First-Line mRNA-4359 Plus Pembrolizumab in Locally Advanced or Metastatic Melanoma: Results From the Phase 1/2 mRNA-4359-P101 Study

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Disclosure information

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Pavlina Spiliopoulou

I have the following relevant financial relationships to disclose:

Advisory board for: Iovance, Sun Pharma

Invited speaker for: BMS

Local PI for: Accession Therapeutics, BioNTech RNA Pharmaceuticals GMBH, C4 Therapeutics, Corbus Pharmaceuticals, Ideaya Biosciences, Immunocore, Iovance Biotherapeutics, Microbiotica, Moderna, Mythic

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Background

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- ICIs have revolutionized the treatment of advanced melanoma, yet in many cases, primary or secondary resistance develops over time so strategies with different therapeutic mechanisms are needed[1,2]
- mRNA-4359[a] was designed to address immune resistance, by priming and expanding T cells to simultaneously kill PD-L1–positive and IDO1-positive tumor cells and deplete the immunosuppressive cells that protect them[3]
  - An ongoing phase 1/2 mRNA-4359-P101 trial (NCT05533697) is evaluating mRNA-4359 as monotherapy or in combination with pembrolizumab for advanced solid tumors[3–6]
  - mRNA-4359 plus pembrolizumab demonstrated a manageable safety profile, antigen-specific T-cell responses, and durable antitumor activity in participants with CPI-R/R melanoma[5,6]

- We report safety, clinical, and translational data of mRNA-4359 plus pembrolizumab in the 1L setting for treatment of locally advanced/metastatic melanoma in the mRNA-4359-P101 study

1L, first-line; CPI-R/R, checkpoint inhibitor–resistant/refractory; ICIs, immune checkpoint inhibitors; IDO1, indoleamine 2,3-dioxygenase 1; PD-L1, programmed cell death ligand 1.
[a]mRNA-4359 is investigational and its efficacy and safety have not been confirmed.
1. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Melanoma: Cutaneous. Version 1.2026. https://www.nccn.org. 2. Chan PY, et al. *Am Soc Clin Oncol Educ Book*. 2024;44:e438654. 3. Powderly JD, et al. *J Clin Oncol*. 2023;41:TPS2676. 4. Khattak MA, et al. *Ann Oncol*. 2024;35(Suppl 2):S521–S522. 5. Pinato DJ, et al. *Ann Oncol*. 2025;36(Suppl 2):S844–S845. 6. Sarker D, et al. *J Immunother Cancer*. 2025;13 (Suppl 2):A694.

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mRNA-4359 is an investigational immune evasion–targeted cancer antigen therapy encoding epitopes of PD-L1 and IDO1 antigens

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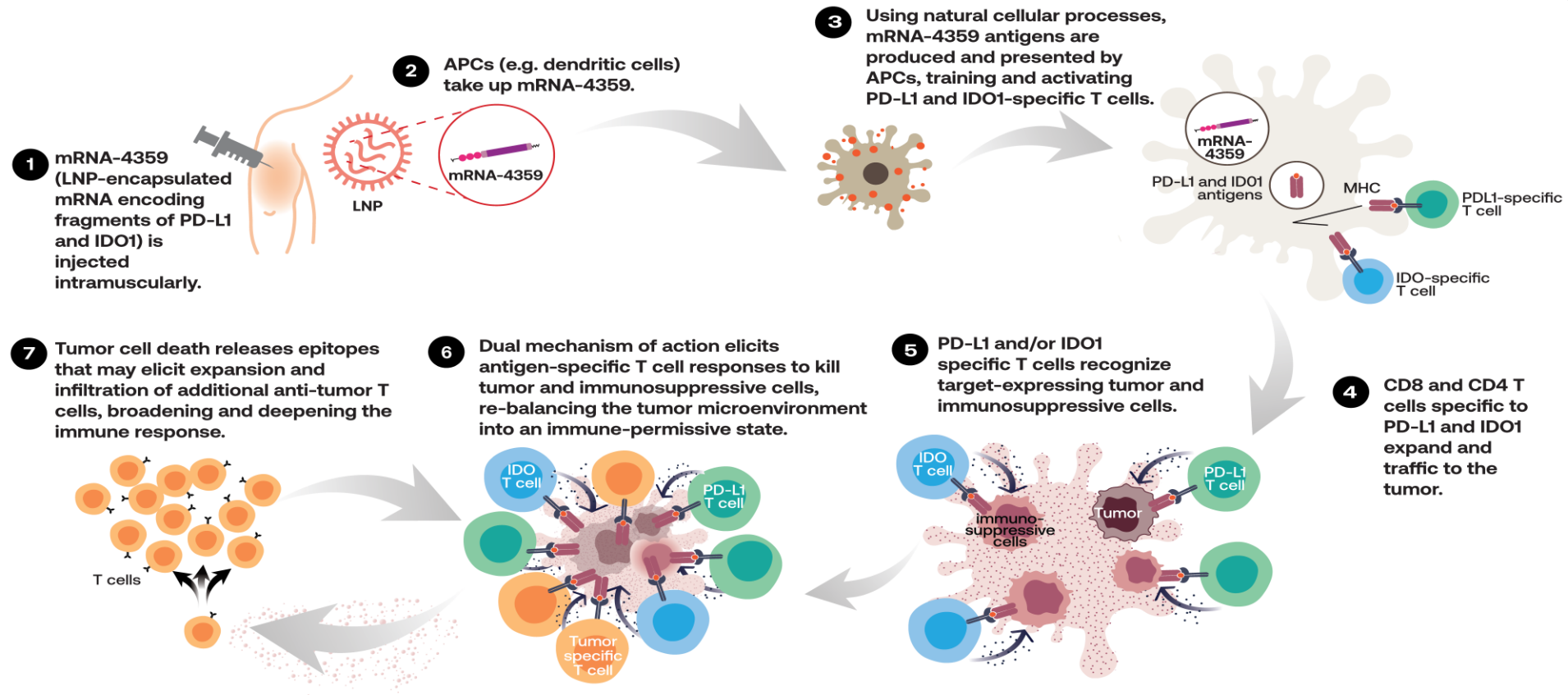

