Moderna Oncology Overview

June 3, 2024

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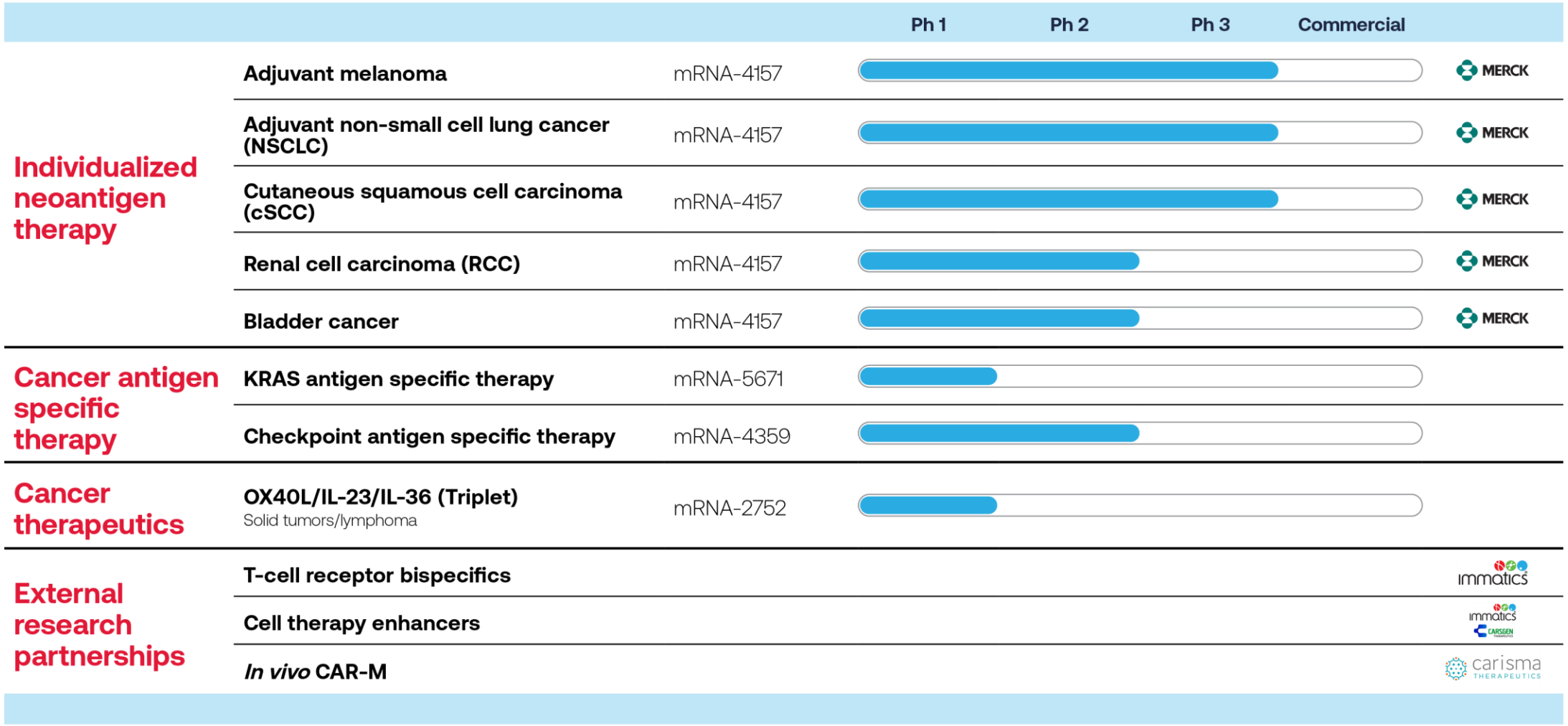
Revolutionizing immuno-oncology with mRNA



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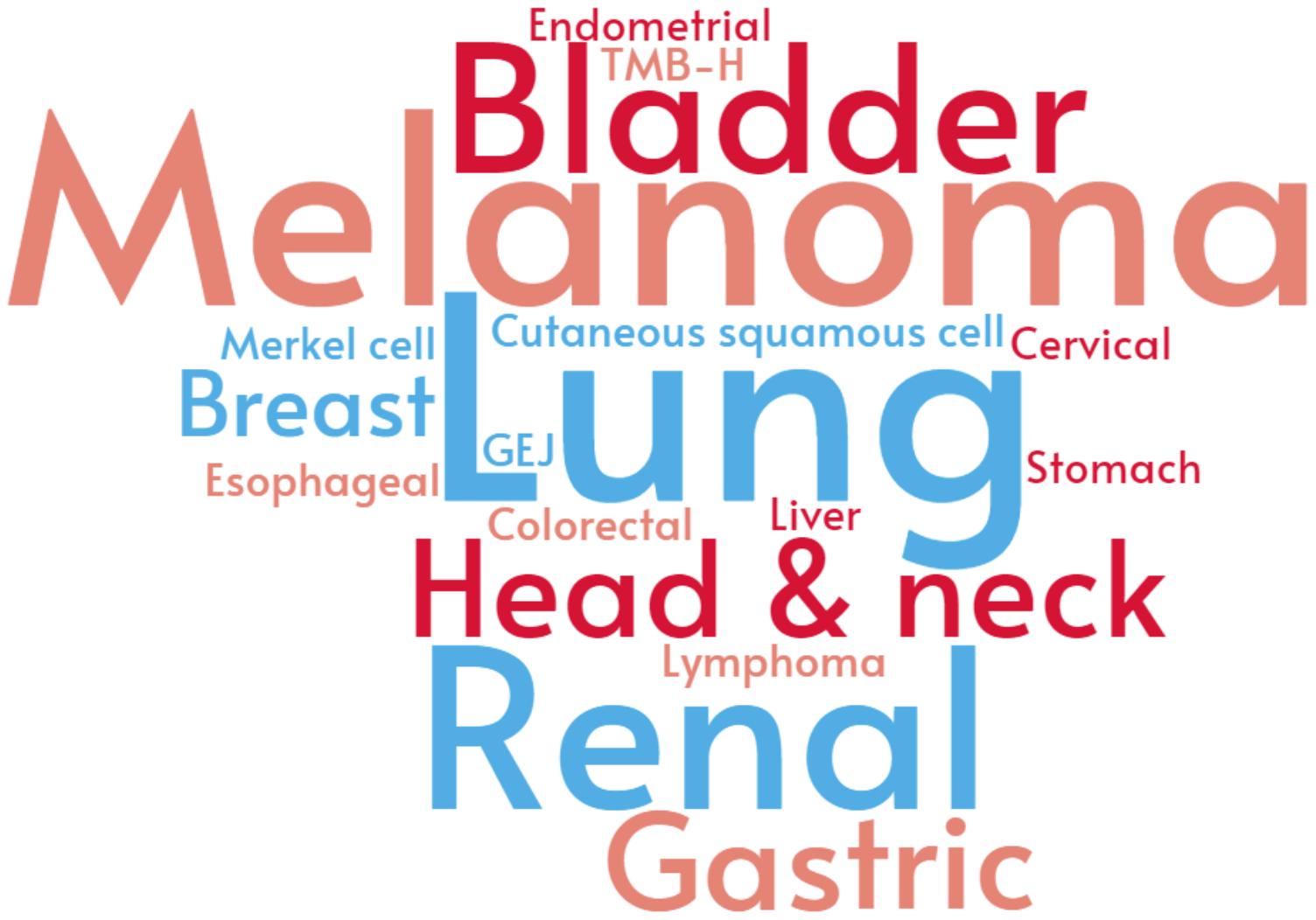
Agenda

INT: transforming cancer care	**Kyle Holen** Senior Vice President, Development, Oncology and Therapeutics
Individualized Neoantigen Therapy (INT)	**Michelle Brown** Vice President, Portfolio Leadership, INT
Early-stage clinical oncology programs	**Kyle Holen** Senior Vice President, Development, Oncology and Therapeutics
External research partnerships	**Rose Loughlin** Senior Vice President, Research and Early Development

Checkpoint inhibitors have had a dramatic impact on cancer treatment



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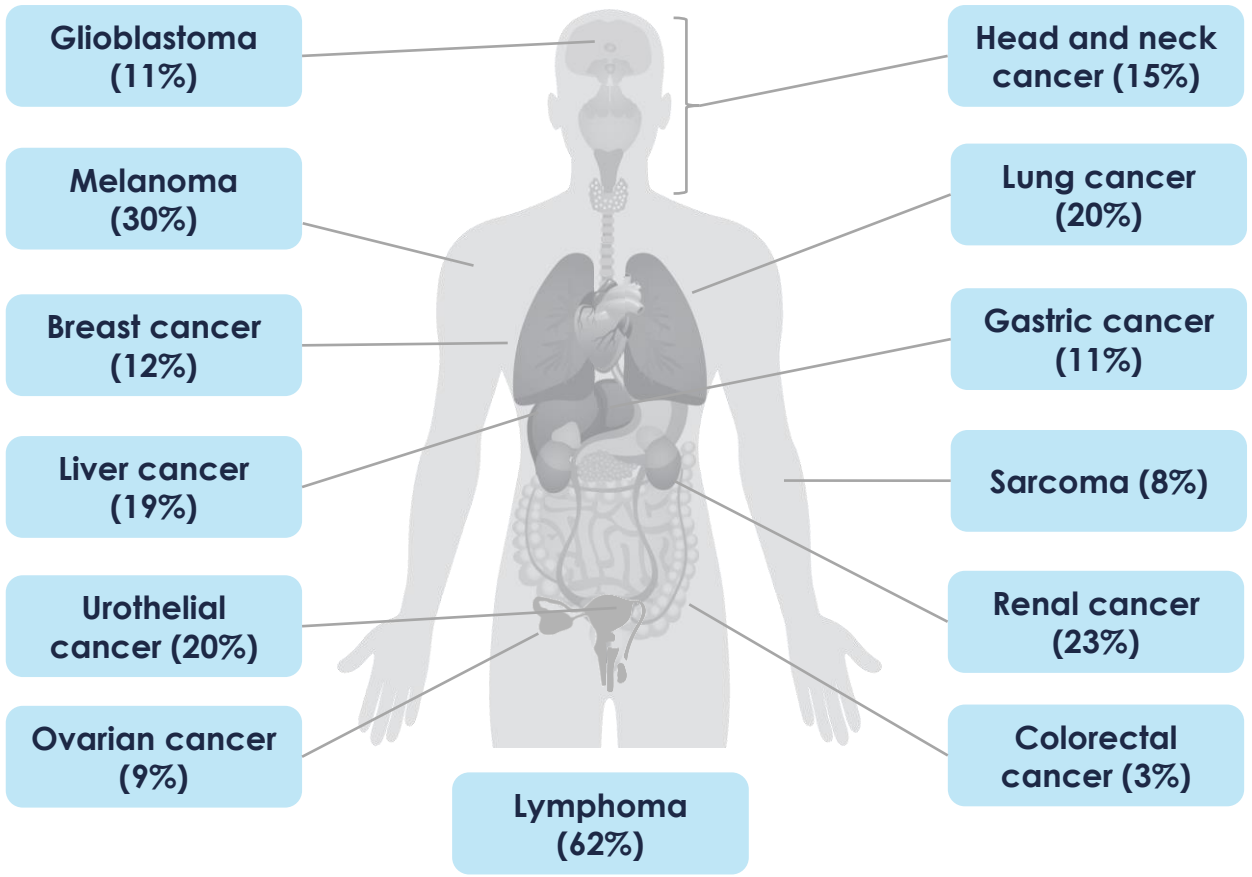
Despite success with checkpoint inhibitors, unmet medical need exists

