2024 ASCO® ANNUAL MEETING

Individualized neoantigen therapy mRNA-4157 (V940) plus pembrolizumab in resected melanoma: 3-year update from the mRNA-4157-P201 (KEYNOTE-942) trial

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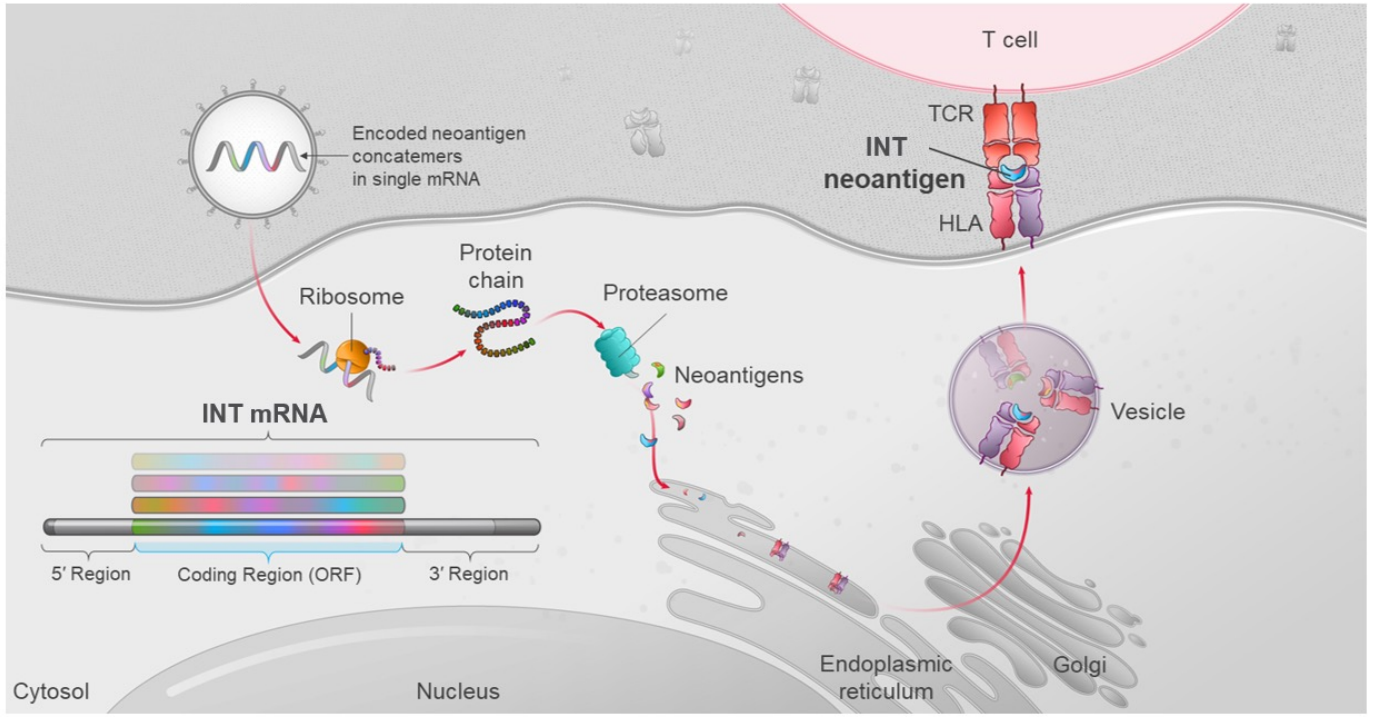
Background/Introduction



mRNA-4157 (V940) is a novel, mRNA-based individualized neoantigen therapy designed to increase endogenous antitumor T-cell responses by targeting unique patient tumor mutations

In the primary analysis of the phase 2 mRNA-4157-P201 (**KEYNOTE-942**) trial (median planned follow-up, 23 months), patients with completely resected high-risk stage IIIB–IV cutaneous melanoma receiving mRNA-4157 + pembrolizumab had **prolonged RFS and DMFS** versus pembrolizumab alone[1]