APC, antigen-presenting cell; LNP, lipid nanoparticle; MHC, major histocompatibility complex.

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mRNA-4359-P101 (NCT05533697)
Study design: Arm 2a

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Key eligibility criteria

- Age ≥18 years
- Locally advanced or metastatic melanoma and no receipt of any prior treatment for melanoma in this setting
- Measurable disease per RECIST version 1.1
- ECOG PS 0 or 1

Arm 2a (n = 12)
Dose expansion

mRNA-4359 1000 µg[a] IM Q3W for up to 9 cycles
+
Pembrolizumab 400 mg IV Q6W for up to 2 years

Primary endpoint

- Safety assessments including DLTs, AEs, SAEs, and AEs of special interest

Secondary endpoints

- ORR, DCR, DOR, and PFS per RECIST version 1.1 by investigator assessment
- Change in tumor T-cell profile from baseline after mRNA-4359 administration

Exploratory translational analyses

- Antigen-specific T-cell responses at baseline and on-treatment in periphery
- Change in peripheral TCR clones
- Baseline tumor PD-L1 and IDO1 expression

AE, adverse event; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious AE. TCR, T-cell receptor.
[a]mRNA-4359 dose was determined in the arm 1b (dose confirmation) data evaluation.

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Treatment disposition

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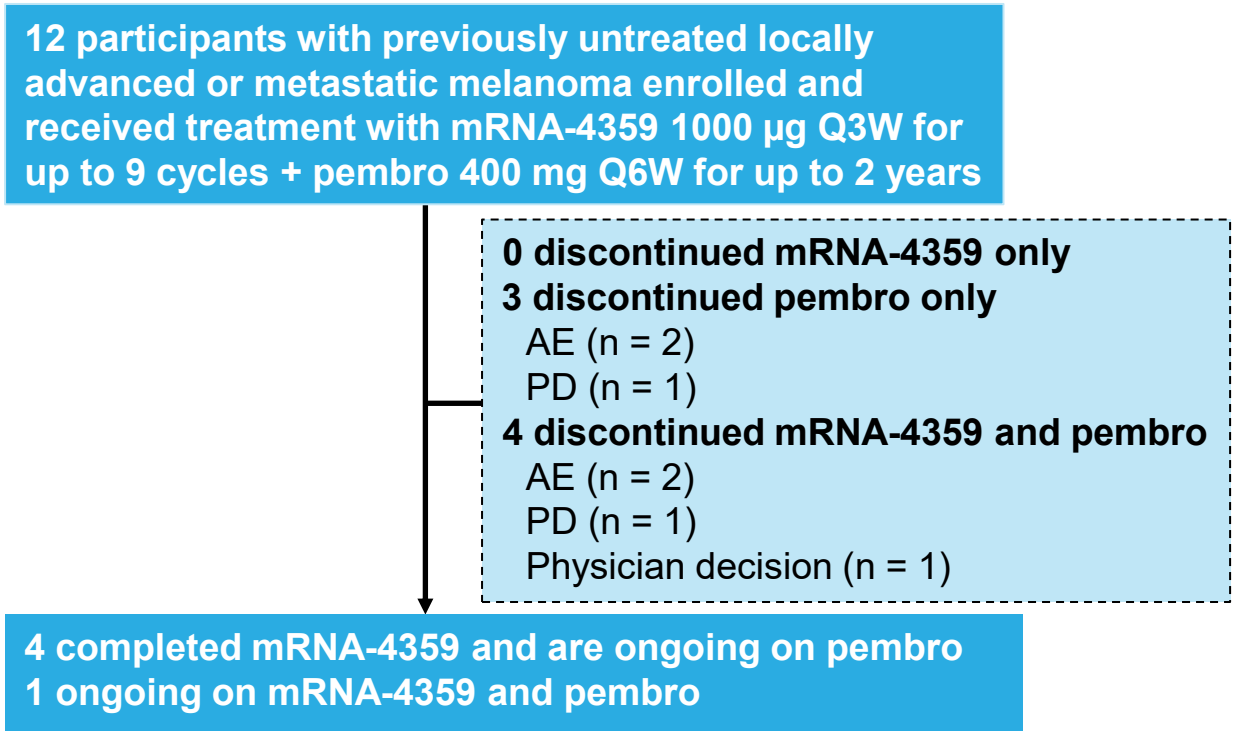
Median follow-up at data cutoff:
54.2 (range, 22.3–76.0) wk

