

First-in-human, phase 1/2, monotherapy, dose-escalation study of mRNA-4359, an mRNA-encoded PD-L1/IDO1 antigen-specific therapy, in advanced/refractory solid tumors

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Background

- Despite checkpoint inhibitor immunotherapy improving clinical outcomes in many patients with cancer, only a subset of patients receiving this type of treatment experience long-term clinical benefit; altering the tumor microenvironment may result in improved clinical outcomes and long-term benefit¹
- Both programmed death-ligand 1 (PD-L1) and indoleamine 2,3-dioxygenase 1 (IDO1) antigens have been hypothesized to contribute to an inhibitory tumor microenvironment that allows tumor cells to bypass immune monitoring and clearance^{2,3}
- mRNA-4359 is a lipid nanoparticle-encapsulated mRNA-based cancer therapy encoding immunogenic peptides PD-L1 and IDO1, administered as an intramuscular injection. mRNA-4359 is hypothesized to elicit antigen-specific T cells, eliminating immunosuppressive cells and cancer cells that express PD-L1 and/or IDO1, potentially tipping the balance towards a more inflammatory and/or immune-permissive tumor microenvironment
- We evaluated mRNA-4359 treatment, with or without pembrolizumab, in patients with advanced solid tumors (phase 1/2 trial), and herein report data from the monotherapy dose-escalation portion of this ongoing study (NCT05533697)⁴



Objective

- To assess the safety/tolerability, anti-tumor clinical activity/T-cell phenotype, and antigen-specific T-cell response of mRNA-4359 monotherapy in patients with advanced solid tumors

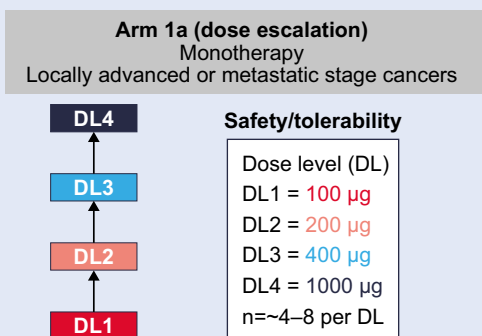


Methods

Study design and participants

- Arm 1a evaluated sequentially escalating doses of mRNA-4359 monotherapy in patients with locally advanced or metastatic solid tumor malignancies, refractory to ≥ 1 prior therapies (**Figure 1**)

Figure 1. Study design



First-in-human, phase 1/2 of mRNA-4359 in adult participants with locally advanced or metastatic recurrent/resistant solid tumor malignancies
DL, dose level

Assessments

Primary:

- Safety/tolerability: Incidence, nature, and severity of dose-limiting toxicities (DLTs), treatment-emergent adverse events (TEAEs), serious AEs, and AEs of special interest including, but not limited to, changes in laboratory results, vital signs, physical examination, and electrocardiogram measurements

Secondary:

- Anti-tumor activity: Objective response rate, disease control rate, duration of response, and progression-free survival based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)

Exploratory:

- Longitudinal assessment of antigen-specific T-cell response via interferon-gamma (IFN- γ) enzyme-linked immunosorbent spot (ELISpot) after *in vitro* expansion and immunophenotyping by flow cytometry were performed using peripheral blood mononuclear cells (PBMCs) and whole blood samples, respectively



Results

Patient disposition and characteristics

- There were 19 patients enrolled who received ≥ 1 doses of mRNA-4359
- Patients had a median age of 58 years, 63% had an Eastern Cooperative Oncology Group (ECOG) Performance Status of 1, and the most common primary cancer type was microsatellite stable colorectal cancer (MSS-CRC; 58%; **Table 1**)

Table 1. Patient characteristics

Characteristic	Arm 1a monotherapy (N=19)
Age	
Median (range), years	58 (44–84)
<65 years	14 (74)
≥ 65 years	5 (26)
Sex	
Male	8 (42)
Female	11 (58)
Race	
White	12 (63)
Black/African American	3 (16)
Unknown/not reported/other	4 (21)
ECOG Performance Status	
0	7 (37)
1	12 (63)
Primary cancer type	
MSS-CRC	11 (58)
HNSCC	3 (16)
NSCLC	2 (11)
TNBC	2 (11)
Melanoma	1 (5)

