (38%)
Age, years		
Median (IQR)	63·0 (53–72)	61·5 (51–69)
Mean (SD)	61·3 (13·5)	59·4 (14·3)
Age group		
<65 years	59 (55%)	28 (56%)
≥65 years	48 (45%)	22 (44%)
Eastern Cooperative Oncology Group performance status score		
0	90 (84%)	40 (80%)
1	15 (14%)	9 (18%)
Missing†	2 (2%)	1 (2%)
Disease stage at randomisation‡		
Stage IIIC	89 (83%)	42 (84%)
Stage IIID	2 (2%)	2 (4%)
Stage IV	16 (15%)	6 (12%)
Number of previous cancer-related surgeries		
1	41 (38%)	24 (48%)
2	36 (34%)	18 (36%)
≥3	30 (28%)	8 (16%)
Lymph node dissection	34 (32%)	15 (30%)
Lactate dehydrogenase (U/L), median (IQR)§	189 (166–211)	185 (162–204)
>upper limit of normal	5 (5%)	3 (6%)
Programmed death ligand 1 status		
Positive	69 (64%)	27 (54%)
Negative	13 (12%)	5 (10%)
Indeterminate¶	25 (23%)	18 (36%)
BRAF‖		
V600K or V600E mutation	41 (38%)	20 (40%)
Wildtype**	66 (62%)	30 (60%)
Tumour mutational burden§		
<175 mutations–exome	26 (24%)	19 (38%)
≥175 mutations–exome	79 (74%)	30 (60%)
Time from most recent surgery of curative intent to first dose of pembrolizumab, weeks§		
Median (IQR)	10·9 (8·4–12·1)	10·1 (7·9–12·0)
Mean (SD)	10·1 (2·5)	9·9 (3·1)

Data are n (%) unless stated otherwise. *Sex was recorded by the investigator in the electronic case report form. †Three patients were not treated and therefore had no baseline Eastern Cooperative Oncology Group performance status score. ‡According to the 8th edition of the American Joint Committee on Cancer staging manual. §Available for 154 patients; missing n=2 for mRNA-4157 plus pembrolizumab and n=1 for pembrolizumab. ¶Patients for whom there was no sample to send for programmed death ligand 1 evaluation or for whom sample quality or quantity was too low to perform the assay. ‖*BRAF* status established by whole exome sequencing on baseline tumour samples. **Wildtype refers to position 600 on the *BRAF* gene.

Table 1: **Demographic and clinical characteristics of patients at baseline**

(PD-L1-evaluable population; appendix p 8) and the proportion of PD-L1-positive patients was similar across study groups among those with evaluable PD-L1 (combination therapy 84% [n=69]; monotherapy 84% [n=27]; appendix p 15). Baseline characteristics in the PD-L1-evaluable patient population were similar to those of the intention-to-treat population (appendix p 8). Recurrence-free survival HR in the PD-L1-positive subgroup was 0·485 (95% CI 0·226–1·039) and in the negative subgroup was 0·162 (95% CI 0·038–0·685) for combination therapy versus monotherapy (appendix pp 6, 15).

Although COVID-19 vaccine-related manufacturing prioritisation was required during the pandemic, results from supportive analyses excluding the patients enrolled after the manufacturing prioritisation in 2021 were similar to the intention-to-treat results. Baseline characteristics were similar in patients enrolled before February, 2021, and those in the intention-to-treat population (table 1, appendix p 5), with a balanced follow-up and consistent recurrence-free survival benefit (before Feb, 2021: HR 0·612 [95% CI 0·310–1·206] *vs* intention-to-treat, HR 0·561 [95% CI 0·309–1·017]; figure 2A, appendix p 16).

The secondary efficacy endpoint of distant metastasis-free survival was hierarchically tested following a positive result for the primary endpoint of recurrence-free survival. In the intention-to-treat population, distant metastasis-free survival was longer in the combination group compared with the monotherapy group (HR for distant recurrence or death, 0·347 [95% CI 0·145–0·828]; p=0·013; figure 3). Distant metastasis-free survival rates in the combination therapy and monotherapy groups at 12 months were 93% (95% CI 85·7–96·6) and 89% (95% CI 76·2–95·4), at 18 months the rates were 92% (95% CI 84·2–95·8) and 77% (95% CI 61·0–86·8), and at 24 months the rates were 92% (95% CI 84·2–95·8) and 73% (95% CI 56·2–84·4), respectively (appendix p 6). At the database cutoff, distant recurrence or death occurred in nine (8%) patients in the combination group and 12 (24%) patients in the monotherapy group (appendix p 6). Longitudinal distant metastasis-free survival analyses showed that in patients who had a distant recurrence or death, 17 (81%) of 21 had a distant recurrence as the initial recurrence event (combination therapy, seven [78%] of nine; monotherapy, ten [83%] of 12; appendix p 17). In the combination therapy group,