Median mRNA-4359 exposure at data cutoff:
9 (range, 3–9) doses

Median pembro exposure at data cutoff:
6.5 (range, 2–12) doses



Pembro, pembrolizumab; PD, progressive disease.
Data cutoff: December 1, 2025.

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Baseline characteristics

	mRNA-4359 1000 µg Q3W + pembro 400 mg Q6W (n = 12)[a]
Age, median (range), y	58 (38–80)
<65 y, n (%)	8 (67)
≥65 y, n (%)	4 (33)
Sex, n (%)	
Male	6 (50)
Female	6 (50)
ECOG PS, n (%)	
0	11 (92)
1	1 (8)
Disease stage, n (%)	
III	1 (8)
IV	11 (92)

	mRNA-4359 1000 µg Q3W + pembro 400 mg Q6W (n = 12)[a]
PD-L1 TPS,[b] n (%)	
≥1%	8 (67)
<1%	3 (25)
Missing	1 (8)
***BRAF* status, n (%)**	
Mutated	6 (50)
Wild-type	6 (50)
Prior (neo)adjuvant therapy,[c] n (%)	4 (33)
Immunotherapy[d]	3 (25)
BRAF/MEK inhibition[e]	2 (17)

TPS, tumor proportion score. [a]1 had mucosal melanoma, 1 acral lentiginous melanoma, and 10 had melanoma of cutaneous (nodular or superficial) or unknown primary origin. [b]PD-L1 testing was assessed centrally using PD-L1 IHC 22C3 pharmDx (Agilent, Santa Clara, CA). [c]3 participants received prior adjuvant therapy and 1 received prior neoadjuvant and adjuvant therapy. [d]All participants received prior nivolumab. [e]Dabrafenib and trametinib or encorafenib and binimetinib. Data cutoff: December 1, 2025.

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All observed mRNA-4359–related AEs were low grade