Data are given as n (%) unless specified otherwise. Percentages may not add to 100% due to rounding
ECOG, Eastern Cooperative Oncology Group; MSS-CRC, microsatellite stable colorectal cancer; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; TNBC, triple-negative breast cancer

Safety

- No DLTs were reported at any dose
- TEAEs related to mRNA-4359 occurred in 13 (68.4%) patients (**Table 2**)
- There were no serious TEAEs related to mRNA-4359 and all TEAEs related to mRNA-4359 were grade 1/2; the most common grade 1/2 TEAEs related to mRNA-4359 were fatigue (n=7; 36.8%), injection-site pain (n=6; 31.6%), and pyrexia (n=4; 21.1%)
- Local injection event (pain) and systemic events (headache, fatigue, chills, etc.) were noted in patients receiving higher monotherapy doses (400 and 1000 μ g) but fewer were observed in patients receiving lower doses (100 and 200 μ g)

Table 2. TEAEs related to mRNA-4359 by monotherapy dose

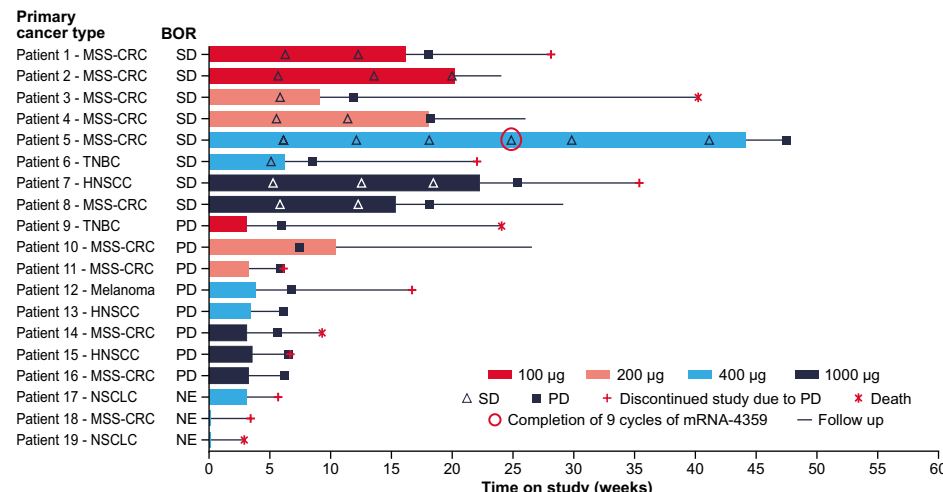
	100 μ g (n=3)	200 μ g (n=4)	400 μ g (n=7)	1000 μ g (n=5)	Total (N=19)
Patients with ≥ 1 TEAE related to mRNA-4359 treatment	2 (66.7)	2 (50.0)	5 (71.4)	4 (80.0)	13 (68.4)
Fatigue	1 (33.3)	1 (25.0)	2 (28.6)	3 (60.0)	7 (36.8)
Injection-site pain	0	0	2 (28.6)	4 (80.0)	6 (31.6)
Pyrexia	1 (33.3)	0	1 (14.3)	2 (40.0)	4 (21.1)
Headache	0	0	1 (14.3)	2 (40.0)	3 (15.8)
Chills	0	0	1 (14.3)	1 (20.0)	2 (10.5)
Vomiting	1 (33.3)	0	1 (14.3)	0	2 (10.5)
Nausea	1 (33.3)	0	1 (14.3)	0	2 (10.5)
Dizziness	0	0	1 (14.3)	1 (20.0)	2 (10.5)

Data are given as n (%)
TEAE, treatment-emergent adverse event

Clinical response

- At data cutoff (April 17, 2024), 50% (8/16) of response-evaluable patients achieved a best overall response (BOR) of stable disease (SD; **Figure 2**)
- There was no clear relationship between dose and achieving or maintaining SD
- One patient with MSS-CRC completed all 9 cycles and remained on mRNA-4359 per investigator discretion due to ongoing clinical benefit