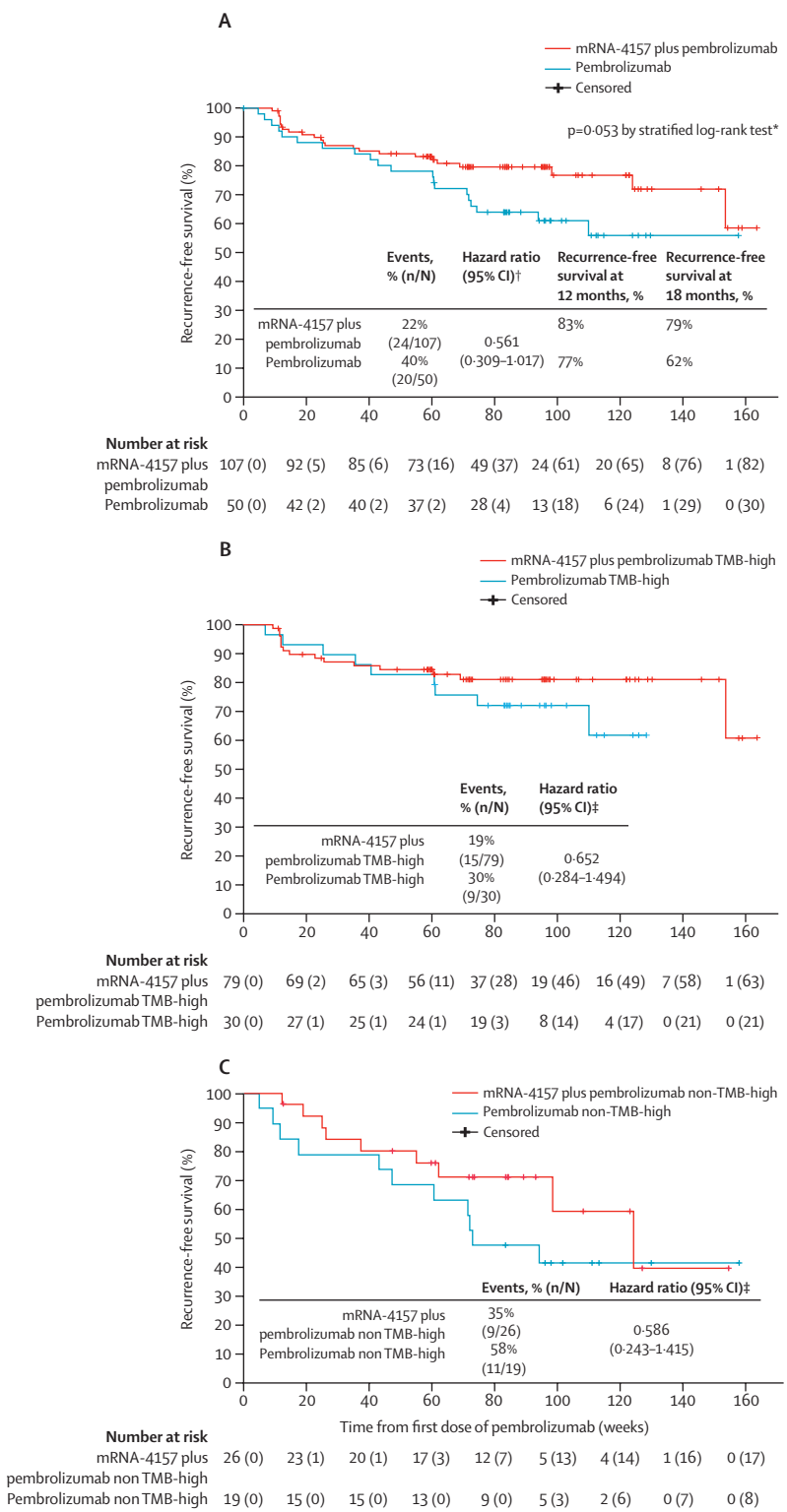


Figure 2: **Kaplan-Meier estimates for recurrence-free survival for intention-to-treat (A), TMB-high (B), and non-TMB-high populations (C)**
TMB=tumour mutational burden. HR=hazard ratio. * The p value is based on the log-rank test stratified by disease stage (stages IIIB or IIIC or IIID *vs* stage IV) used for randomisation. †The HR and 95% CI for mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy were estimated by use of a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID *vs* stage IV) used for randomisation. ‡The HR and 95% CI for combination therapy versus pembrolizumab monotherapy were estimated by use of an unstratified Cox proportional hazards model with an interaction between treatment group and TMB status (high *vs* non-high) as a covariate. The model includes all participants with evaluable TMB at baseline.

one patient developed a new primary melanoma before a distant recurrence and one died (not due to melanoma); in the monotherapy group, two patients had a local recurrence before a distant recurrence. Four patients in each group developed a distant metastasis within 20 weeks.