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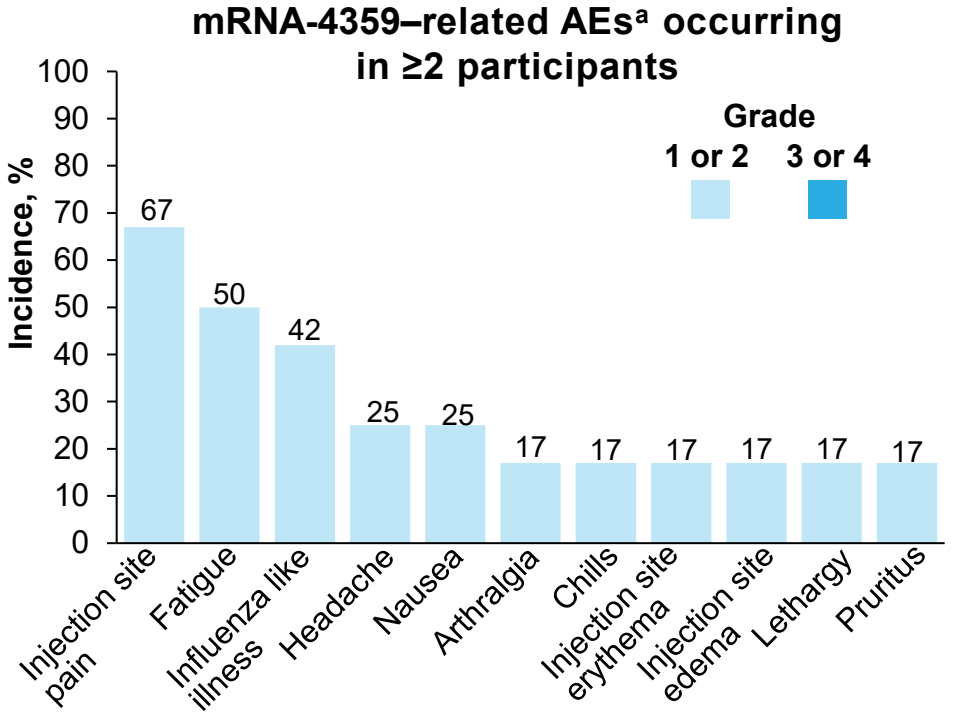
	mRNA-4359 1000 µg Q3W + pembro 400 mg Q6W (n = 12)
mRNA-4359–related AEs,[a] n (%)	11 (92)
DLTs	0
Grade ≥3	0
Serious	1 (8)
Led to mRNA-4359 delay	2 (17)
Led to mRNA-4359 discontinuation	0
Led to pembro discontinuation	0
Led to death	0



[a]Defined as AEs not present before study or worsened on study and deemed related to study drug by investigator.
Data cutoff: December 1, 2025.

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Pembrolizumab-related AEs were predominantly low-grade

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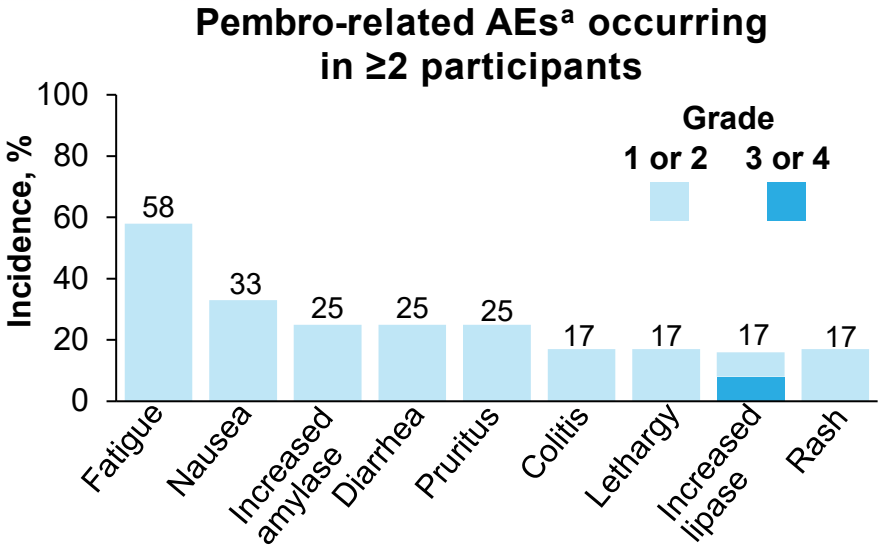
	mRNA-4359 1000 µg Q3W + pembro 400 mg Q6W (n = 12)
Pembro-related AEs,[a] n (%)	11 (92)
DLTs	0
Grade 3 or 4	4 (33)
Serious	6 (50)
Led to pembro delay	7 (58)
Led to pembro interruption	1 (8)
Led to pembro discontinuation	3 (25)[b]
Led to mRNA-4359 discontinuation	1 (8)[c]
Led to death	0



- 1 pembro-related grade 4 event occurred (increased lipase)
- Pembro-related grade 3 events included immune-mediated pancreatitis in 1 participant, dyspnea in 1 participant, and immune-mediated hepatitis in 1 participant

[a]Defined as AEs not present before study or worsened on study and deemed related to study drug by investigator. [b]Due to grade 1 peripheral sensorimotor neuropathy, grade 2 colitis, and grade 2 immune-mediated pancreatitis (n = 1 each). [c]Due to grade 2 colitis.
Data cutoff: December 1, 2025.