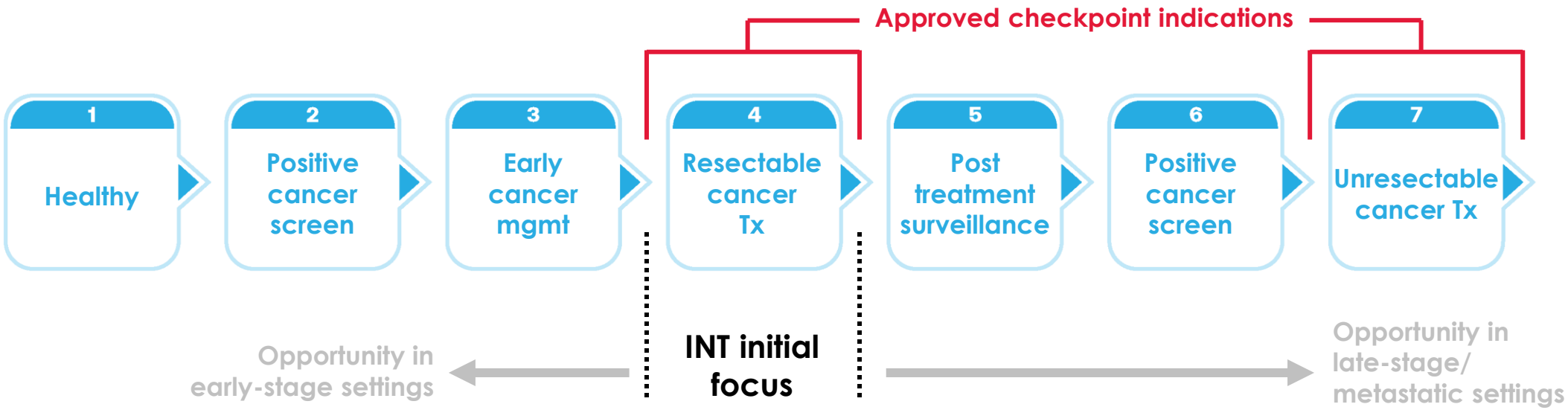
Anti-PD-L1/PD-1 response rates among various tumor types[1]



Response rates to ICIs typically range from 10% to 30% depending on the tumor type[1-3]

1. Zhao B, et al. *Ther Adv Med Oncol.* 2020;12:1–22; 2. Sun JY, et al. *Biomark Res.* 2020;8:35; 3. Zhang T, et al. *Oncotarget.* 2016;7(45):73068–73079.

INT may meet the unmet need by specifically harnessing T-cells



Individualized Neoantigen Therapy (INT)

Michelle Brown

Vice President, Portfolio Leadership, INT

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Phase 2 INT adjuvant melanoma study: 3-year update

Reprise of ASCO 2024 presentation

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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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[a]Manju Morrissey,[20] Igor Feldman,[20] Vasudha Sehgal,[20] Huzhang Mao,[20] Jia Guo,[20] Min Liu,[20] Anjali Rao,[20] Wei Zheng,[20] Praveen Aanur,[20] Lakshmi Srinivasan,[20] Mo Huang,[21] Tal Zaks,[20] Michelle Brown,[20] Tracey Posadas[20]

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Sponsored by Moderna, Inc., in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

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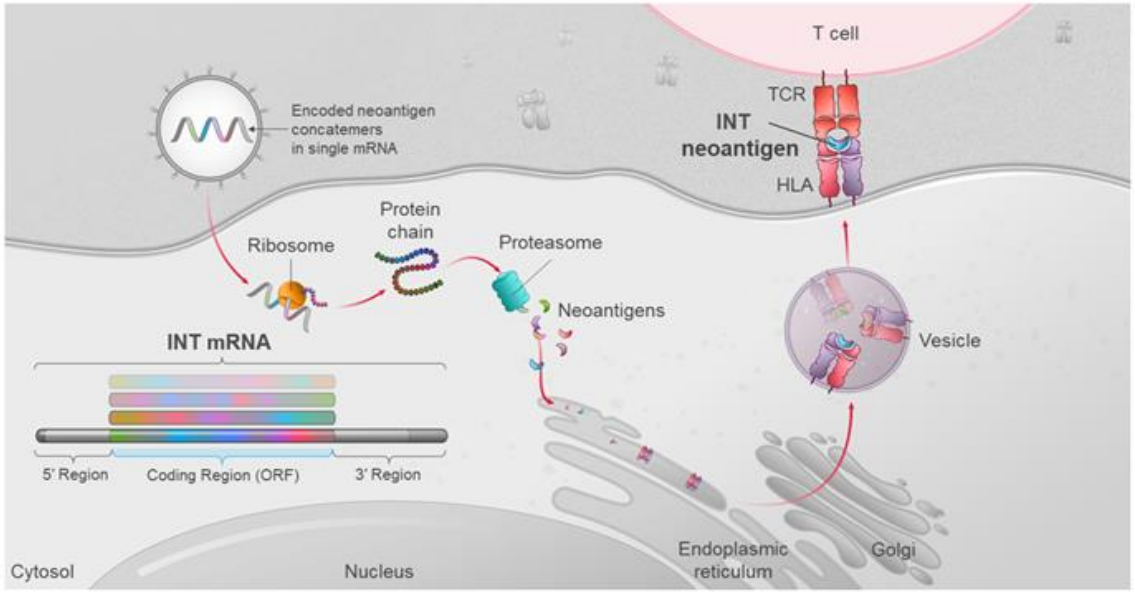
Background/Introduction



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.

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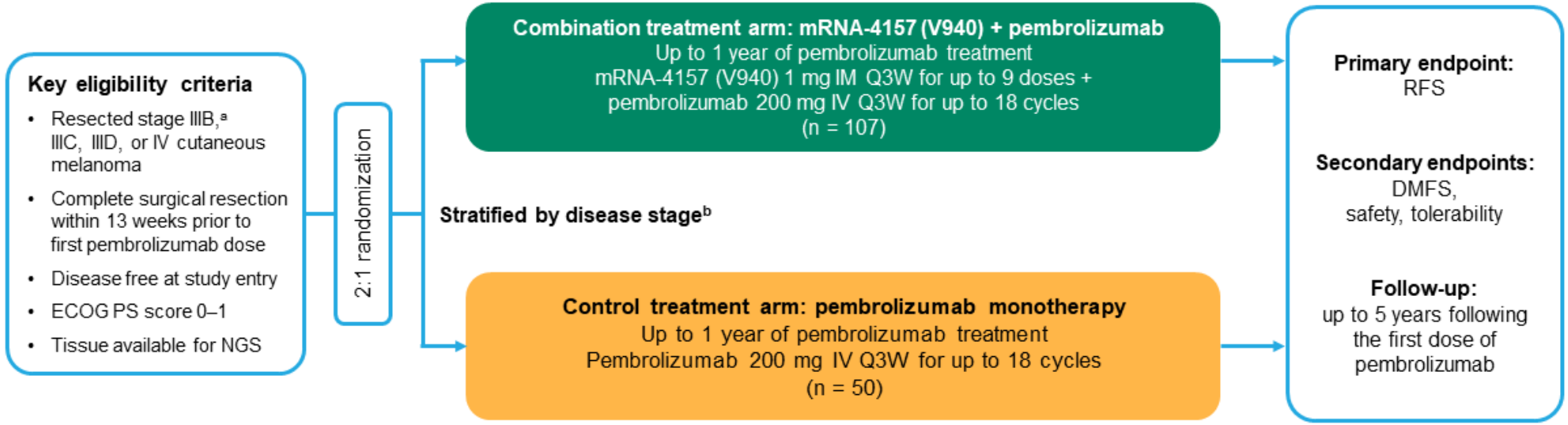
mRNA-4157-P201/KEYNOTE-942 (NCT03897881) study design

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.

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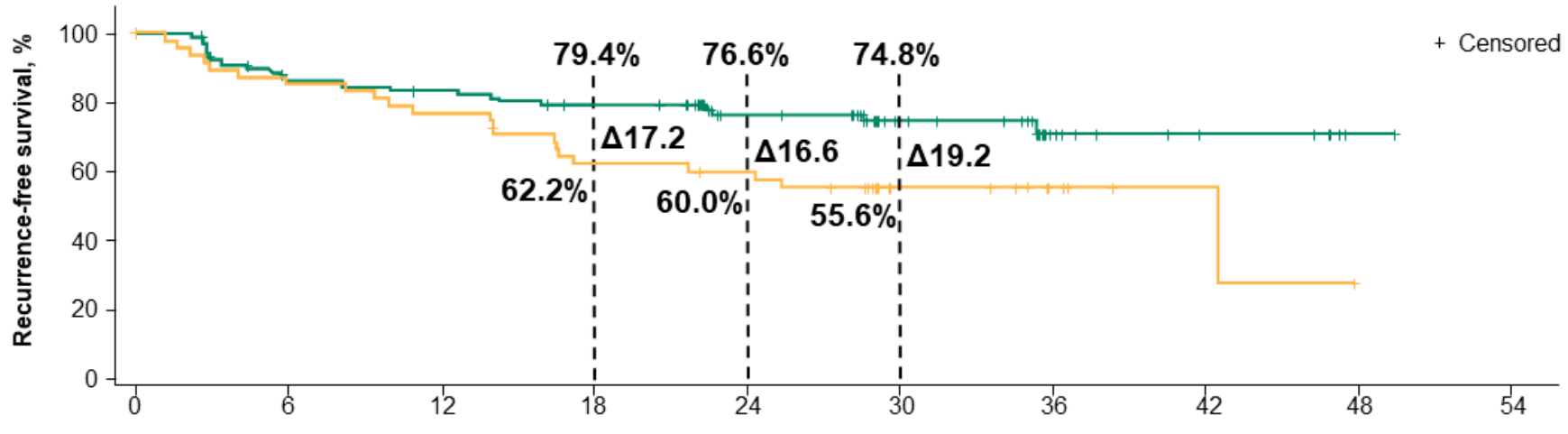
Sustained improvement of RFS primary efficacy endpoint



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.

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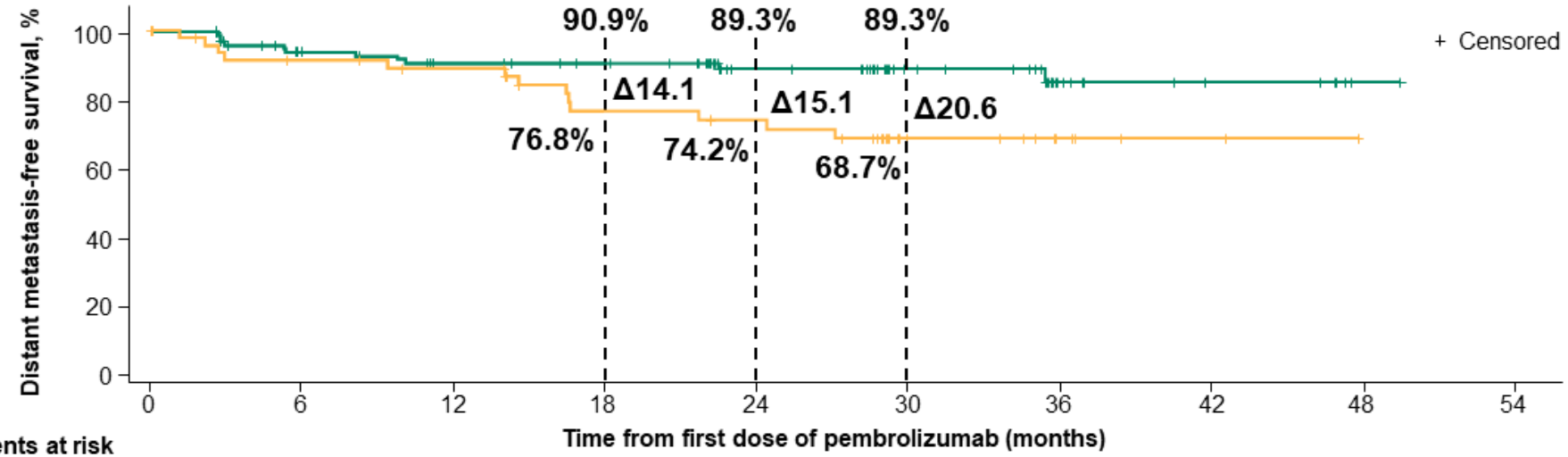
Sustained improvement of DMFS secondary endpoint



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.