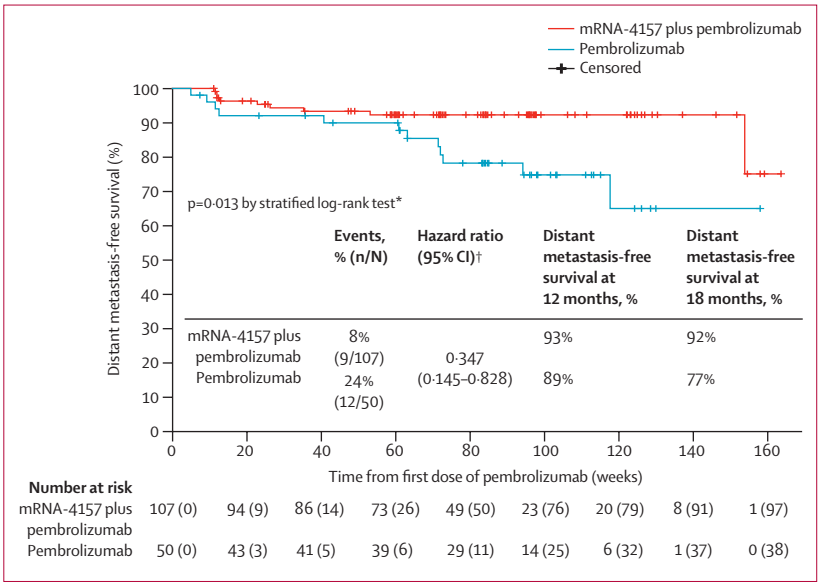
ctDNA-evaluable patients at baseline (n=125 [80%]; combination, n=90; monotherapy, n=35) had similar baseline characteristics to the intention-to-treat population (appendix p 9). As part of the exploratory biomarker analyses, in the ctDNA-evaluable population with combined treatment groups, HRs showed a trend for shorter recurrence-free survival and distant metastasis-free survival in patients with a ctDNA-positive (n=15) versus ctDNA-negative (n=110) result at baseline (recurrence-free survival 0·150 [95% CI 0·073–0·306]; distant metastasis-free survival HR, 0·081 [95% CI 0·033–0·200]; figure 4A, appendix p 6). In patients with a ctDNA-negative result at baseline (combination, n=77; monotherapy, n=33) a trend of recurrence-free survival and distant metastasis-free survival benefit was observed following combination therapy versus monotherapy (recurrence-free survival 0·225 [95% CI 0·095–0·531]; distant metastasis-free survival (HR, 0·048 [95% CI 0·006–0·380]; figure 4B, 4C, appendix p 6). The same trend was also observed in patients with a ctDNA-positive result, but interpretation was further limited by the small number of patients.

The safety analysis population included 154 patients (combination therapy n=104; monotherapy n=50). Treatment-related adverse events occurred in 104 patients (100%) in the combination group and 41 patients (82%) in the monotherapy group (appendix p 10).

Adverse events related to mRNA-4157 (attributed to mRNA-4157 alone or both mRNA-4157 and pembrolizumab) were primarily grade 1–2 (86 [83%] patients; table 2), with most resolving after a median (IQR) of 3 days (2–4); the most common adverse events related to mRNA-4157 were fatigue (63 [61%]), injection-site pain (58 [56%]), and chills (52 [50%]). Grade 3 adverse events related to mRNA-4157 were reported in 12 (12%) patients; the most common event was fatigue (5 [5%]). No grade 4–5 adverse events related to mRNA-4157 occurred (table 2). Adverse events related to either drug led to discontinuation of mRNA-4157 in 16 (15%) patients (appendix p 8). mRNA-4157-related injection-site reactions occurred in 72 (69%) patients, mostly during the initial treatment cycle.

In the combination therapy group, adverse events related to pembrolizumab (attributed to either pembrolizumab alone or both pembrolizumab and mRNA-4157) were grade 1–2 in 77 (74%) patients and grade 3–4 in 24 (23%) patients (table 2); no grade 5-related adverse events were reported. Adverse events led to discontinuation of pembrolizumab in 26 (25%) patients in the combination group and nine (18%) patients in the monotherapy group. Serious adverse events related to pembrolizumab occurred in 14 (14%) patients in the combination group and five (10%) patients in the monotherapy group.

Immune-mediated adverse events occurred in 37 (36%) patients in the combination group and 18 (36%) patients in the monotherapy group (appendix p 11). Most immune-mediated adverse events were grade 1–2; grade ≥3 events occurred in 11 (11%) patients in the combination group and seven (14%) patients in the monotherapy group.