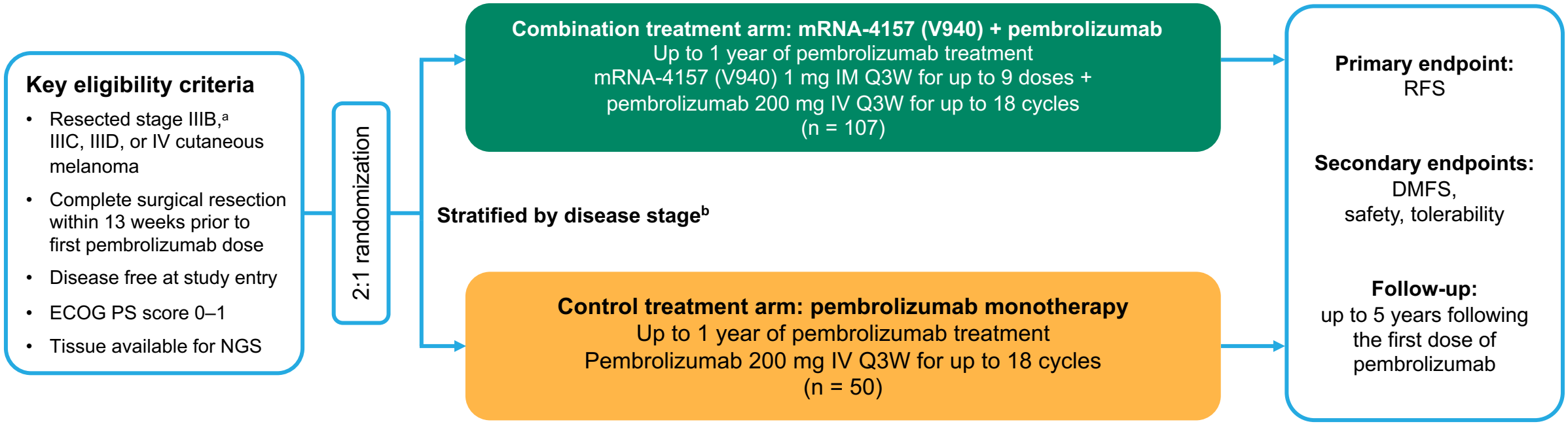
Objective: Assess 3-year median planned follow-up (median [range], 34.9 [25.1–51.0] months)

DMFS, distant metastasis-free survival; RFS, recurrence-free survival.

1. Weber JS, et al. *Lancet*. 2024;403:632-644.

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

Randomized, phase 2, open-label study in patients with adjuvant resected melanoma at high risk of recurrence