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Response[a] was observed in most participants irrespective of PD-L1 status

	mRNA-4359 1000 µg Q3W + pembro 400 mg Q6W		
	PD-L1 TPS ≥1% (n = 8)	PD-L1 TPS <1% (n = 3)	All participants (N = 12)
ORR (95% CI),[b] %	88 (47–100)	67 (9–99)	83 (52–98)
Best overall response,[c] n (%)			
CR	2 (25)	0	2 (17)
PR	5 (63)	2 (67)	8 (67)
SD	0	1 (33)	1 (8)
PD	1 (13)	0	1 (8)
DCR (95% CI),[b] %	88 (47–100)	100 (29–100)	92 (62–100)
DOR, median (95% CI),[d] wk	NR (NR–NR)	NR (NR–NR)	NR (NR–NR)
TTR, median (range),[e] wk	6.0 (5.6–18.1)	15 (6.0–24.0)	6.0 (5.6–24.0)

CR, complete response; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response. [a]Assessed per RECIST version 1.1 by investigator assessment. [b]Unconfirmed ORR and unconfirmed DCR were based on Clopper-Pearson method. [c]Best overall response was unconfirmed. [d]Estimated using Kaplan-Meier method. [e]Calculated based on observed values.
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Majority of participants remain progression-free[a] and in follow-up

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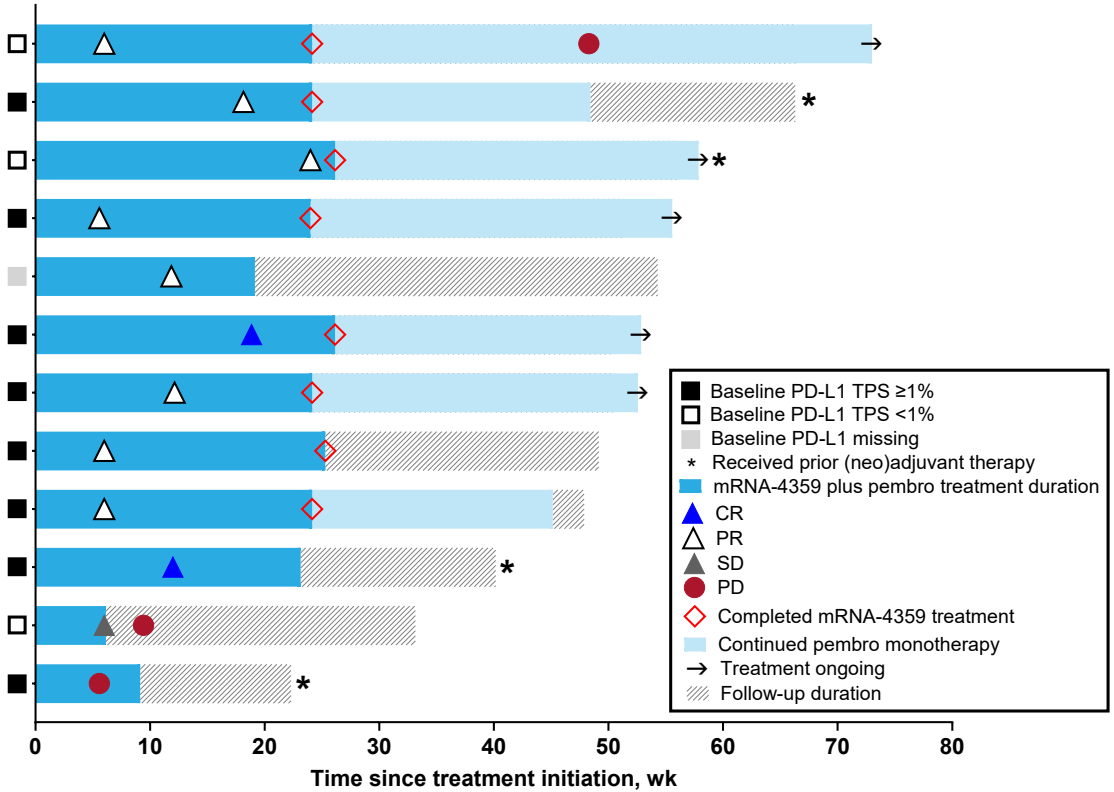

- Three of four participants with prior (neo)adjuvant therapy had an objective response
  - 2 received prior nivolumab and 1 received prior dabrafenib and trametinib
- Overall, 3 of 12 participants experienced PD, of whom 2 had a PFS event[b]
  - Median PFS was NR (95% CI, 9.4 weeks–NR)[c]
- Most participants continue follow-up without any further PFS events observed to date

[a]Assessed per investigator assessment. [b]1 participant with PD was censored due to ≥2 missing tumor assessments. [c]Estimated using Kaplan-Meier method.
Data cutoff: December 1, 2025.