	Events, % (n/N)	Hazard ratio (95% CI)†	Distant metastasis-free survival at 12 months, %	Distant metastasis-free survival at 18 months, %
mRNA-4157 plus pembrolizumab	8% (9/107)	0·347 (0·145–0·828)	93%	92%
Pembrolizumab	24% (12/50)		89%	77%

Figure 3: **Kaplan-Meier estimates for distant metastasis-free survival in the intention-to-treat population**
*The p value is based on the log-rank test stratified by disease stage (stages IIIB or IIIC or IIID *vs* stage IV) used for randomisation. †The HR and the 95% CI for combination therapy versus pembrolizumab monotherapy were estimated by use of a Cox proportional hazards model with treatment group as a covariate, stratified by disease stage (stages IIIB or IIIC or IIID *vs* stage IV) used for randomisation.

Discussion

Tumour-associated antigen vaccines have engendered considerable scientific interest but have not shown meaningful success in clinical trials.[3–5,7–9,16,17] Immune-checkpoint inhibitors have previously shown prolonged recurrence-free survival and distant metastasis-free survival, and are FDA-approved as adjuvant therapy in patients with resected high-risk melanoma.[10,18] The current phase 2b trial in patients with resected, high-risk, stage IIIB–IV cutaneous melanoma shows a positive and clinically meaningful outcome in the randomised setting for an individualised neoantigen therapy approach. The risk of recurrence or death was lower in patients treated with combination mRNA-4157 and pembrolizumab versus pembrolizumab monotherapy, with a lower rate of recurrence or death (22% *vs* 40%). The 18-month recurrence-free survival rate was numerically higher in the combination therapy group compared with the monotherapy group, wherein recurrence-free survival results were similar to those