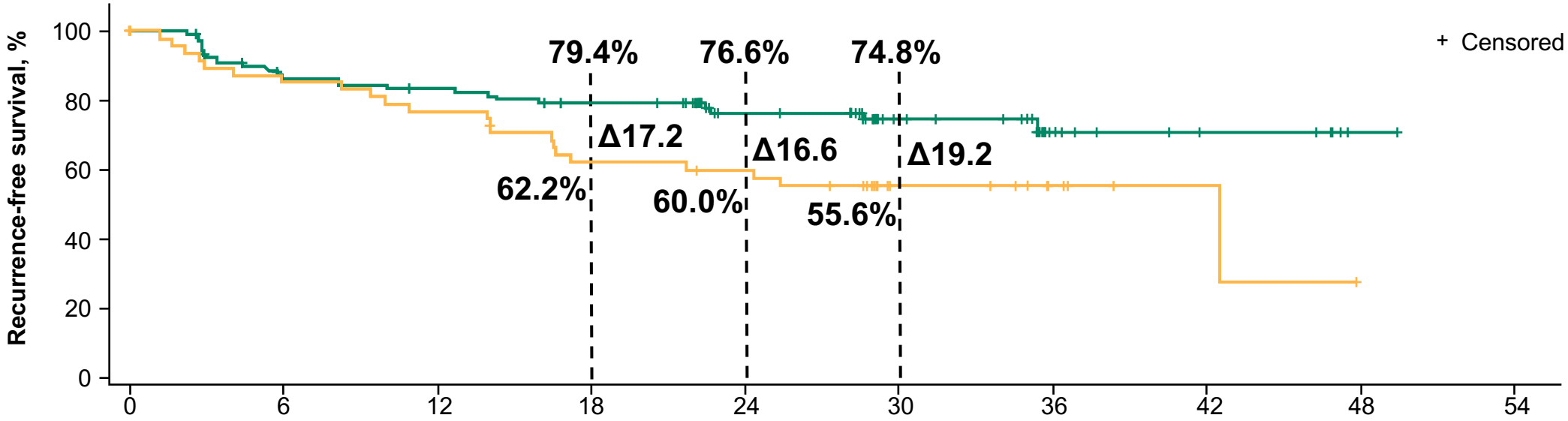


Designed with 80% power to detect a hazard ratio of 0.5 with 40 RFS events (with a 1-sided alpha of 0.1 per protocol)
Primary analysis **triggered after a minimum of 1-year planned follow-up[c]** (November 14, 2022 data cut) and at least 40 RFS events have been observed. DMFS analysis was prespecified for testing following positive RFS in the ITT population

Supportive analysis was **triggered after a minimum of 2 years of planned follow-up[c]** (November 3, 2023 data cut)
Median planned follow-up[c]: ~3yrs

[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 American Joint Committee on Cancer Staging Manual [c]Defined as the time from the first dose date (or date of randomization if not treated) to date of clinical cut-off.
ECOG PS, Eastern Cooperative Oncology Group performance status; IM, intramuscular; ITT, intent-to-treat; IV, intravenous; NGS, next-generation sequencing; Q3W, every 3 weeks.

Sustained improvement of RFS primary efficacy endpoint

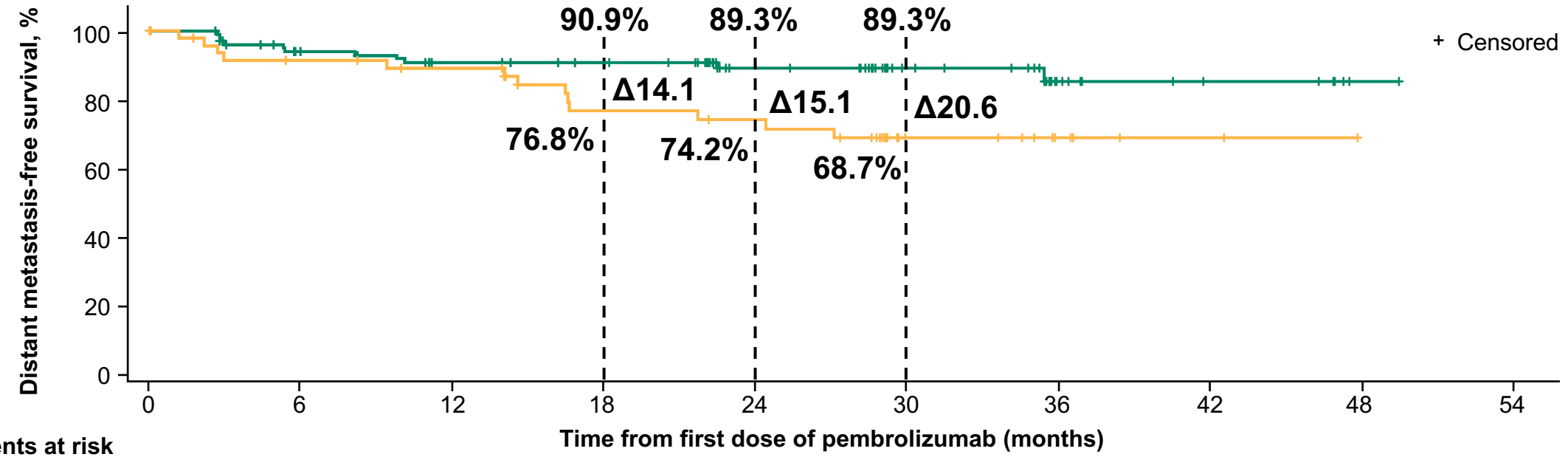


Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	87	83	77	52	29	12	6	1	0
Pembrolizumab	50	41	37	29	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	23.4 (25/107)	0.510 (0.288–0.906) *P* = 0.019[b]
pembrolizumab	42.51 (16.59–NE)	44.0 (22/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) + pembrolizumab versus pembrolizumab were estimated using 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 randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of RFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing. NE, not estimable.