Figure 2. Treatment response based on investigator assessment per RECIST v1.1 and survival follow-up in arm 1a



BOR, best overall response; HNSCC, head and neck squamous cell carcinoma; MSS-CRC, microsatellite stable colorectal cancer; NE, non-evaluable; NSCLC, non-small cell lung cancer; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TNBC, triple-negative breast cancer

Translational and biomarker data

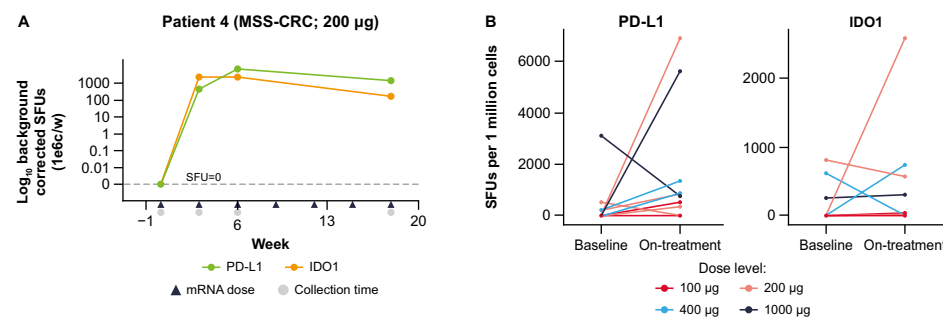
- Antigen-specific T-cell responses in the periphery, as assessed by ELISpot in PBMCs after *in vitro* cell expansion in response to either PD-L1 or IDO1, were detectable in 13/14 (93%) patients with evaluable peripheral samples (**Table 3**)
- Antigen-specific T-cell responses post-treatment were observed (**Figure 3**)
- Induction of activated, cytotoxic, and memory T cells, along with reduction in regulatory T cells and myeloid-derived suppressor cells (MDSCs) post-treatment were observed by flow cytometry in the periphery (**Figures 4 and 5**)

Table 3. PD-L1- or IDO1-specific T-cell response on-treatment

Antigen-specific T-cell responses by ELISpot	
Analyte	Patients with antigen-specific T-cell response
PD-L1	10/14 (71)
IDO1	7/14 (50)
Either PD-L1 or IDO1	13/14 (93)
Both PD-L1 and IDO1	4/14 (29)

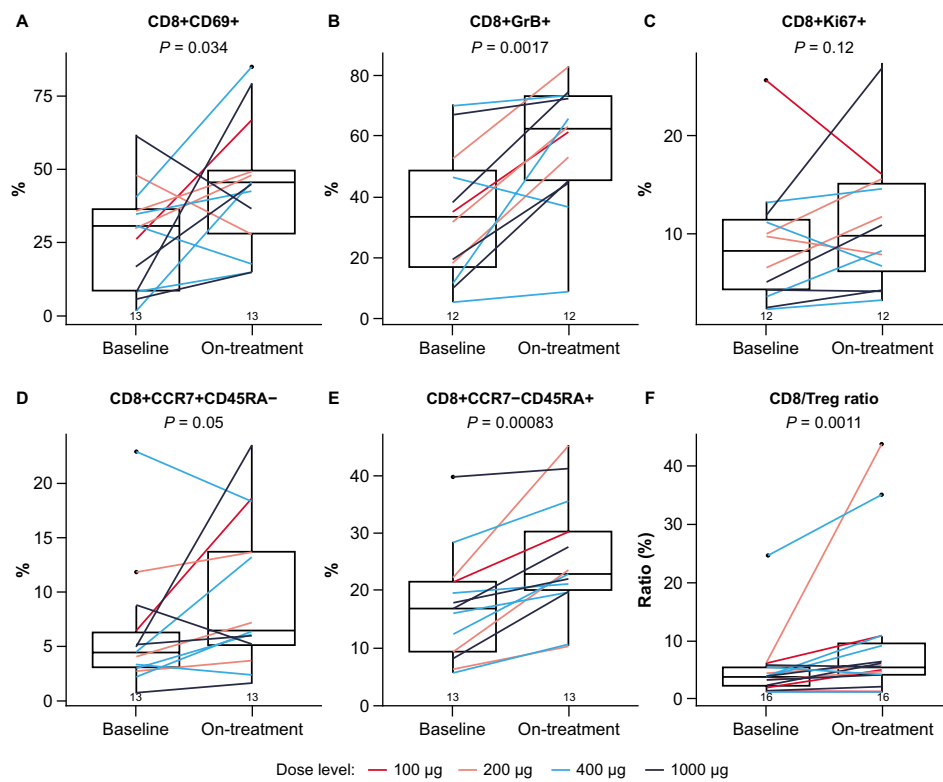
Data are given as n/N (%). Antigen-specific T-cell response is defined as a value >0 after subtraction of background response (peptide-specific response - [mean of background + 3 x standard deviations of background])
ELISpot, enzyme-linked immunosorbent spot; IDO1, indoleamine 2,3-dioxygenase 1; PD-L1, programmed death-ligand 1