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Most participants had a reduction in tumor burden[a] irrespective of PD-L1 status

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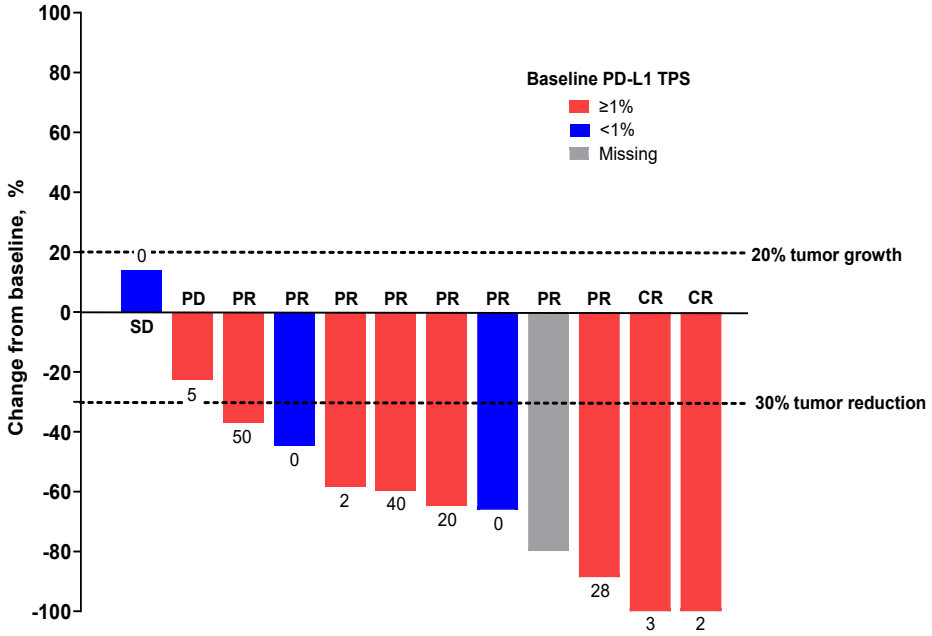
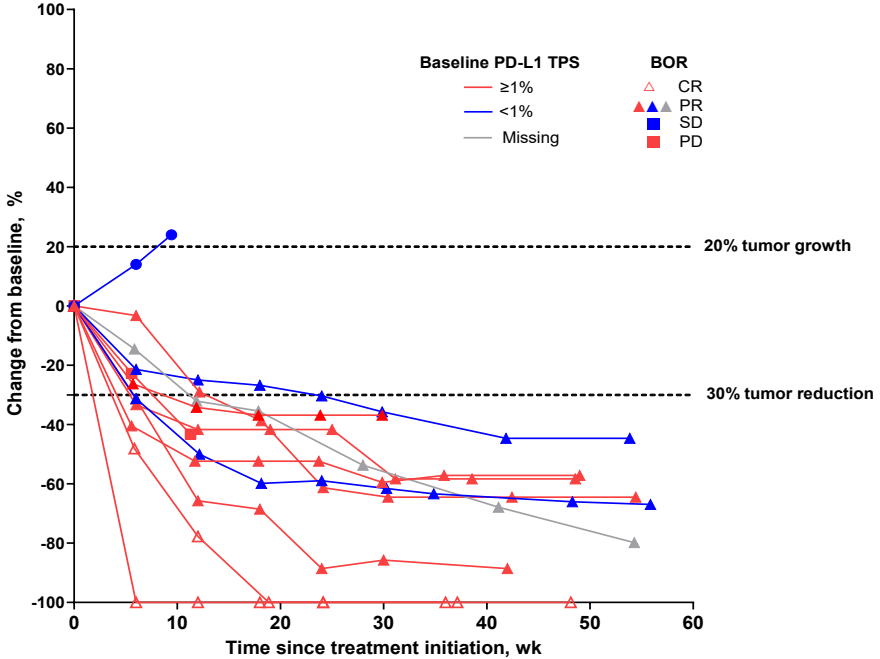
Maximum percent reduction from baseline in sum of diameter of target lesions[b]



Percent change from baseline in sum of diameter of target lesions over time



[a]Assessed per investigator assessment. [b]1 participant had a reduction in target lesions but was classified as PD due to the development of a new lesion in the liver.
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Baseline tumors exhibit PD-L1/IDO1 expression linked to inflammatory gene signatures