Sustained improvement of DMFS secondary endpoint

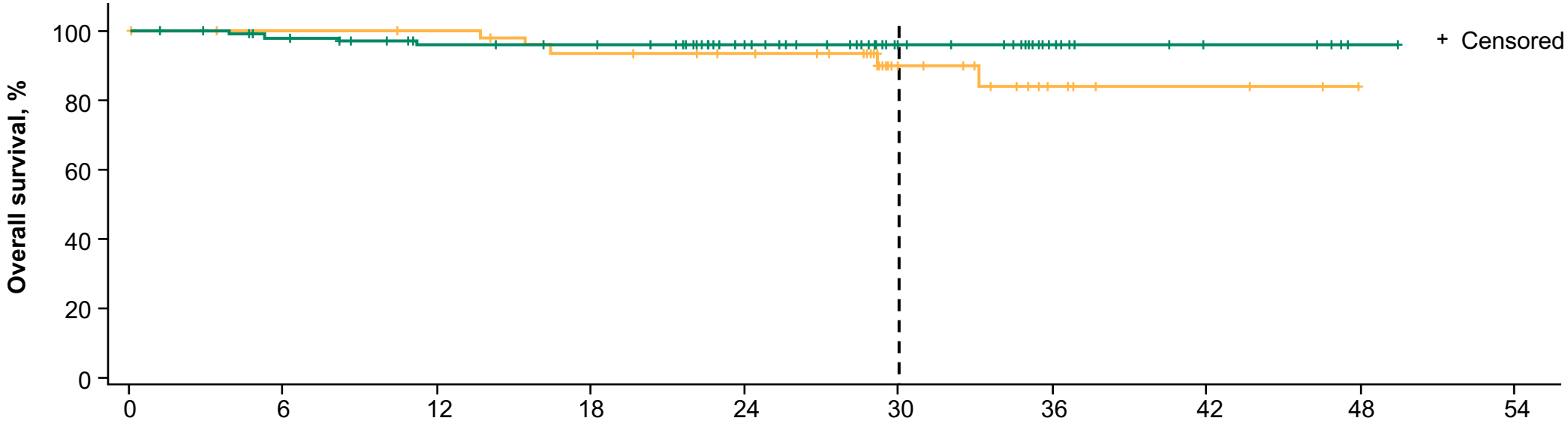


Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	89	82	78	52	30	12	6	1	0
Pembrolizumab	50	42	39	30	27	10	5	2	0	0

	Median (95% CI), months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	10.3 (11/107)	0.384 (0.172–0.858) *P* = 0.015[b]
Pembrolizumab	NE	26.0 (13/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using 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 randomization. The *P* value is based on a 2-sided log-rank test stratified by disease stage (stages IIIB or IIIC or IIID vs stage IV) used for randomization; [b]Formal hypothesis testing of DMFS was performed using November 2022 data cut. *P* value reported above used the November 2023 data cut; it's nominal and not for formal hypothesis testing.