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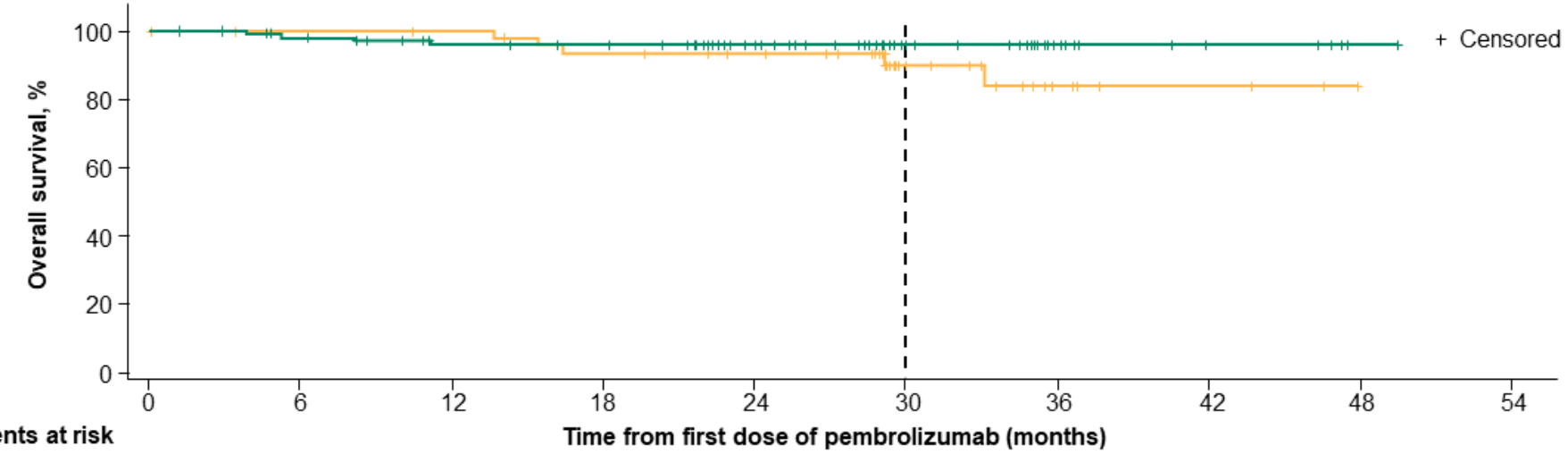
Overall survival shows encouraging trend with mRNA-4157 (V940) + pembrolizumab



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.

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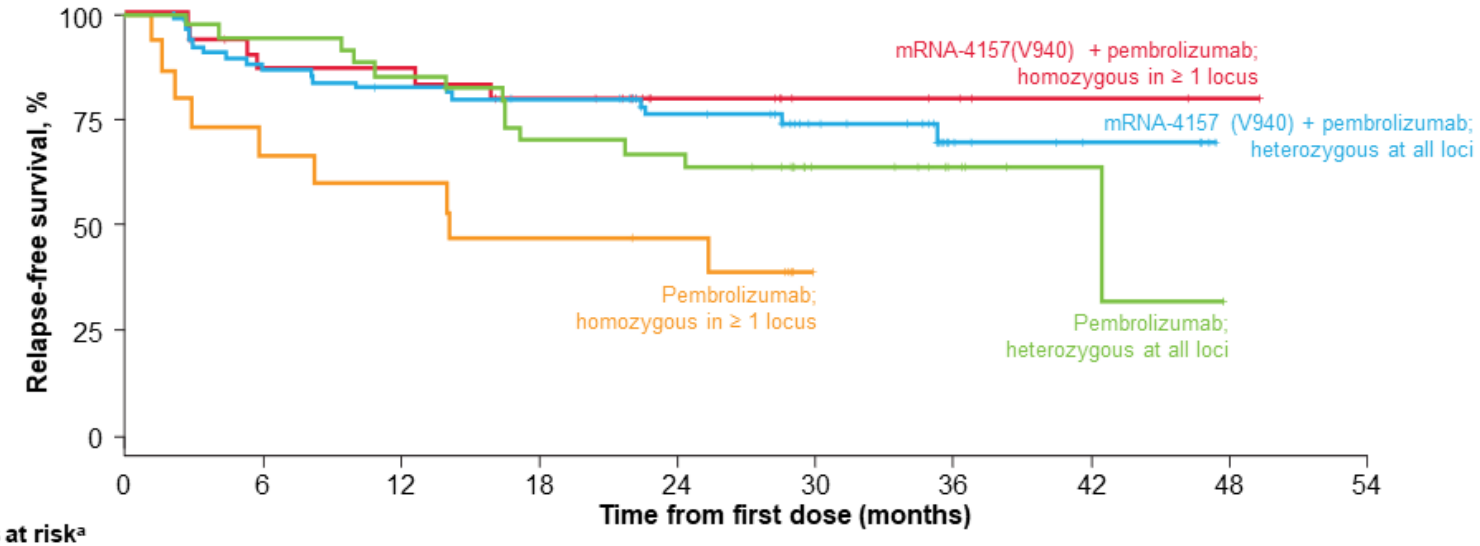
Biomarker analyses suggest mRNA-4157 (V940) + pembrolizumab may benefit a broad patient population

- 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.

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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.

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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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Acknowledgments

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- The patients and their families, along with all of the site staff
- The personnel at all our vendors and collaborators
- The scientists, regulatory, operations, and manufacturing teams who discovered, improved, and enabled mRNA-4157 (V940)

The following were members of the INT Research and Development Author Group[a]:

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

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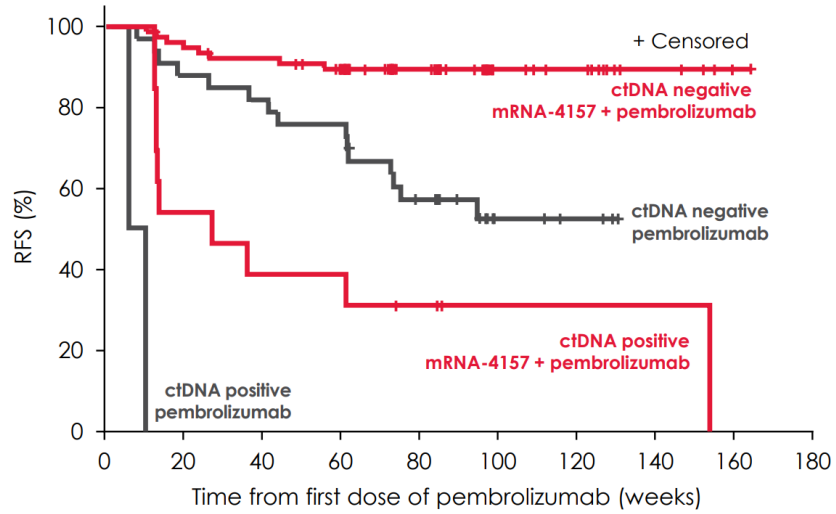
INT P201 ctDNA analysis

Reprise of excerpt from ESMO 2023 presentation

Improved RFS and DMFS observed with mRNA-4157 (V940) and pembrolizumab versus pembrolizumab monotherapy irrespective of baseline ctDNA status

RFS in patients with high-risk melanoma by baseline ctDNA status

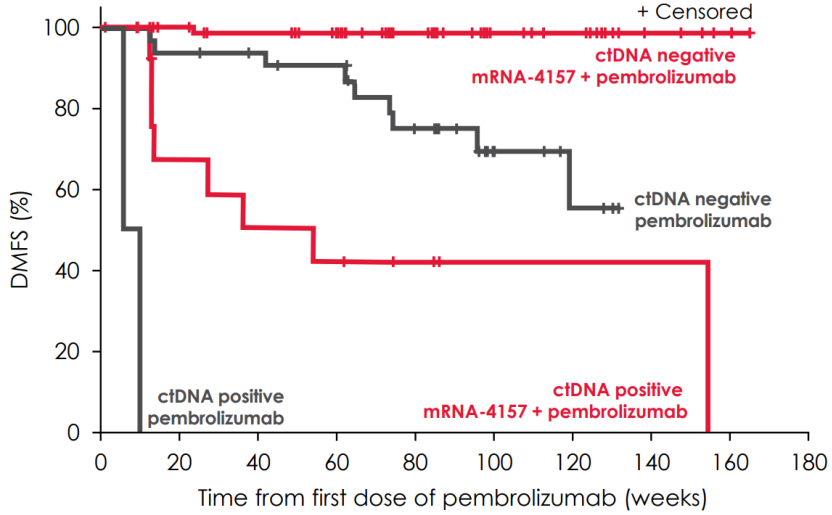


Number at risk

ctDNA negative mRNA-4157 + pembrolizumab	77	72	69	57	38	18	15	6	1
ctDNA negative pembrolizumab	33	29	27	25	17	6	4	0	0
ctDNA positive mRNA-4157 + pembrolizumab	13	7	5	5	3	1	1	1	0
ctDNA positive pembrolizumab	2	0	0	0	0	0	0	0	0

	mRNA-4157 (V940) + pembrolizumab Events, n/N (%)	pembrolizumab Events, n/N (%)	mRNA-4157 (V940) + pembrolizumab versus pembrolizumab HR (95% CI)
ctDNA positive	10/13 (76.9)	2/2 (100)	NE
ctDNA negative	8/77 (10.4)	15/33 (45.5)	**0.225** (0.095–0.531)

DMFS in patients with high-risk melanoma by baseline ctDNA status



Number at risk

ctDNA negative mRNA-4157 + pembrolizumab	77	73	69	57	38	18	15	6	1
ctDNA negative pembrolizumab	33	30	28	26	18	7	4	0	0
ctDNA positive mRNA-4157 + pembrolizumab	13	8	6	5	3	1	1	1	0
ctDNA positive pembrolizumab	2	0	0	0	0	0	0	0	0

	mRNA-4157 (V940) + pembrolizumab Events, % (n/N)	pembrolizumab Events, % (n/N)	mRNA-4157 (V940) + pembrolizumab versus pembrolizumab HR (95% CI)[a]
ctDNA positive	61.5 (8/13)	100 (2/2)	NE
ctDNA negative	1.3 (1/77)	27.3 (9/33)	**0.048** (0.006–0.380)

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ctDNA was NE at baseline for 20.4% (32/157) patients from this study due to unavailability of the sample at baseline (mRNA-4157 (V940) + pembrolizumab, n = 15; pembrolizumab monotherapy, n = 14) or insufficient number of RaDaR® (Inivata) variants identified by WES (quality control flag: mRNA-4157 (V940) + pembrolizumab, n = 2; pembrolizumab monotherapy, n = 1). Results limited by small sample size and event number.
ctDNA, circulating tumor DNA; DMSF, distant metastasis-free survival; HR, hazard ratio; mRNA, messenger RNA; NE, not evaluable; RFS, recurrence-free survival; WES, whole exome sequencing.
Khattak A, et al. Presented at the American Society of Clinical Oncology® (ASCO) Annual Meeting; June 2–6, 2023; Chicago, IL, USA. LBA9503.