Figure 3. Induced antigen-specific T-cell responses on-treatment



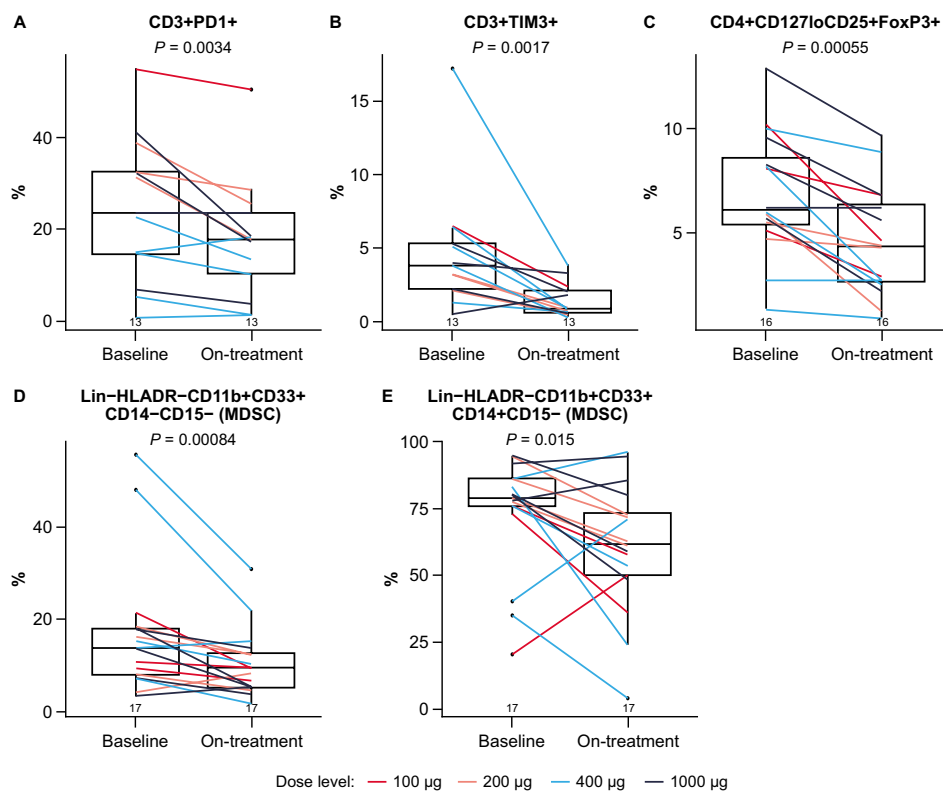
A) A representative PD-L1- and IDO1-specific T-cell response by ELISpot from a patient with MSS-CRC dosed with 200 μ g mRNA-4359 monotherapy, who also showed stable disease. SFUs were normalized to 1×10^6 cells and log transformed after background correction. **B)** Summary of PD-L1- and IDO1-specific T-cell responses in PBMCs of patients with paired samples measured by the IFN- γ ELISpot assay at baseline and on-treatment. On-treatment responses were selected from the 'best' ELISpot response at different time points for each patient
c/w, cells per well; ELISpot, enzyme-linked immunosorbent spot; IDO1, indoleamine 2,3-dioxygenase 1; IFN, interferon; MSS-CRC, microsatellite stable colorectal cancer; PBMC, peripheral blood mononuclear cell; PD-L1, programmed death-ligand 1; SFU, spot-forming unit