Overall survival shows encouraging trend with mRNA-4157 (V940) + pembrolizumab



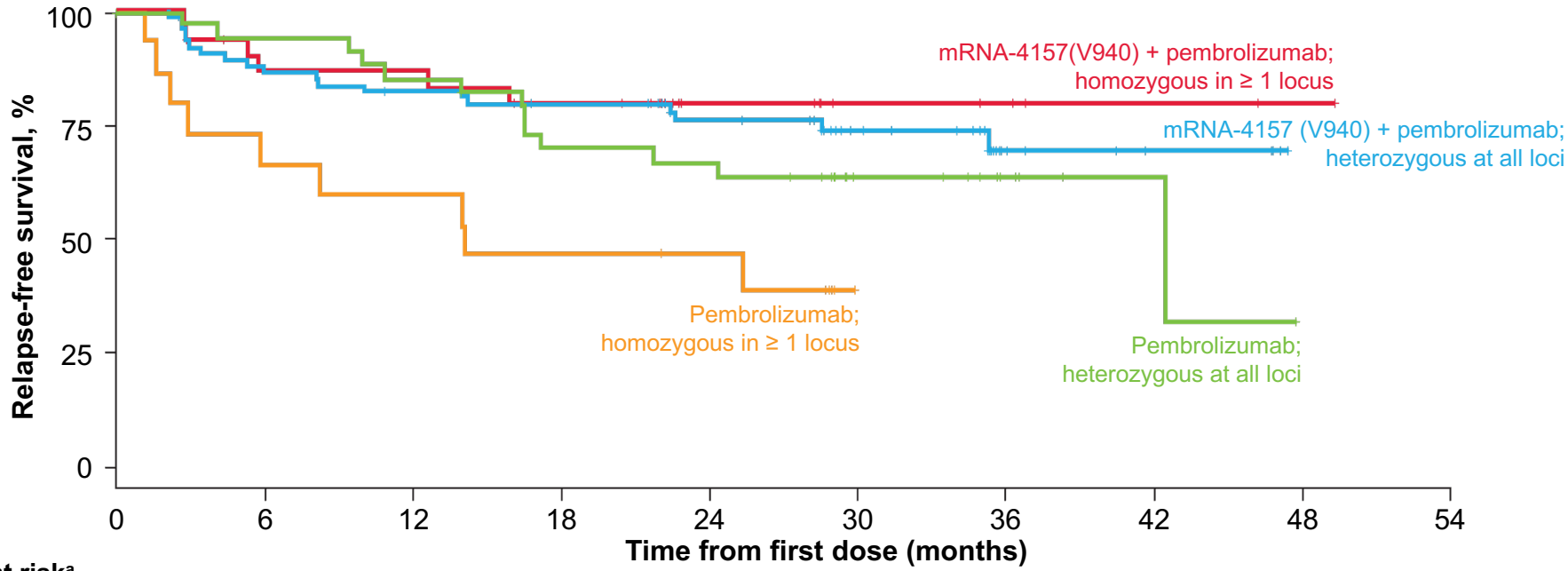
Patients at risk										
mRNA-4157 (V940) + pembrolizumab	107	100	92	90	65	35	14	6	1	0
Pembrolizumab	50	48	47	43	40	18	7	3	0	0

	Median (95% CI), Months	Events, % (n/N)	Hazard ratio (95% CI)[a]
mRNA-4157 (V940) + pembrolizumab	NE	3.7 (4/107)	0.425 (0.114–1.584)
Pembrolizumab	NE	10.0 (5/50)	

[a]The hazard ratio and 95% CI for mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab were estimated using 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 randomization.

Biomarker analyses suggest mRNA-4157 (V940) + pembrolizumab may benefit a broad patient population

- HLA class I plays a key role in CD8 T cell immunosurveillance
- HLA diversity has been linked with differential immune responses to infection and autoimmune diseases
- No significant associations between individual HLA alleles and RFS were observed for mRNA-4157 + pembrolizumab



Patients at risk[a]

mRNA-4157 (V940) + pembrolizumab; heterozygous at all loci[b]	74	62	58	55	42	24	8	4	0	0
mRNA-4157(V940) + pembrolizumab; homozygous in ≥ 1 locus[c]	31	25	25	22	10	5	4	2	1	0
Pembrolizumab; heterozygous at all loci[b]	34	31	28	22	21	10	5	2	0	0
Pembrolizumab; homozygous in ≥ 1 locus[c]	15	10	9	7	6	0	0	0	0	0

The benefit of mRNA-4157 (V940) + pembrolizumab continued to be observed irrespective of PD-L1, TMB, and ctDNA status,[d] as presented previously