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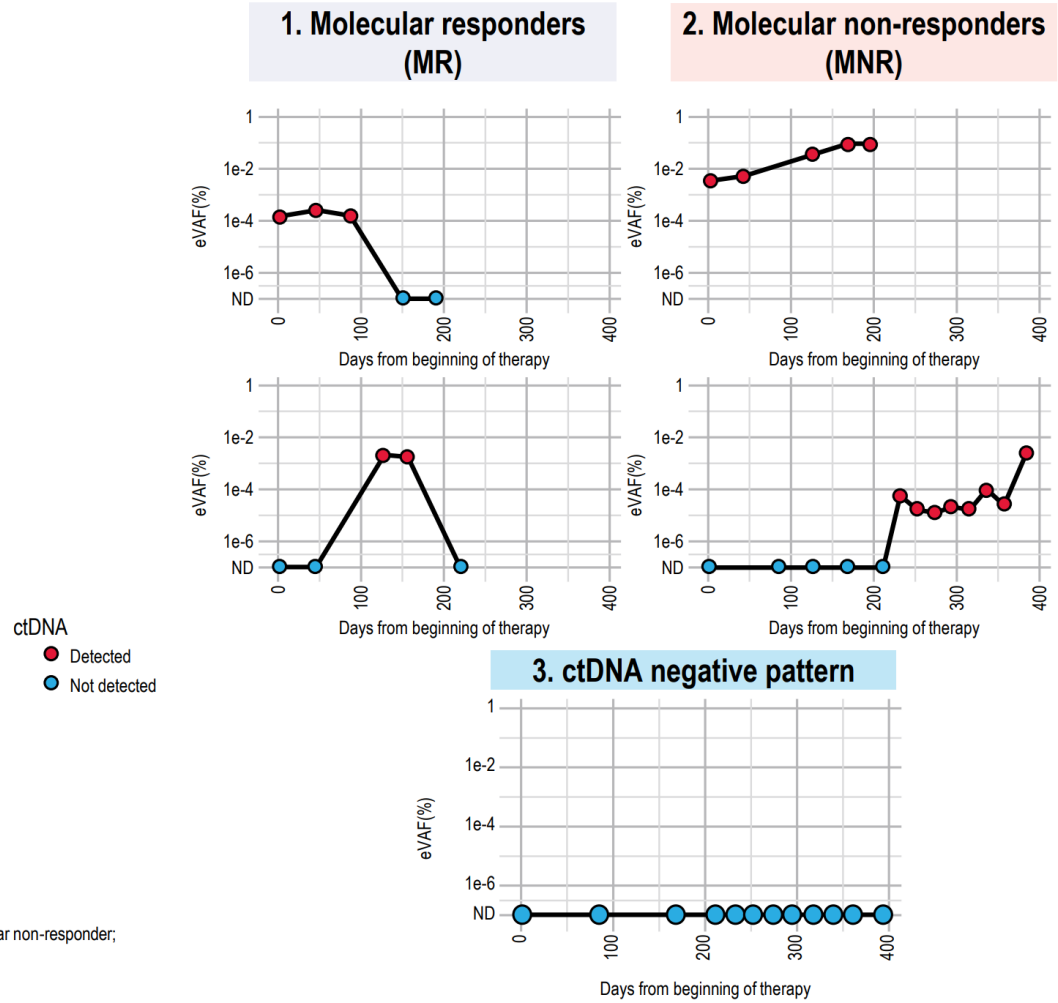
Longitudinal ctDNA measurements fall into one of three response patterns

Characterization of observed ctDNA patterns

ctDNA subgroup	Patient criteria
1. Molecular responders (MR)	ctDNA was not detected at the last time point
2. Molecular non-responders (MNR)	ctDNA was detected at the last time point
3. ctDNA negative pattern	ctDNA not detected at any time point

Patients were not required to have a baseline (pre-treatment) evaluable sample.



RaDaR was used to measure plasma ctDNA during treatment and follow-up.
ctDNA, circulating tumor DNA; eVAF, estimated variant allele frequency; MNR, molecular non-responder; MR, molecular responder; mRNA, messenger RNA; ND, not detected.

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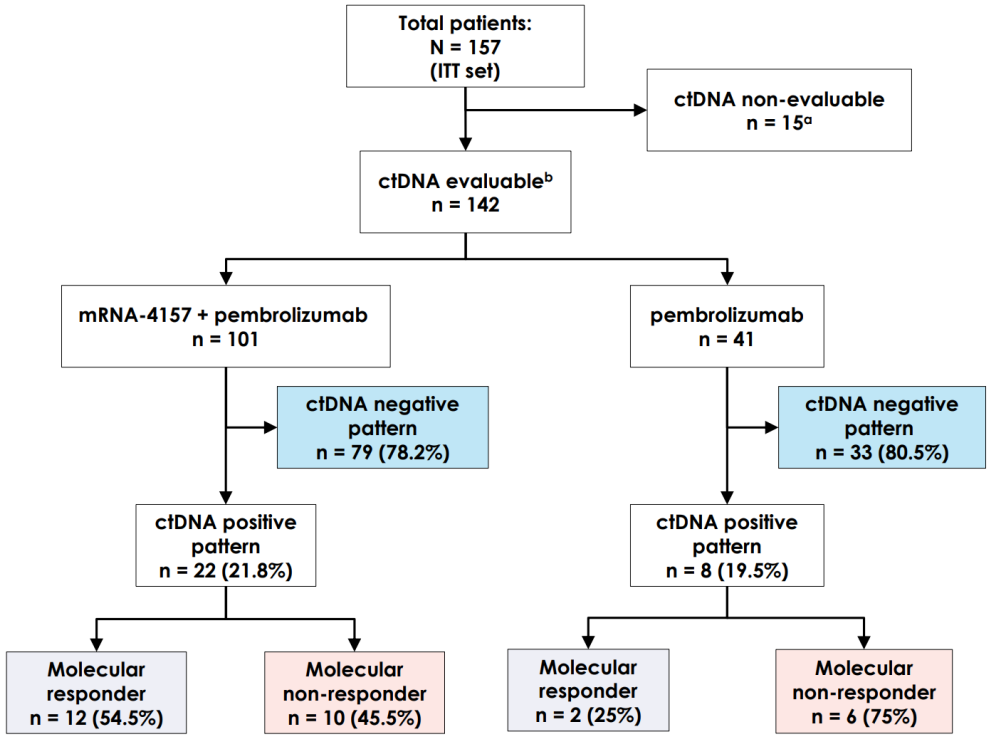
Molecular non-responder ctDNA patterns associated with the highest frequency of recurrence events



ctDNA longitudinal pattern n = 142 (101+41)	Recurrence event[c] 42/142
ctDNA negative pattern n = 112 (79+33)	19/112 (17%)
ctDNA positive MR n = 14 (12+2)	8/14 (57%)
ctDNA positive MNR n = 16 (10+6)	**15/16 (94%)**

- Although limited by small numbers, in patients with a ctDNA positive result, MNR patterns are observed with higher frequency in the pembrolizumab monotherapy arm than the combination arm (6/8 [75%] vs 10/22 [45.5%]). This will require additional evaluation with more patients, events, and temporal assessment of the longitudinal pattern with treatment cycle

MADRID 2023 ESMO congress

[a]n = 15 treated patients non-evaluable for ctDNA (6/107 in combination and 9/50 in pembrolizumab) due to RADaR QC failures (low input, low variants, and cross-contamination). 2/15 patients with non-evaluable ctDNA reported recurrence events.
[b]Patients were not required to have a baseline (pre-treatment) evaluable sample. [c]Recurrence event defined as the first recurrence [local, regional, or distant metastasis], a new primary melanoma, or death from any cause.
ctDNA, circulating tumor DNA; ITT, intent to treat; MNR, molecular non-responder; MR, molecular responder; mRNA, messenger RNA.

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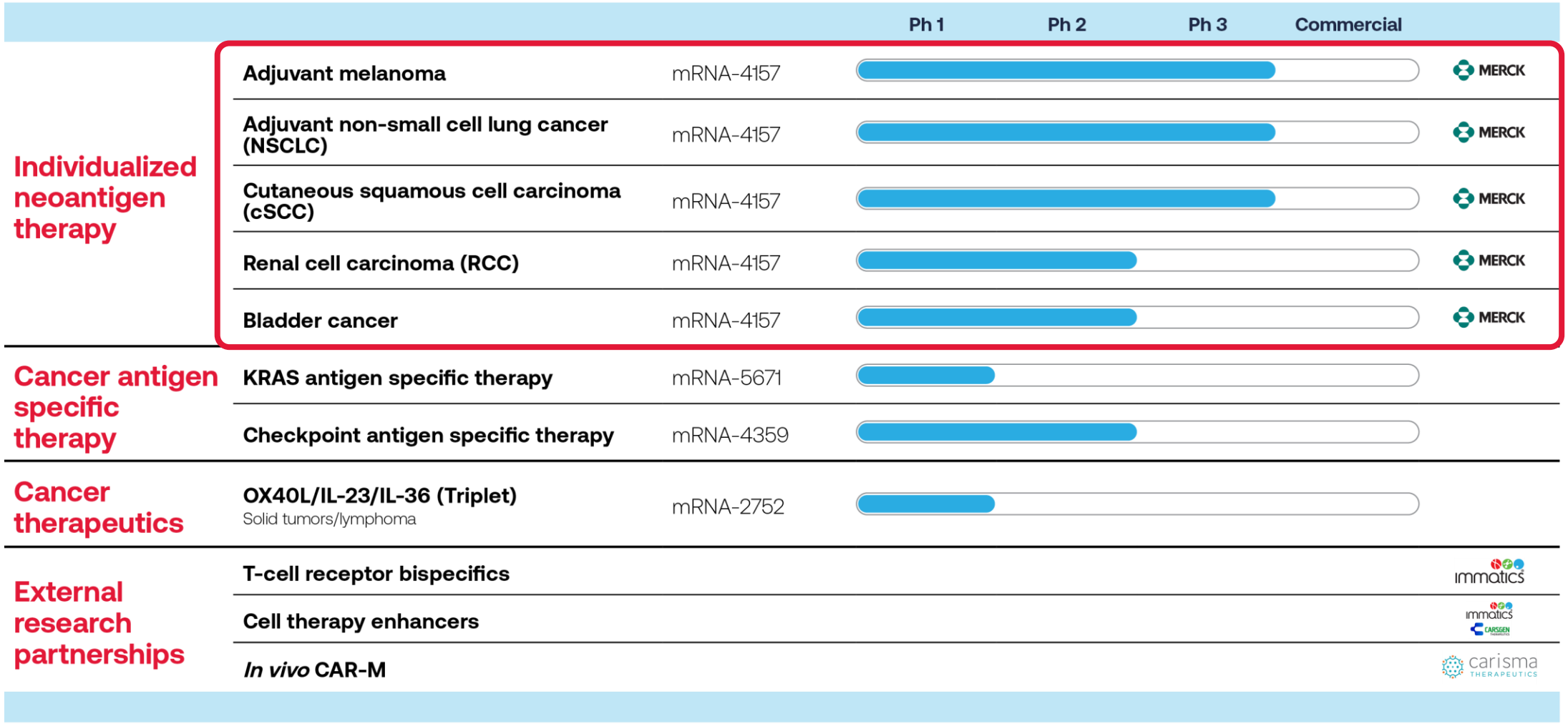
INT clinical development program