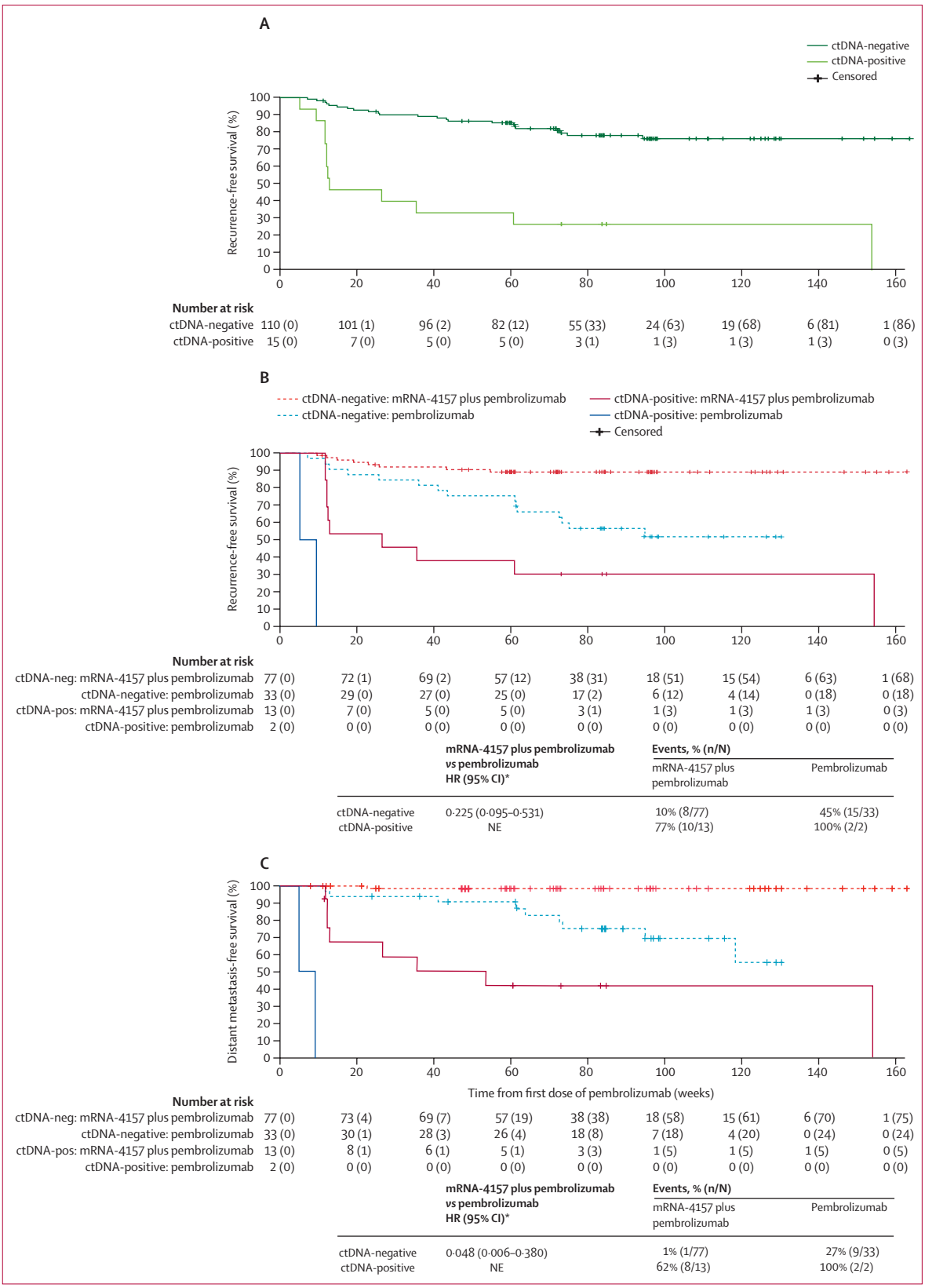


Figure 4: **Kaplan-Meier estimates for recurrence-free survival comparing ctDNA status at baseline regardless of treatment group (A), recurrence-free survival (B), and distant metastasis-free survival (C) based on ctDNA status at baseline by treatment group**
ctDNA=circulating tumour DNA. HR=hazard ratio. NE=not estimable. *The HR and 95% CIs for mRNA-4157 plus pembrolizumab versus pembrolizumab monotherapy were estimated by use of an unstratified Cox proportional hazards model that included treatment as a covariate within each biomarker subgroup.

reported in previous studies of pembrolizumab[18] and nivolumab[19] in this population. Distant metastasis-free survival was also longer with the combination therapy compared with monotherapy, with a numerically higher 18-month rate in the combination versus the monotherapy group. Longitudinal distant metastasis-free survival analysis showed that most patients who had a distant recurrence had it as the initial recurrence event, similar to previous studies that have shown that distant metastasis is often the site of first recurrence after melanoma resection.[20,21] Although patients in both groups had a low risk of distant recurrence or death within the first year, patients in the combination therapy group appeared to have a delayed risk of distant recurrence after stopping pembrolizumab treatment. This aligned with the numerically higher proportion of patients in the monotherapy group having distant recurrence events as their recurrence-free survival event compared with the combination group.

The translational data from the study, although exploratory, supported the observed efficacy (recurrence-free survival and distant metastasis-free survival) benefit of mRNA-4157 combined with pembrolizumab. Although the combination therapy group, compared with the monotherapy group, had a numerically higher percentage of TMB-high patients, the recurrence-free survival benefit in the combination therapy group was similar in magnitude in both TMB-high and non–TMB-high subgroups. Furthermore, the multivariate analysis of recurrence-free survival adjusting for TMB provided a treatment effect estimation similar to that for the unadjusted analysis in the intention-to-treat population. These data suggest that the TMB imbalance across study groups did not affect the observed clinical benefit and that the benefit observed with the mRNA-4157 combination was irrespective of the size of the TMB. In the biomarker-evaluable population, the proportion of PD-L1-positive patients was similar between the combination and monotherapy groups, and recurrence-free survival trended favourably for the combination versus monotherapy group in both the PD-L1-positive and negative subgroups. Although these subgroup analyses were exploratory, and the smaller size of the biomarker-evaluable population limits direct comparison with the overall population, these analyses suggest that mRNA-4157 provides clinical benefit to patients irrespective of immunogenic phenotype of the resected tumour. The apparent benefit might have been driven by the hypothesised mechanism of action of mRNA-4157 to broaden antitumour responses while strengthening those already present or activated by pembrolizumab. Analysis of ctDNA in pretreatment biopsies could be used as a prognostic marker of clinical outcome by identifying patients with a higher relapse risk; despite the low shedding of ctDNA in melanoma, ctDNA is used to measure minimal residual disease post-resection in the adjuvant setting.[22,23] In this study, patients with a ctDNA-positive versus ctDNA-negative result at baseline had a numerically shorter recurrence-free survival and distant metastasis-free survival, regardless of treatment. The proportion of patients with a ctDNA-positive versus ctDNA-negative result at baseline was numerically higher in the combination therapy group than in the monotherapy group. In patients with a ctDNA-negative result, recurrence-free survival and distant metastasis-free survival showed favourable trends in the combination therapy versus monotherapy group, with earlier separation of the Kaplan-Meier curve compared with the overall population. A similar trend was observed for patients with a ctDNA-positive result; however, the small sample size further limited interpretation. These data suggest that minimal residual disease detected with ctDNA might have prognostic value in high-risk resected melanoma patients treated with adjuvant immune therapy.

Limitations of this work are that this is a moderately sized phase 2b study designed with one-sided α of 0·1; there was a relatively short follow-up for the primary analysis, which limits assessment of long-term recurrence-free survival and distant metastasis-free survival benefit. Both a longer follow-up and a larger phase 3 study are