RNA sequencing analysis of PD-L1 and IDO1 expression

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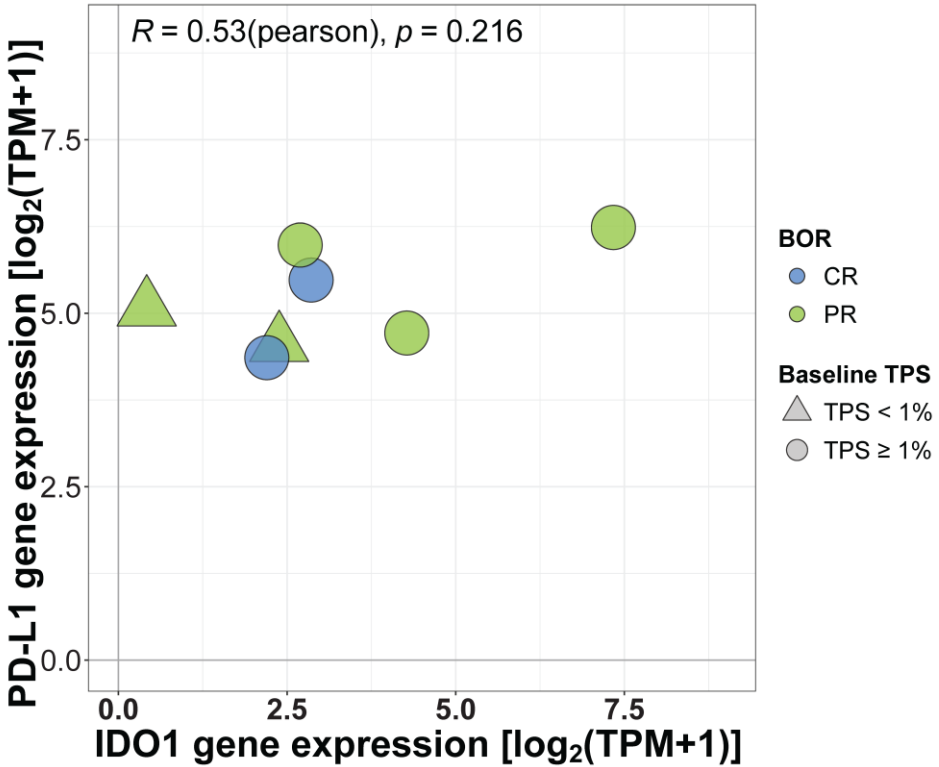
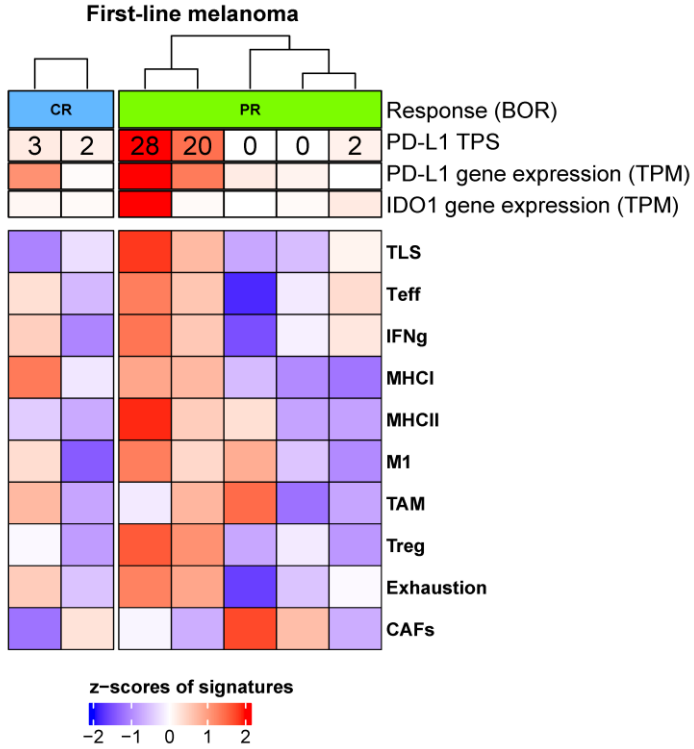
PD-L1 and IDO1 gene expression[a]



Inflammatory gene signatures[a]



[a]Data available for RNA sequencing from 7 participants (all responded to treatment).

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mRNA-4359 plus pembrolizumab elicits antigen-specific T-cell responses and expands novel clones