Moderna's immuno-oncology pipeline: INT



*in partnership with Merck

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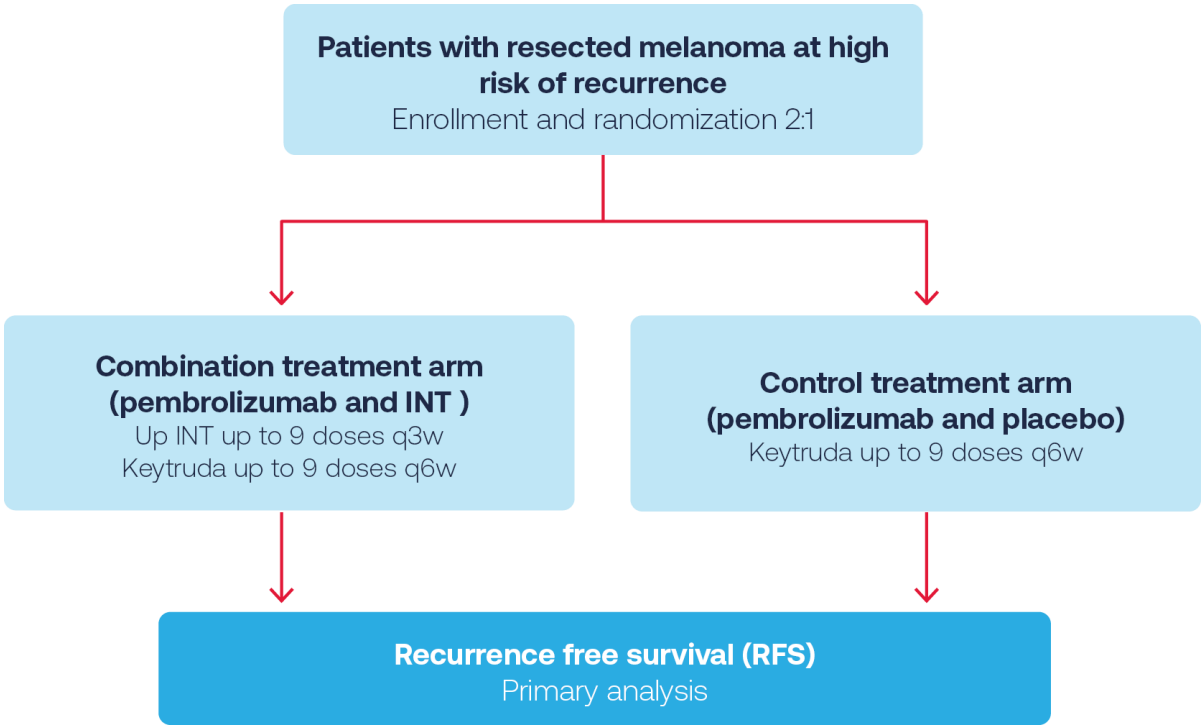
Adjuvant melanoma Phase 3 (mRNA-4157 / V940) trial design

Primary endpoint is recurrence free survival compared to pembrolizumab



Randomized, double-blind placebo controlled, INT + pembrolizumab (KEYTRUDA®) vs. placebo + pembrolizumab (2:1) (INTerpath-001)

Resected melanoma patients: stage IIB or IIC, III, IV

Primary endpoint: recurrence free survival (RFS)

Secondary endpoints: Distant Metastasis-Free Survival (DMFS), Overall-Survival (OS)

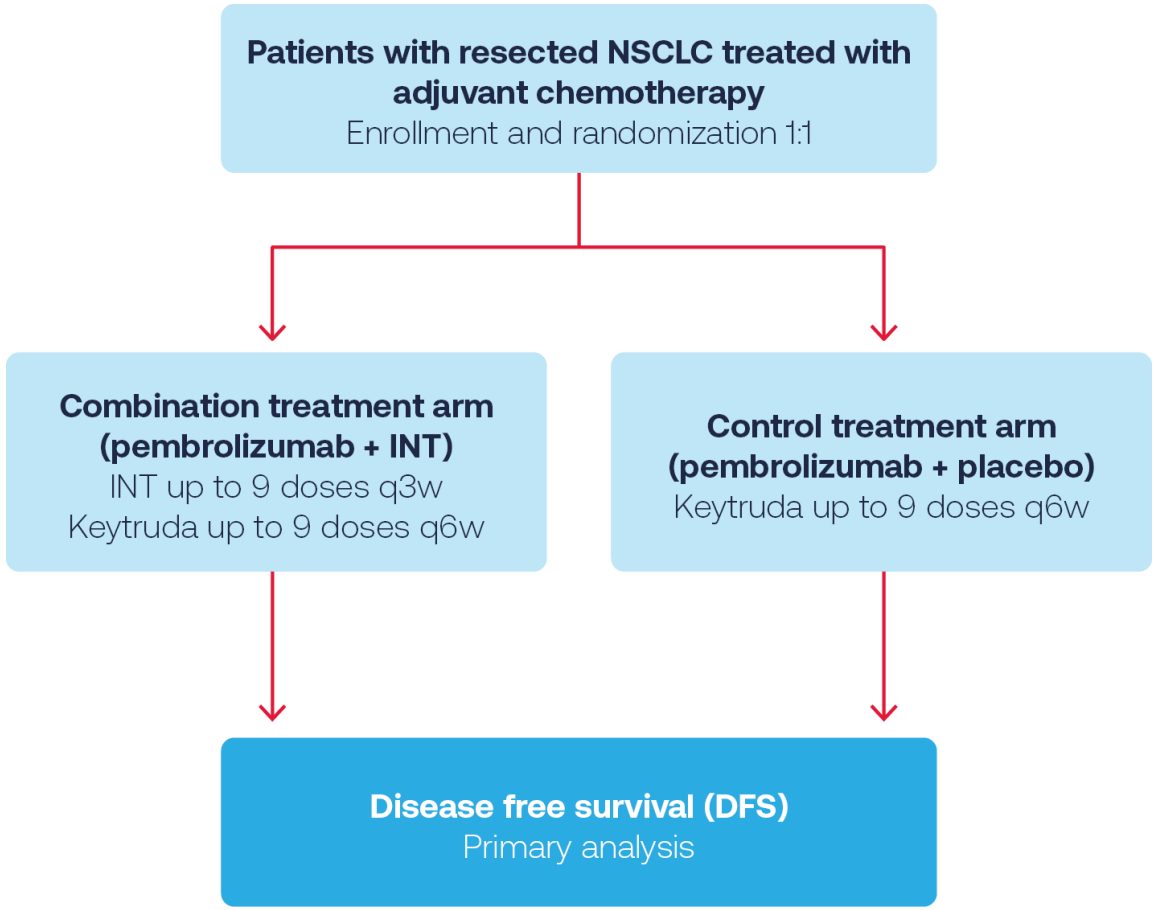
Number of participants: ~1,089

Currently enrolling

NCT05933577

NSCLC Phase 3 (mRNA-4157 / V940) trial design

Primary endpoint is disease free survival compared to pembrolizumab



Randomized, double-blind placebo and active comparator controlled, INT + pembrolizumab (KEYTRUDA®) vs. placebo + pembrolizumab (1:1) (INTerpath-002)

Resected non-small cell lung cancer (NSCLC) patients: stage II, IIIA, IIIB previously treated with adjuvant chemotherapy

Primary endpoint: disease free survival (DFS)

Secondary endpoints: Overall-Survival (OS), Distant Metastasis-Free Survival (DMFS), Safety, patient reported outcomes (PRO)

Number of patients: ~868

Currently enrolling

NCT06077760

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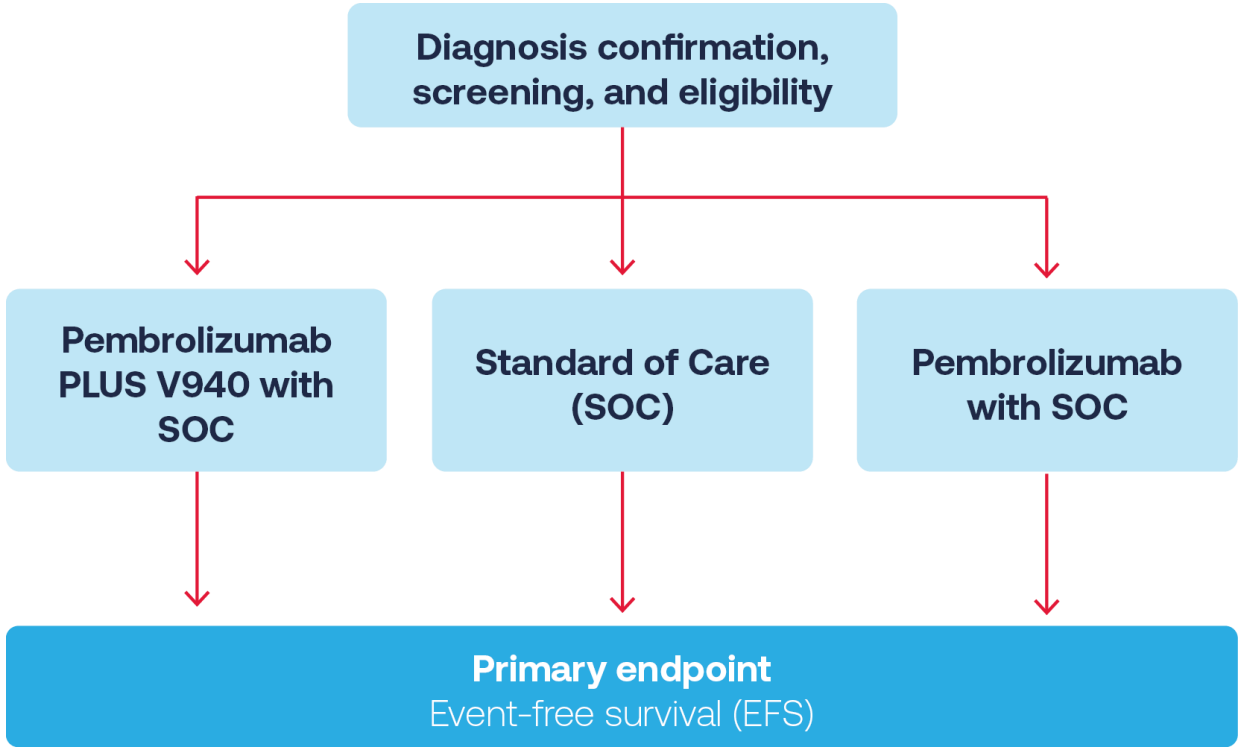
Neoadjuvant/adjuvant cutaneous squamous cell carcinoma (mRNA-4157 / V940) trial design



Phase 2/3, adaptive, randomized, open-label, clinical study (INTerpath-007)

Resectable cSCC patients: locally advanced stage
II – IV (m0) without distant metastases