	mRNA-4157 plus pembrolizumab (n=104)		Pembrolizumab (n=50)	
	Any grade	Grade ≥3†	Any grade	Grade ≥3
Any adverse event‡	104 (100%)	36 (35%)	47 (94%)	18 (36%)
mRNA-4157 treatment-related adverse events§				
Any	98 (94%)	12 (12%)	..	..
Fatigue	63 (61%)	5 (5%)	..	..
Injection-site pain	58 (56%)	0	..	..
Chills	52 (50%)	0	..	..
Pyrexia	50 (48%)	1 (1%)	..	..
Headache	33 (32%)	0	..	..
Injection-site erythema	33 (32%)	0	..	..
Influenza-like illness	32 (31%)	0	..	..
Nausea	26 (25%)	0	..	..
Myalgia	22 (21%)	1 (1%)	..	..
Pembrolizumab treatment-related adverse events¶				
Any	101 (97%)	24 (23%)	41 (82%)	9 (18%)
Fatigue	72 (69%)	6 (6%)	20 (40%)	0
Diarrhoea	31 (30%)	2 (2%)	5 (10%)	0
Pruritus	30 (29%)	0	10 (20%)	0
Nausea	23 (22%)	0	5 (10%)	0
Chills	22 (21%)	0	1 (2%)	0
Pyrexia	22 (21%)	0	0	0

Values are n (%). Grading is per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. *A summary of investigator-attributed adverse events with a start date on or after the date study treatment began (treatment-related adverse events). †No grade 4 or 5 adverse events related to mRNA-4157 occurred in the combination therapy group. ‡No deaths were related to mRNA-4157 or pembrolizumab. §mRNA-4157–related adverse events include events attributed by the investigator to mRNA-4157 alone as well as events attributed to both mRNA-4157 and pembrolizumab. ¶Adverse events related to pembrolizumab include events attributed by the investigator to pembrolizumab alone and events attributed to both mRNA-4157 and pembrolizumab.

Table 2: **Treatment-related adverse events occurring in ≥20% of patients***

needed to make more definitive conclusions. The study was also affected by the COVID-19 pandemic, resulting in a proportion of patients being manually allocated. As the focus of the study was clinical outcomes, it was not powered for biomarker and immunogenicity analyses, which were exploratory in nature and involved small sample sizes, but these merit further study. Finally, as the treatment paradigm is shifting, additional data in both neoadjuvant and adjuvant settings is needed to contextualise these findings and the potential role for mRNA-4157.[24]

Logistical complexity is intrinsic to personalised neoepitope selection and manufacture. Although inadequate tissue quantity or quality, or both, for mRNA-4157 manufacture was uncommon (<7% of those screened), future development must continue to optimise methods to ensure sufficient tissue collection, facilitate timely manufacturing, and coordinate patient schedules. Identifying tumour neoantigens inducing beneficial immune responses has been challenging historically. Neoantigen burden varies among tumours and individuals; some neoantigens might be less immunogenic and elicit immune responses that evade or suppress the host immune system.[25,26] The effect of tumour heterogenicity, immune fitness, and the number of neoantigens in eliciting a clinically meaningful immune response is unknown; several studies have suggested that generating an immune response against a single neoantigen could be sufficient for antitumour activity.[27,28] Hence, an iterative, comprehensive, and completely individualised approach leveraging advances in sequencing and antigen selection strategies might optimise identification of sufficient neoantigens.

mRNA technology has driven a whole new field for scientific discovery and medical breakthroughs and its application in mRNA-4157 might confer advantages over other approaches. Some of those advantages include that mRNA can encode multiple neoantigens, has a rapid turnaround time, and can induce potent $CD4^+$–$CD8^+$ T-cell responses.[5,7] Preliminary phase 1 study data showed that mRNA-4157 induced T-cell responses to targeted tumour neoantigens and also established the immunogenicity of mRNA-4157 with pembrolizumab in the adjuvant setting.[6]

In this study, and consistent with the literature,[29,30] there was delayed separation of the recurrence-free survival curves. Supportive analyses to evaluate the robustness of treatment effect estimation considering the delayed separation showed a trend towards improved recurrence-free survival over time in the combination therapy group compared with the monotherapy group (appendix p 7). However, the proportional hazard assumption was not violated. Further, earlier separation was observed in the ctDNA versus clinical recurrence-free survival and distant metastasis-free survival Kaplan-Meier curves (overall and in TMB and PD-L1 subgroups); additional analyses are required to establish the clinical implications. The delayed separation might be partly attributable to the manufacturing time of mRNA-4157, during which patients in both groups received pembrolizumab monotherapy. Yet it might also indicate the induction of durable, functional, and robust antitumour neoantigen-specific T-cell responses and immunological memory that support sustained disease control beyond completion of treatment. However, the study is ongoing, and a longer follow-up is required to establish durability of the treatment effect.

The safety profile of mRNA-4157 plus pembrolizumab in this trial was encouraging, with infrequent clinically meaningful adverse events reported compared with pembrolizumab monotherapy. Most treatment-related adverse events were grade 1–2, with rates of treatment-related grade 3 and worse and serious adverse events numerically higher in the combination versus monotherapy group, as expected with the addition of a second therapy and reflecting the individual components, with fatigue being the overlapping toxicity. The most common mRNA-4157-related adverse events were influenza-like symptoms and local injection-site reactions, which were generally self-limited and decreased in subsequent dosing cycles, similar to previous observations.[15] Additionally, although the frequency of adverse events was numerically higher in the combination versus monotherapy group, this was expected owing to addition of a second agent, and adverse events were managed with established standard-of-care therapy. There was no evidence of an increase in immune-mediated adverse events with the addition of mRNA-4157 to pembrolizumab, despite these being common with immuno-oncology combinations. This safety profile supports testing of future combinations with mRNA-4157 in other cancer types and settings.