ELISpot and TCR sequencing analysis in periphery

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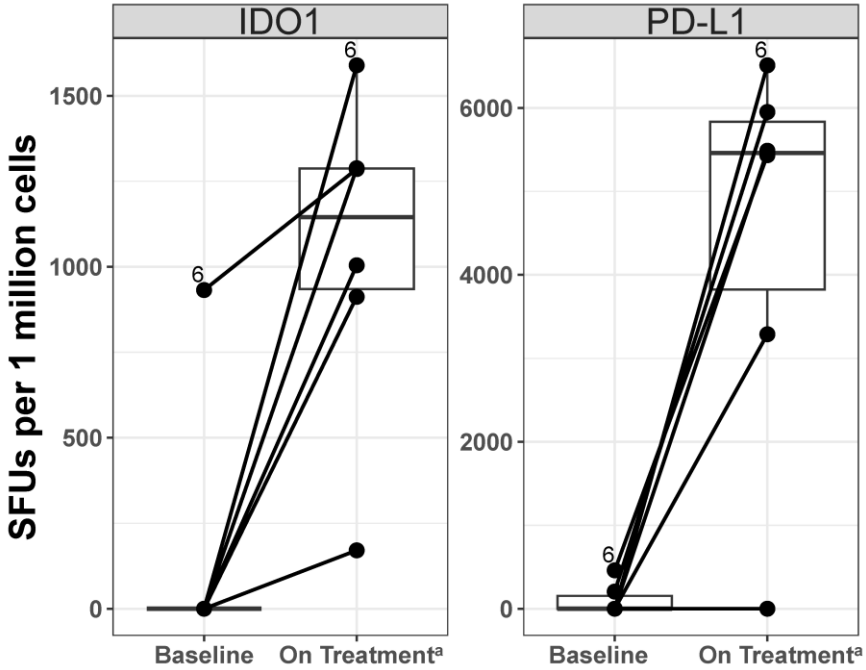
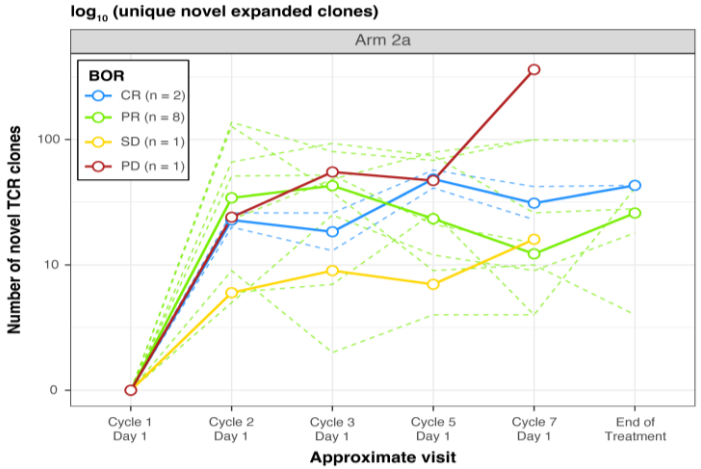
PD-L1- and IDO1-specific T-cell responses (IFN-γ ELISpot)[a]



Novel expanded TCR clones (TCR sequencing)[b,c]



Median unique novel expanded clones by visit and BOR

Arm 2a

	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 5 Day 1	Cycle 7 Day 1	End of Treatment
CR	0	22	18	48	32	42
PR	0	36	42	22	12	25
SD	0	5	8	6	15	
PD	0	23	54	46	360	

SFU, spot-forming unit. [a]On-treatment antigen-specific T-cell responses were defined as the best ELISpot response across timepoints for each participant, measured after in vitro expansion of peripheral blood mononuclear cells (PBMCs). [b]Solid lines represent median data for each response group, and dotted lines represent each individual participant. [c]1 participant demonstrated rapid target lesion reduction but was classified as PD due to the development of a new lesion in the liver.

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Conclusion

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- mRNA-4359 plus pembrolizumab demonstrated a manageable safety profile in participants previously untreated for locally advanced or metastatic melanoma
  - The proportion of participants who discontinued treatment due to treatment-related AEs was low (none due to mRNA-4359–related AEs; 25% due to pembro-related AEs)
  - Observed toxicity of mRNA-4359 was mostly low-grade injection site reactions and self-limited systemic AEs, and was consistent with other mRNA-based therapies
- Encouraging antitumor activity and durable responses were observed in most participants (83%), irrespective of baseline tumor PD-L1 expression or prior (neo)adjuvant therapy
- All evaluable participants demonstrated antigen-specific T-cell responses and expansion of novel TCR clones, consistent with the hypothesized mechanism of mRNA-4359 and pembrolizumab
- Although interpretation is limited due to the small sample size, findings from this analysis support further clinical development of mRNA-4359 for this patient population

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Acknowledgments

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"We wish to express our sincere appreciation to the study participants, their families, the investigators, site personnel, research teams, our vendors, and collaborators who contributed to this mRNA-4359-P101 study."

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We also thank the following employees of Moderna Inc., Cambridge, MA, USA, who supported the study: Ann Leighton-Swayze, Stephanie Pascarella, Jessica Lempke, Lindsay Levine, Jingting Xu, Jacky Chow, and Sujeethraj Koppolu.

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