Primary endpoint: event-free survival

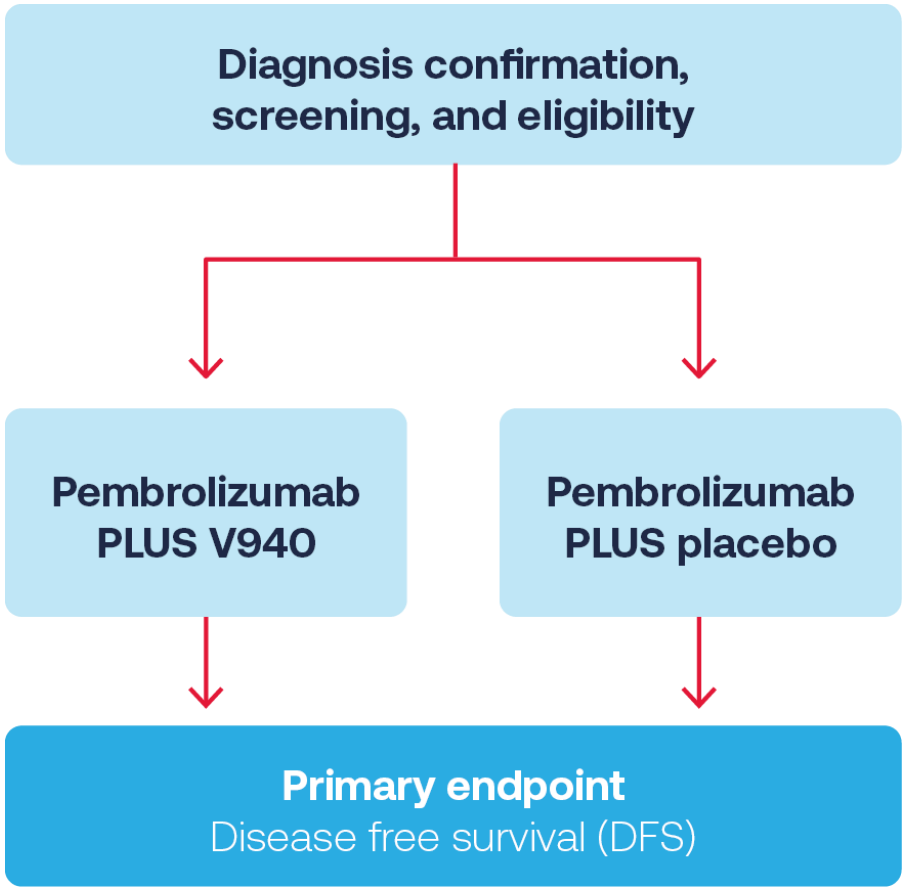
Secondary endpoints: Overall response rate (ORR), freedom from surgery (FFS) rate, pathological complete response (pCR) rate, major pathological response (mPR) rate, disease-free survival (DFS), disease-specific survival (DSS), overall survival (OS)

Number of patients: 1,012

Currently enrolling

NCT06295809

Adjuvant high risk muscle invasive bladder cancer (mRNA-4157 / V940) trial design



Phase 2, randomized, double-blind, placebo and active-comparator controlled clinical study (INTerpath-005)

Patients with high-risk muscle invasive urothelial cancer (MIUC), dominant histology of urothelial cancer (UC) and high-risk pathologic disease after radical resection

Primary endpoint: disease free survival (DFS)

Secondary endpoints: Overall survival (OS), distant metastasis-free survival (DMFS), number of participants who experience an adverse event (AE), number of participants who discontinue study treatment due to an AE

Number of participants: 200

Currently enrolling

NCT06305767

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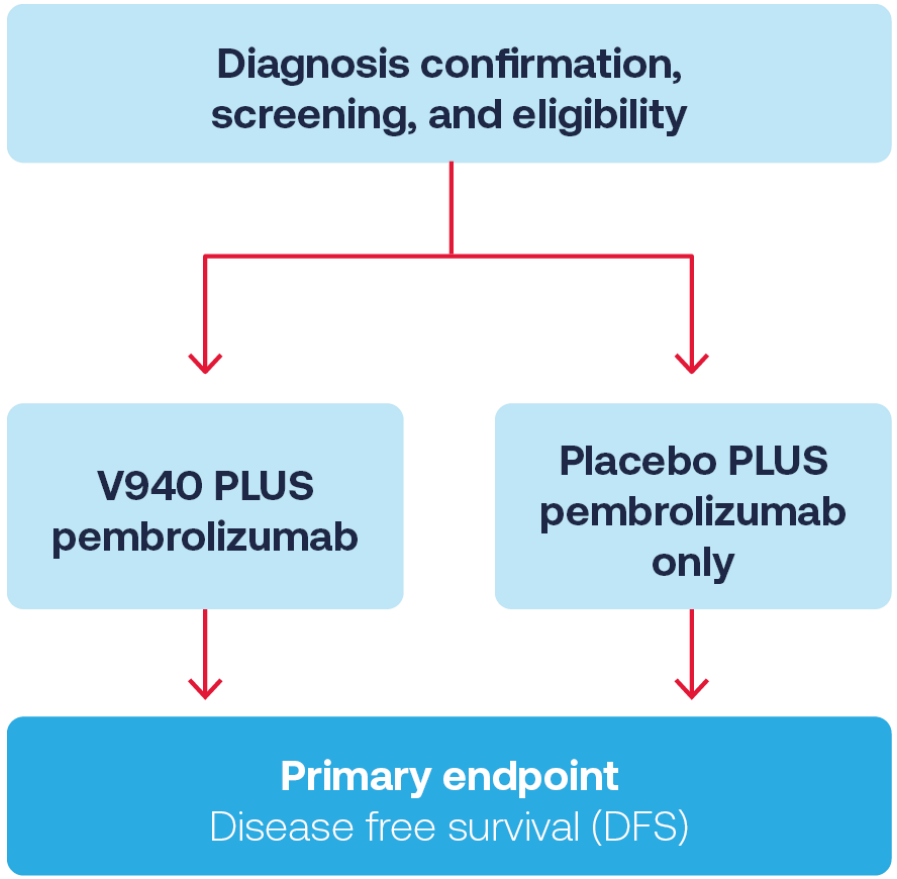
Adjuvant renal cell carcinoma (mRNA-4157 / V940) trial design



Phase 2, randomized, double-blind, clinical study (INTerpath-004)

Patients with histologically or cytologically confirmed diagnosis of RCC with clear cell or papillary histology and intermediate-high-risk, high-risk, or M1 no evidence of disease (NED) RCC

Primary endpoint: disease-free survival

Secondary endpoints: Overall survival (OS), distant metastasis-free survival (DMFS), percentage of participants who experience an adverse event (AE), percentage of participants who discontinue study treatment due to an AE

Number of participants: 272 participants

Currently enrolling

NCT06307431

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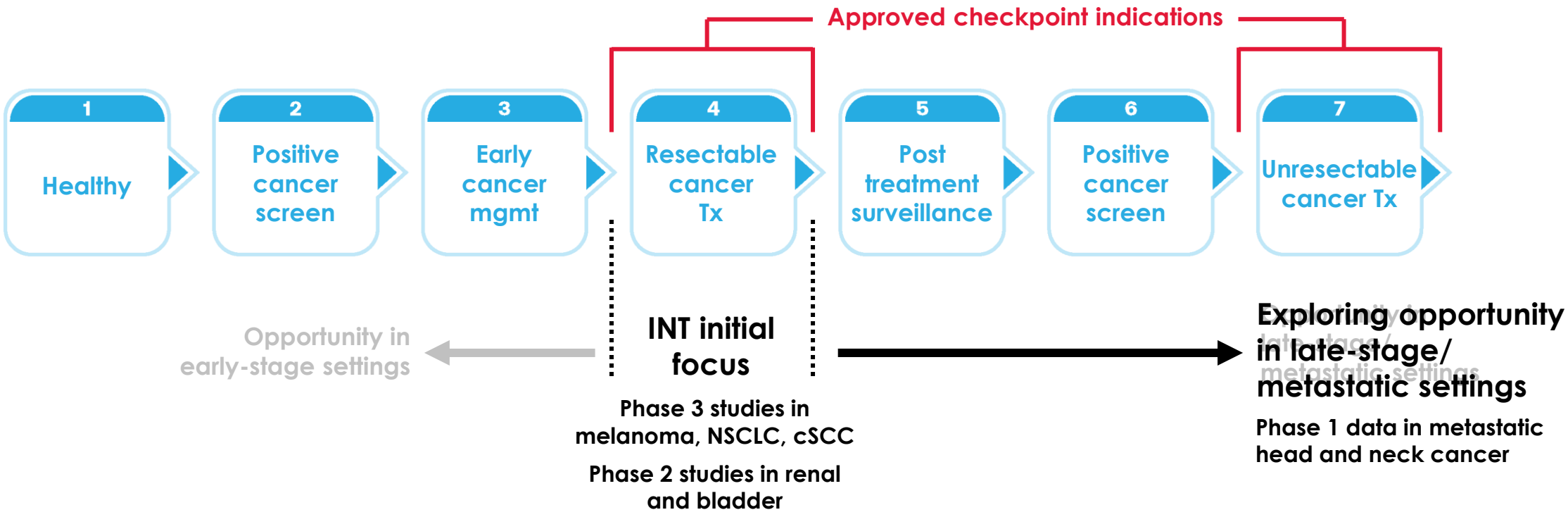
INT has the potential to transform the continuum of cancer treatment by specifically harnessing T-cells



mRNA-4157 (V940) Individualized Neoantigen Therapy + Pembrolizumab in Advanced Unresectable HPV-negative Head and Neck Carcinoma: Clinical Analysis

Julie E. Bauman,[1] Ricklie A. Julian,[2] Jessica L. Geiger,[3] Janice M. Mehnert,[4] Jeffrey M. Clarke,[5] Manish R. Patel,[6,7] Martin Gutierrez,[8] Justin F. Gainor,[9] Shyam Srivats,[10] Zhaojie Zhang,[10] Anjali Rao,[10] Vasudha Sehgal,[10] Peijie Hou,[10] Manju Morrissey,[10] Igor Feldman,[10] Lakshmi Srinivasan,[10] Praveen Aanur,[10] Michelle Brown,[10] Robert S. Meehan[10]

[1]George Washington University, Washington, DC, USA; [2]University of Arizona Cancer Center, Tucson, AZ, USA; [3]The Cleveland Clinic Foundation, Cleveland, OH, USA; [4]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [5]Duke University Medical Center, Durham, NC, USA; [6]Florida Cancer Specialists, Sarasota, FL, USA; [7]Sarah Cannon Research Institute, Nashville, TN, USA; [8]Hackensack University Medical Center, Hackensack, NJ, USA; [9]Massachusetts General Hospital, Boston, MA, USA; [10]Moderna Inc., Cambridge, MA, USA