Note: In a large dataset, HLA diversity has not been shown as a determinant of response to pembrolizumab.[1]
[a]Analyses are based on subpopulation with HLA data (n = 154) and excluded 3 patients who did not receive treatment in either arm; [b]HLA heterozygous: heterozygous at all HLA-A/B/C loci; [c]HLA homozygous: homozygous at ≥ 1 locus of HLA-A, HLA-B, and HLA-C; [d]Supportive analysis RFS HR (95% CI) for mRNA-4157 + pembrolizumab versus pembrolizumab in TMB-high: 0.564 (0.253–1.258); TMB-non-high: 0.571 (0.245–1.331); PD-L1-positive: 0.471 (0.226–0.979); PD-L1-negative: 0.147 (0.034–0.630); and ctDNA-negative: 0.207 (0.091–0.470) subgroups; ctDNA-positive HR was not estimable. CD, cluster of differentiation; ctDNA, circulating tumor DNA; HLA, human leukocyte antigen; PD-L1, programmed death ligand 1; TMB, tumor mutational burden.
1. Chhibber A, et al. *Immunity* 2022;55:56-64.e4.

3-year safety follow-up on safety demonstrates a manageable profile consistent with the primary analysis

	mRNA-4157 (V940) + pembrolizumab (n = 104)		Pembrolizumab (n = 50)	
Event, n (%)	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Any AE	104 (**100%**)	36 (**34.6%**)	46 (**92.0%**)	18 (**36.0%**)
Any treatment-related AE	104 (**100%**)	26 (**25.0%**)	41 (**82.0%**)	10 (**20.0%**)
Serious AE[a]	15 (**14.4%**)		5 (**10.0%**)	
Immune-related AE[b]	39 (**37.5%**)	11 (**10.6%**)	18 (**36%**)	7 (**14.0%**)

mRNA-4157 (V940) + pembrolizumab (n = 104), n (%)	Grade 1	Grade 2	Grade 3	Grade 4/5	Total (n = 104)
Patients with mRNA-4157 (V940)–related AE[c]	**35 (33.7%)**	**51 (49.0%)**	**12 (11.5%)**	**0**	**98 (94.2%)**
Fatigue	40 (38.5%)	18 (17.3%)	5 (4.8%)	0	63 (60.6%)
Injection site pain	37 (35.6%)	22 (21.2%)	0	0	59 (56.7%)
Chills	48 (46.2%)	3 (2.9%)	0	0	51 (49.0%)
Pyrexia	34 (32.7%)	15 (14.4%)	1 (1.0%)	0	50 (48.1%)
Headache	20 (19.2%)	13 (12.5%)	0	0	33 (31.7%)
Injection site erythema	29 (27.9%)	4 (3.8%)	0	0	33 (31.7%)
Influenza-like illness	21 (20.2%)	10 (9.6%)	0	0	31 (29.8%)
Nausea	23 (22.1%)	3 (2.9%)	0	0	26 (25.0%)
Myalgia	16 (15.4%)	5 (4.8%)	1 (1.0%)	0	22 (21.2%)

Safety analyses were conducted in the safety population, which was defined as all randomly assigned patients who received ≥ 1 dose of treatment. Grading per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0. [a]Serious AEs were not evaluated by toxicity grade; [b]Based on established list of pembrolizumab immune-related AEs (CMQ Pembrolizumab AEOSI); [c]mRNA-4157 (V940)–related AEs included events attributed by the investigator to mRNA-4157 (V940) alone as well as events attributed to both mRNA-4157 (V940) and pembrolizumab.
AE, adverse event; AEOSI, adverse event of special interest; CMQ, customized MedDRA queries.

Conclusions

mRNA-4157 (V940) + pembrolizumab demonstrated a durable **clinically significant improvement in RFS & DMFS** compared with standard of care pembrolizumab in high-risk resected melanoma, with a **49% reduction in the risk of recurrence or death** and a **62% reduction of distant recurrence or death** with 3 years of follow-up

3-year exploratory endpoint showed an **encouraging trend in overall survival** with the combination versus pembrolizumab monotherapy

mRNA-4157 (V940) + pembrolizumab has a **manageable safety profile** without potentiation of immune-related AEs compared with pembrolizumab monotherapy

Translational analyses suggest mRNA-4157 (V940) + pembrolizumab may benefit a **broad patient** population **irrespective of the status of PD-L1, TMB, ctDNA, and HLA heterozygosity**

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[a]The authors would like to acknowledge Jane Healy's contributions to the study.

THANK YOU!