In conclusion, these results indicate that an mRNA-based individualised neoantigen therapy added to PD-1 blockade might provide increased clinical benefit in the adjuvant treatment of high-risk resected melanoma compared with PD-1 blockade alone. This combination is being evaluated in a phase 3 trial (NCT05933577).

Contributors

RSM and TZ contributed equally to the study concept and design. All authors collected, analysed, and interpreted the data. All authors had access to study data reported in the manuscript, contributed to the drafting and revision of the manuscript, approved the final version, and had final responsibility for the decision to submit for publication. All authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol.

Declaration of interests

JSW has been a consultant for AstraZeneca, Bristol Myers Squibb, Merck, and Regeneron; has received research grants (to institution) from Merck and Moderna; has received travel support from Moderna; and is named on a PD-1 patent with Biodesix (not related to this trial). MSC has been a consultant for Amgen, Bristol Myers Squibb, Eisai, Ideaya, Merck Sharp & Dohme, Nektar, Novartis, Oncosec, Pierre-Fabre, Qbiotics, Regeneron, Roche, Merck Serono, and Sanofi; and has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, and Sanofi. AK has received honoraria from Merck Sharp & Dohme. TaM has received research grants (to institution) from Moderna; has been a consultant or served on a data safety monitoring–advisory board