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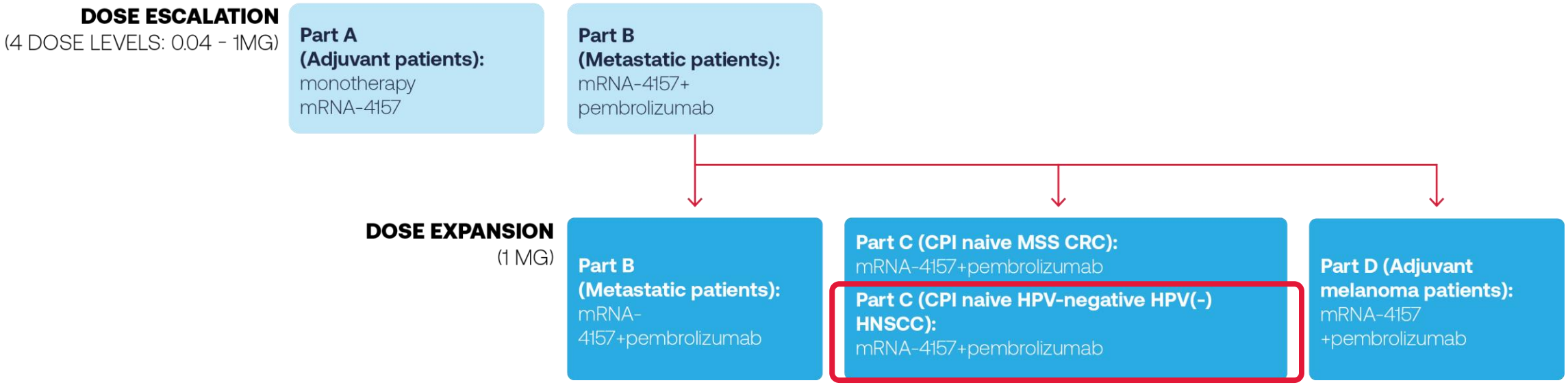
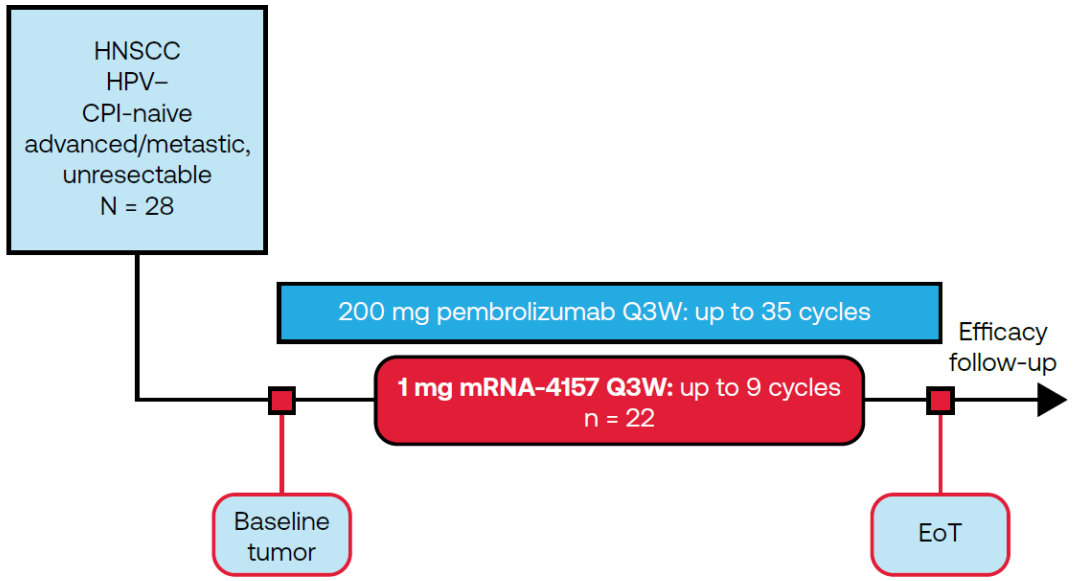
mRNA-4157-P101/KEYNOTE-603 (NCT03313778) is an ongoing Phase 1 study



Patients with human papillomavirus negative(HPV-) head and neck squamous cell carcinoma (HNSCC) have poor prognosis with a 5-year survival rate <50%[1]; limited durable clinical responses to PD1/PD-L1 blockade may be due to diminished effector cytolytic activity and clonal diversity[2–5]

1. Schiff BA. 2022. Oropharyngeal Squamous Cell Carcinoma. https://www.msdmanuals.com/en-gb/professional/ear,-nose,-and-throat-disorders/tumors-of-the-head-and-neck/oropharyngeal-squamous-cell-carcinoma. Accessed March 7, 2024.; 2. Lechner A, et al. Oncotarget 2017;8:44418–44433.; 3. Wang J, et al. Sci Rep 2019;9:13404.; 4. Tosi A, et al. J Exp Clin Cancer Res 2022;41:279.; 5. Xu K, et al Br J Cancer 2020;123:932–941.

mRNA-4157-P101/KEYNOTE-603 Part C trial design



EoT, end of treatment.

Part C of this study enrolled patients ˜18 years old with checkpoint inhibitor (CPI)-naive, recurrent/metastatic HPV- HNSCC

Eligible patients received 200 mg pembrolizumab Q3W IV during a 6-week lead-in (during mRNA-4157 manufacture), then combined with 1 mg mRNA-4157 for up to 9 doses Q3W IM, followed by pembrolizumab, until disease progression, unacceptable toxicity, or 35 total cycles of pembrolizumab

Safety, tolerability, and preliminary clinical response were assessed per RECIST v1.1 criteria

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Baseline characteristics

Baseline characteristics	mRNA-4157 + pembrolizumab N = 22
Sex, n (%)	
Male	14 (63.6)
Female	8 (36.4)
Age, median (range), years	62.5 (29–81)
⩾65 years, n (%)	9 (40.9)
ECOG PS score, n (%)	
0	9 (40.9)
1	13 (59.1)
Prior immuno-oncology therapy, n	0
Number of prior systemic therapies, n (%)	
0	3 (13.6)
1	15 (68.2)
⩾2	4 (18.2)
PD-L1, n	
Not evaluable	7
CPS ⩾1	15

CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand-1.

Of 28 enrolled patients, 22 received mRNA-4157 + pembrolizumab; six discontinued prior to receiving mRNA-4157 due to death or disease progression/ deterioration and were not included in this analysis. All patients are off treatment as of the clinical cutoff date (May 4, 2023)

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Results: safety summary

Table 2. Summary of TEAEs in ⩾2 patients

TEAE[a]	mRNA-4157 + pembrolizumab N = 22	
	Any grade	Grade 3
All TEAEs, n (%)	22 (100.0)	14 (63.6)
mRNA-4157-related TEAE	15 (68.2)	3[b] (13.6)
Influenza-like illness	9 (40.9)	0
Injection-site pain	8 (36.4)	0
Pyrexia	8 (36.4)	1 (4.5)
Fatigue	6 (27.3)	0
Vaccination-site pain	6 (27.3)	0
Chills	3 (13.6)	0
Nausea	3 (13.6)	0
Headache	2 (9.1)	0
Injection-site erythema	2 (9.1)	0
Lipase increased	2 (9.1)	1 (4.5)
Lymphocyte count decreased	2 (9.1)	1 (4.5)
Pain in extremity	2 (9.1)	0

[a]Defined as any event not present before exposure to mRNA-4157 or pembrolizumab, or any present event that worsens in intensity or frequency after exposure to study drug; [b]Grade 3 AEs were related to both mRNA-4157 and pembrolizumab; there were no grade 4 or 5 AEs related to mRNA-4157.

TEAE, treatment-emergent adverse event.

- Most mRNA-4157–related TEAEs were grade 1–2; the most common being influenza-like illness, injection-site pain, and pyrexia
- The safety profile was consistent with mRNA-4157 monotherapy and the well-characterized safety profile of pembrolizumab, with AEs being managed with established management guidelines

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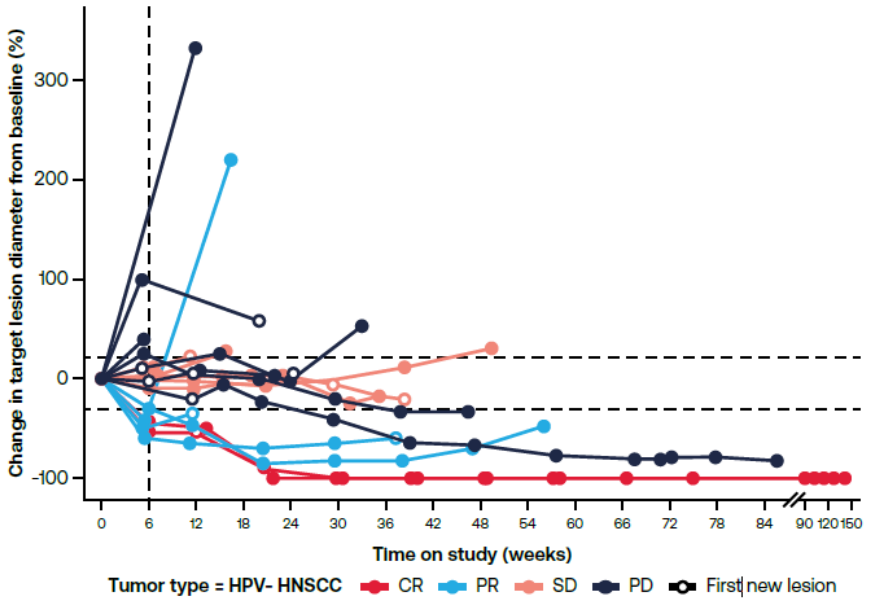
Results: clinical response

Percent change of target lesion from baseline over time



The vertical reference line marks the scheduled start of mRNA-4157 + pembrolizumab dosing Q3W that followed the pembrolizumab Q3W lead-in dose. The horizontal reference lines are plotted at y = 20 for PD (≥20% increase in the sum of diameters of target lesions) and y = –30 for PR (≥30% decrease in the sum of diameters of target lesions).

CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

- The objective response rate was 27.3% (6/22, 95%CI 10.7–50.2) and disease control rate was 63.6%(14/22, 95% CI 40.7–82.8), with best overall responses of 2 (9.1%) complete and 4 (18.2%) partial responses, and 8 (36.4%) stable disease at data cutoff
- Kaplan–Meier estimated median (95% CI) progression-free survival and overall survival were 15.0 (11.6–38.6) weeks and 107.1 (42.7–NE) weeks, respectively
- After the clinical cutoff date, the median (range) follow-up was 38.4 (11.7–194.9) weeks
- 8 (36.4%) patients completed 9 doses of mRNA-4157 (median 5.5 doses, range 1–9). Median (range) treatment duration of mRNA-4157 was 13.8 (0.1–26.1) weeks, and 20.1 (6.1–68.0) weeks for pembrolizumab. Most patients (n = 19/22, 86.4%) received 2 cycles of lead-in pembrolizumab (range, 2–4 cycles)

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Early-stage clinical oncology programs