Figure 4. Increased peripheral CD8 T-cell activation, proliferation, memory subsets, and cytotoxic function on-treatment



Summary of changes in CD8+ T-cell phenotype (population percentages of CD8+ activation [CD69+], cytotoxic function [GrB+], proliferation [Ki67+], central memory [CCR7+CD45RA-], terminally differentiated effector memory [CCR7-CD45RA+], and CD8/Treg ratio) in whole blood of patients with paired samples, measured by flow cytometry at baseline and on-treatment. Box plots show baseline vs maximum increase on-treatment. Exploratory *P*-values from one-sided Wilcoxon signed rank test for paired difference
CCR, C-C motif chemokine receptor; CD, cluster of differentiation; GrB, granzyme B; Ki67, Ki67; RA, exon A; Treg, regulatory T

Figure 5. Reduced peripheral regulatory T cells, MDSCs, and T-cell exhaustion on-treatment



Summary of reduced cell responses (population percentages of exhausted CD8 T cells [PD1+ and TIM3+], Tregs [CD4+CD127loCD25+FoxP3+], MDSCs [Lin-HLADR-CD11b+CD33+CD14+CD15-], and M-MDSCs [Lin-HLADR-CD11b+CD33+CD14+CD15-]) in whole blood of patients with paired samples measured by flow cytometry at baseline and on-treatment. Box plots show baseline vs maximum reduction on-treatment. Exploratory *P*-values from one-sided Wilcoxon signed rank test for paired difference
CD, cluster of differentiation; HLADR, human leukocyte antigen - DR isotype; MDSC, myeloid-derived suppressor cell; M-MDSC, monocyte MDSC; PD1, programmed death protein 1; TIM, T-cell immunoglobulin and mucin domain-containing protein; Treg, regulatory T



Conclusions

- mRNA-4359 monotherapy was tolerable at all dose levels tested; most AEs were of low grade (grade 1–2) and manageable
- In this population of patients with heavily pre-treated, advanced stage cancers, 8/16 response-evaluable patients achieved disease control (BOR of SD)
- Translational data showed antigen-specific T-cell responses were elicited by mRNA-4359 treatment; a proportion of activated, cytotoxic, and memory T cells were elevated and a proportion of regulatory T cells and MDSCs were diminished on-treatment
- The study is currently enrolling into disease-specific cohorts (melanoma and NSCLC), combining mRNA-4359 with pembrolizumab

References

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Acknowledgments

The study was sponsored by Moderna, Inc., and editorial assistance was provided by Caudex, a division of IPG Health Medical Communications, New York, NY, USA, in accordance with Good Publication Practice 2022 guidelines, funded by Moderna Inc., and under the direction of the authors

Thank you to the: patients and their families; site staff; vendors; collaborators; scientists; and regulatory, operations, and manufacturing teams who discovered, improved, and enabled mRNA-4359

Disclosures

DS has participated in an advisory board for AAA, AstraZeneca, Bayer, Eisai, Incyte, Ipsen, and Surface Oncology; was an invited speaker for AstraZeneca, Bayer, Eisai, Incyte, MSD, and Servier; received travel and conference fees from Ipsen and MINA Therapeutics; provided expert testimony for AbbVie and Boehringer Ingelheim; acted as a local Principal Investigator (PI) for Adaptimmune, AstraZeneca, Blueprint, Bayer, Eisai, GSK, H3, Ipsen, Medivir AB, MSD, RedX, Regeneron, Starpharma, and Taiho; acted as coordinating PI for MINA Therapeutics and UCB; received funding from Inspirata and Roche; and has had an advisory role with Medivir, MINA Therapeutics, and UCB

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