for AstraZeneca, Bristol Myers Squibb, Eisai, GlaxoSmithKline, Merck Sharp & Dohme, and Novartis; has received payment or honoraria from AstraZeneca; and has received travel support from AstraZeneca and Bristol Myers Squibb. MHT has received research grants from Bristol Myers Squibb, Exelixis, and Merck; has been a consultant for Cascade Prodrug, Incyte, and Immune-Onc; has received payment or honoraria from Array Biopharma, Bayer, Blueprint Medicines, Bristol Myers Squibb, Eisai, Merck, Novartis, and Sanofi/Regeneron; and has served on a data safety monitoring or advisory board for Oncosec. KBK has received research grants from Merck and Moderna. MMc has received research grants (to institution) from Aadi Biosciences, Alpine Immune Sciences, Arcus Biosciences, Arvinas, Ascentage Pharma Group, ASCO, Astellas, Bayer, Bicycle Therapeutics, BioMed Valley Discoveries, BioNTech, C4 Therapeutics, Dragonfly Therapeutics, EMD Serono, Epizyme, Erasca, Exelixis, Foghorn Therapeutics, G1 Therapeutics, Genentech–Roche, Gilead Sciences, GlaxoSmithKline, IDEAYA Biosciences, Ikena Oncology, ImmVira Pharma, Infinity Pharmaceuticals, Jacobio Pharmaceuticals, Kechow Pharma, Kezar Life Sciences, Kinnate BioPharma, MedImmune, Merck, Mereo BioPharma, Metabomed, Moderna, NBE Therapeutics, Nektar, Novartis, OncoC4, Oncorus, PACT Pharma, Pfizer, Plexxikon, Poseida, Prelude Therapeutics, Pyramid Biosciences, Regeneron, Sapience Therapeutics, Scholar Rock, Seattle Genetics, Synthrox, Takeda Pharmaceuticals, Teneobio, Tempest Therapeutics, Tizona Therapeutics, TMUNITY Therapeutics, TopAlliance Biosciences, and Xilio; and has been a consultant (payment to institution) for Castle Biosciences, Eisai, IQVIA, Merck, Moderna, and Pfizer. GVL has been a consultant for Agenus, Array Biopharma, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Evaxion, Hexal (Sandoz Company), Highlight Therapeutics, Innovent Biologics USA, Merck Sharp & Dohme, Novartis, OncoSec, PHMR, Pierre Fabre, Provectus, Qbiotics, and Regeneron; has received honoraria from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, and Pierre Fabre; and has served on an advisory board for Bristol Myers Squibb, Merck Sharpe & Dohme, Novartis, OncoSec, Pierre Fabre, Provectus, Qbiotics, and Regeneron. RJS has received research grants from Merck; has royalties or licences from Up-to-Date; has been a consultant for Marengo, Merck, Novartis, Pfizer, and Replimune; and has served on a data safety monitoring or advisory board for Duke University and Yale University. MF has received research grants from Moderna; and has served on an advisory board for Bristol Myers Squibb, Instil Bio, Merck, Novartis, and Regeneron. CLC has been a consultant for and has served on an advisory board for EMD Serono, Eisai, Iovance, Merck, Regeneron, and Replimune. AP has had a leadership position in Cota Healthcare and OMI; and holds stock options in Celularity and OMI. ThM has received research grants from Agenus, Anaveon, Bioatla, Bristol Myers Squibb, Day One, Genentech, InflaRx, Iovance, Merck, Regeneron, Replimune, Trisalus, and Ultimovacs; has received payment or honoraria from Honor Health; and has served on a data safety monitoring or advisory board for University of Colorado Cancer Center. VA has received speaker fees from Bristol Myers Squibb, Merck Sharp & Dohme, Novartis, and Pierre Fabre; has received travel support from Bristol Myers Squibb and Pierre Fabre; and has served on an advisory board for Bristol Myers Squibb, Immunocore, Limbic, Merck Sharp & Dohme, Novartis, and QBiotics. GTG has received research grants (to institution) from Exelixis and Lucerno Dynamics; has been a consultant for Bristol Myers Squibb, Eisai, Exicure, Genentech, Immunocore, Incyte, Iovance, Lyell Immunopharma, Merck, Novartis, Regeneron, and Sapience Therapeutics; has received payment or honoraria from Immunocore; and has served on a data safety monitoring or advisory board for Huyabio. JJL has received research support (all to institution for clinical trials) from AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, Corvus, Day One, EMD Serono, Fstar, Genmab, Ikena, Immatics, Incyte, Kadmon, KAHR, Macrogenics, Merck Sharp & Dohme, Moderna, Nektar, Next Cure, Numab, Palleon, Pfizer, Replimmune, Rubius, Servier, Scholar Rock, Synlogic, Takeda, Trishula, Tizona, and Xencor; has been a consultant for 7 Hills, AbbVie, Actym, Alnylam, Alphamab Oncology, Arch Oncology, Atomwise, Bayer, Bright Peak, Bristol Myers Squibb, Castle, Checkmate, Codiak, Crown, Cugene, Curadev, Day One, Duke Street Bio, Eisai, EMD Serono, Endeavor, Exo, Flame, Fstar, G1 Therapeutics, Genentech, Gilead, Glenmark, HotSpot, Kadmon, Kanaph, KSQ, Janssen, Ikena, Inzen, Immatics, Immunocore, Incyte, Instil, Inzen, IO Biotech, Macrogenics, Mavu, Merck Sharp & Dohme, Mersana, Nektar, NeoTx, Novartis, Onc.AI, OncoNano, Partner, Pfizer, Pioneering Medicines, PsiOxus, Pyxis, RefleXion, Regeneron, Ribon, Roivant, Saros, Servier, STINGthera, Stipe, Synlogic, Synthekine, Tempest, and Xilio; has served on an advisory board for AbbVie, Evaxion, and Immutep; is a board member of the Society for Immunotherapy of Cancer; holds stock options in Actym, Alphamab Oncology, Arch Oncology, Duke Street Bio, Kanaph, Mavu, NeoTx, Onc.AI, OncoNano, Pyxis, Saros, STipe, and Tempest; and has applied for patents (both provisional) for Serial 15/612,657 (Cancer Immunotherapy) and PCT/US18/36052 (Microbiome Biomarkers for Anti-PD-1/PD-L1 Responsiveness: diagnostic, prognostic and therapeutic uses thereof). ST has received speaker fees from Bristol Myers Squibb and honoraria from Pfizer; and has served as a paid expert witness for malpractice cases. EIB has received research grants (to institution) from Genentech; has been a consultant for Instilbio, Iovance, Merck, Nektar, Novartis, Sanofi, and Xilio; and has served on a data safety monitoring–advisory board for Asher. JAH is an employee of and holds stock options in Merck & Co, Rahway, NJ, USA. MH is an employee of Merck &Co, Rahway, NJ, USA. MaM, LZ, CR-T, PH, and PA are employees of and hold stock options in Moderna. IF is an employee of and holds stock options in Moderna; and was a co-inventor on the individualised neoantigen therapy Moderna patent. VS is an employee of Moderna; and holds stock options in AbbVie and Moderna. MB is an employee of Moderna; and holds stock options in Bristol Myers Squibb, Moderna, and Novartis. RSM is an employee of and holds stock and options in Moderna; and was a co-inventor on the individualised neoantigen therapy patent and other seminal Moderna patents. TZ is an employee of and holds stock options in Moderna; was a co-inventor on some seminal Moderna patents; and has served as a paid board member for Adaptimmune and Teva Pharmaceuticals. GA, TTT, MS, and JS declare no competing interests.

Data sharing

As the trial is ongoing, access to patient-level data presented in the article and supporting clinical documents by qualified external researchers who provide methodologically sound scientific proposals can be available upon reasonable request for products or indications that have been approved by regulators in the relevant markets and subject to review from 24 months after study completion. Such requests can be made to Moderna, 200 Technology Square, Cambridge, MA 02139, USA, data_sharing@modernatx.com. A materials transfer or data access agreement with the sponsor will be required for accessing shared data. All other relevant data are presented in the paper. .

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