Kyle Holen

Senior Vice President, Development,
Oncology and Therapeutics

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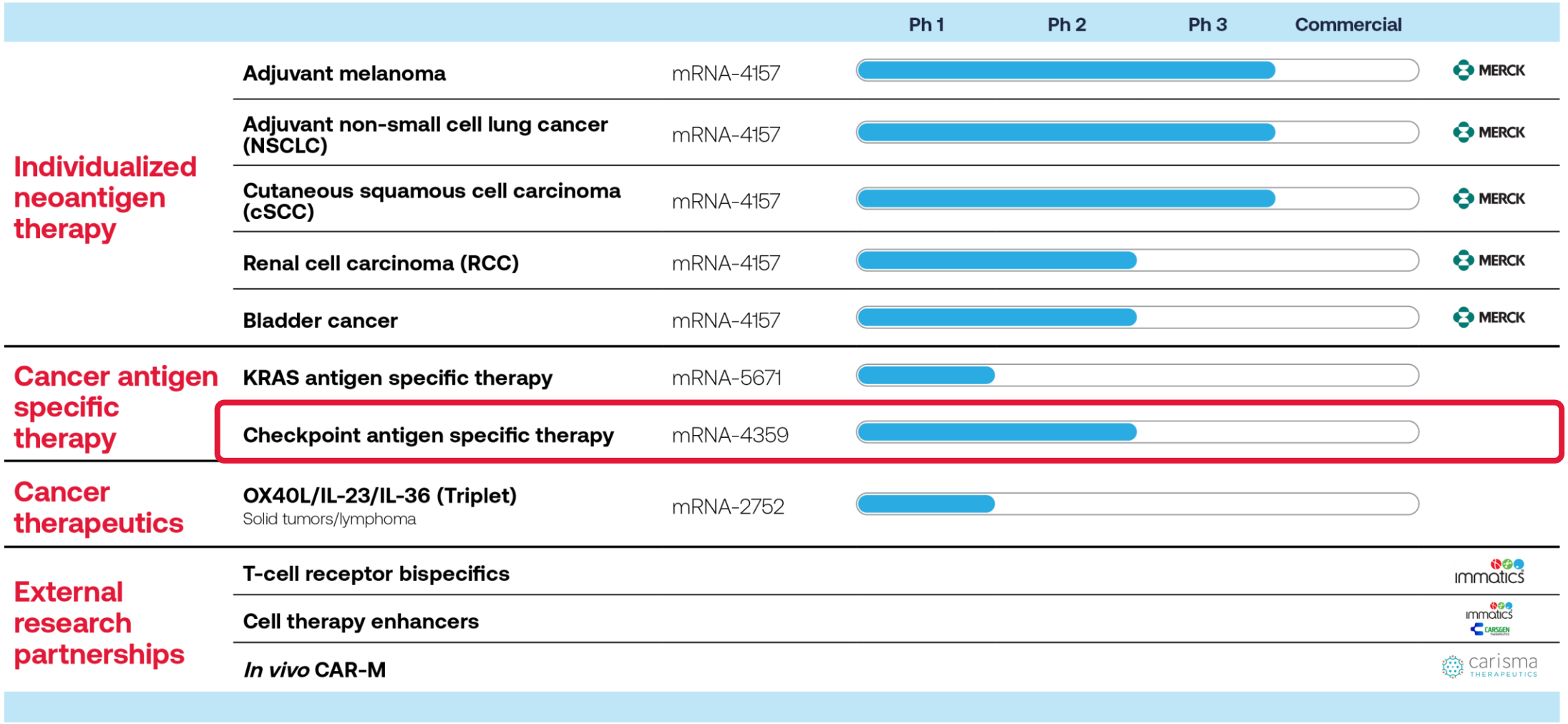
Moderna immuno-oncology pipeline: Checkpoint



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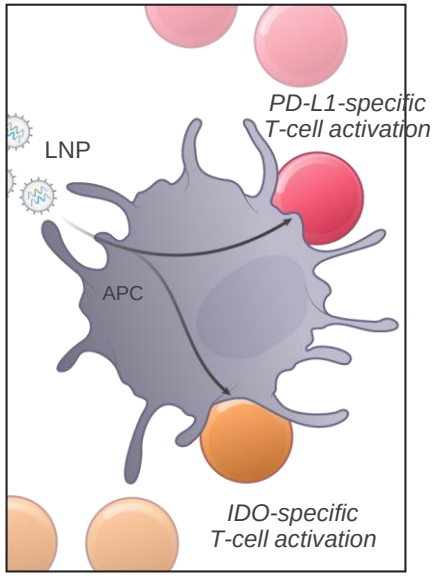
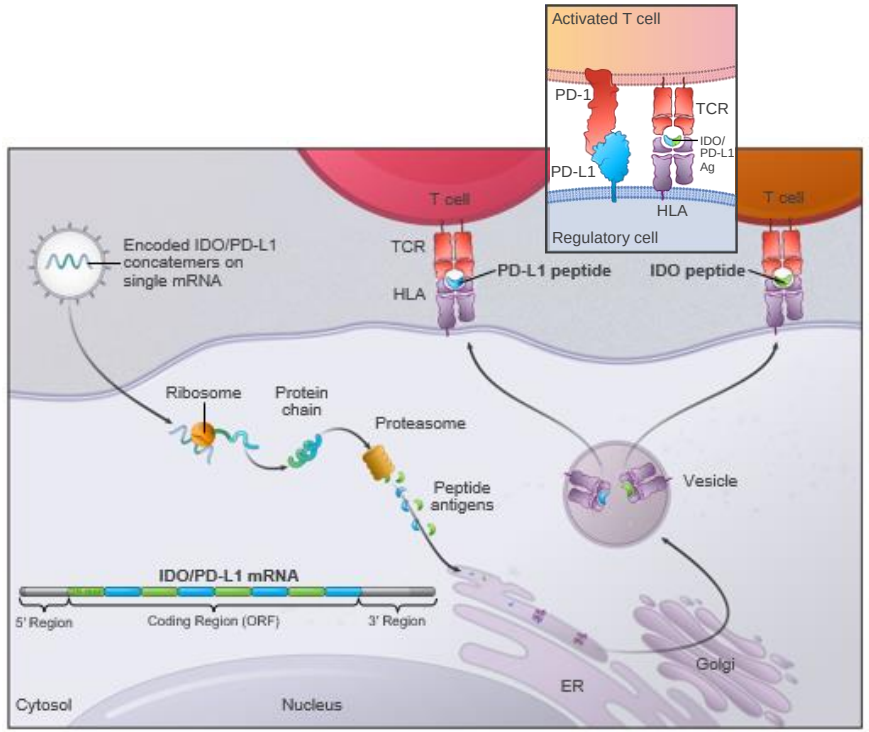
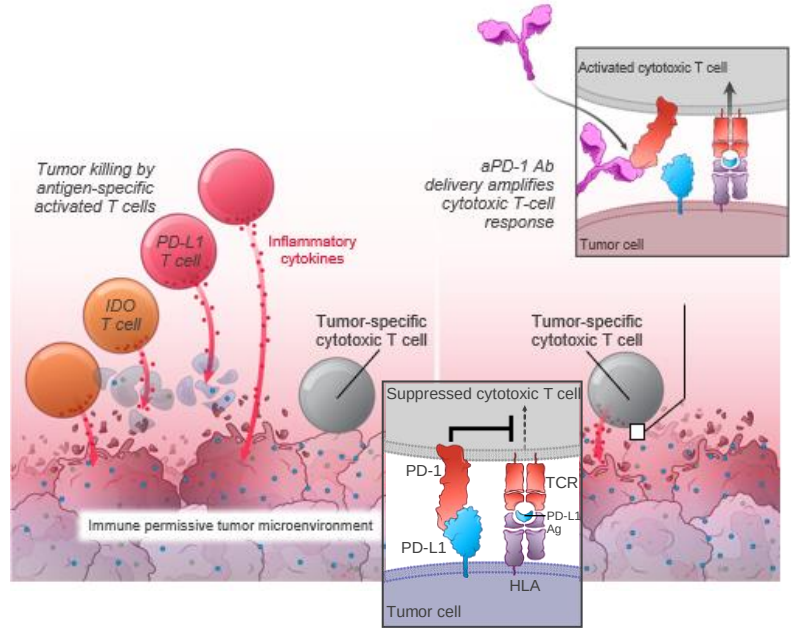
mRNA-4359 mechanism of action



Encoded IDO/PD-L1 concatemers on a single mRNA formulated in lipid nanoparticles is administered through intramuscular (IM) injection.



Polypeptides encoding immunogenic sequences are translated from mRNAs released into the cytosol of antigen presenting cells, are processed via the antigen presentation machinery, and displayed via HLAs to prime and boost specific T cell clones against IDO and PD-L1.



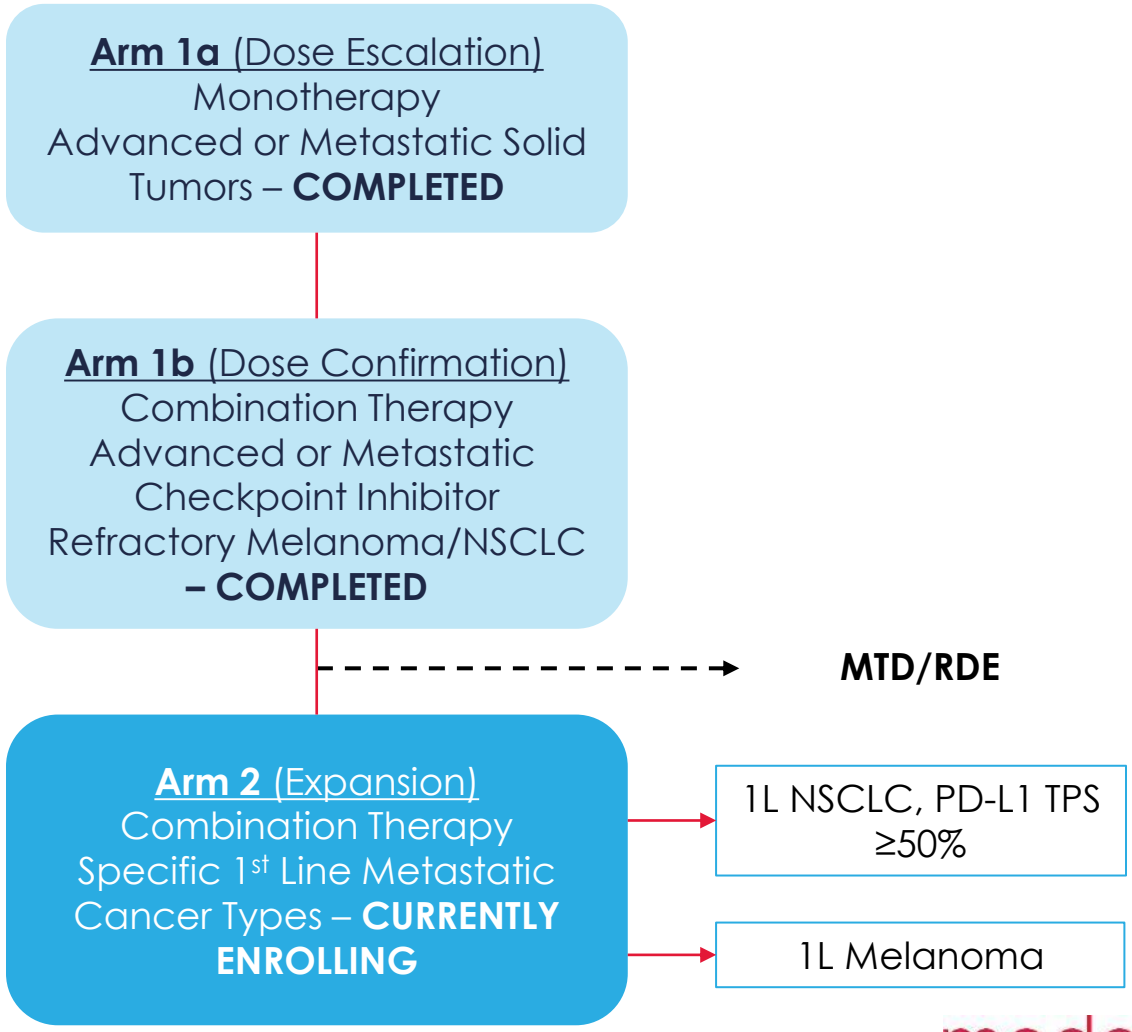
Cancer cell killing and the reduction of regulatory immune cells within the tumor microenvironment by IDO/PD-L1-specific activated T cells. This creates an immune-permissive tumor microenvironment. Further T cell priming leads to recognition of additional tumor-associated antigens and to tumor killing by additional tumor-specific cytotoxic T cells.

Systemic PD-1/PD-L1 blockade may further amplify the effect, leading to further immune activation and superior disease control.

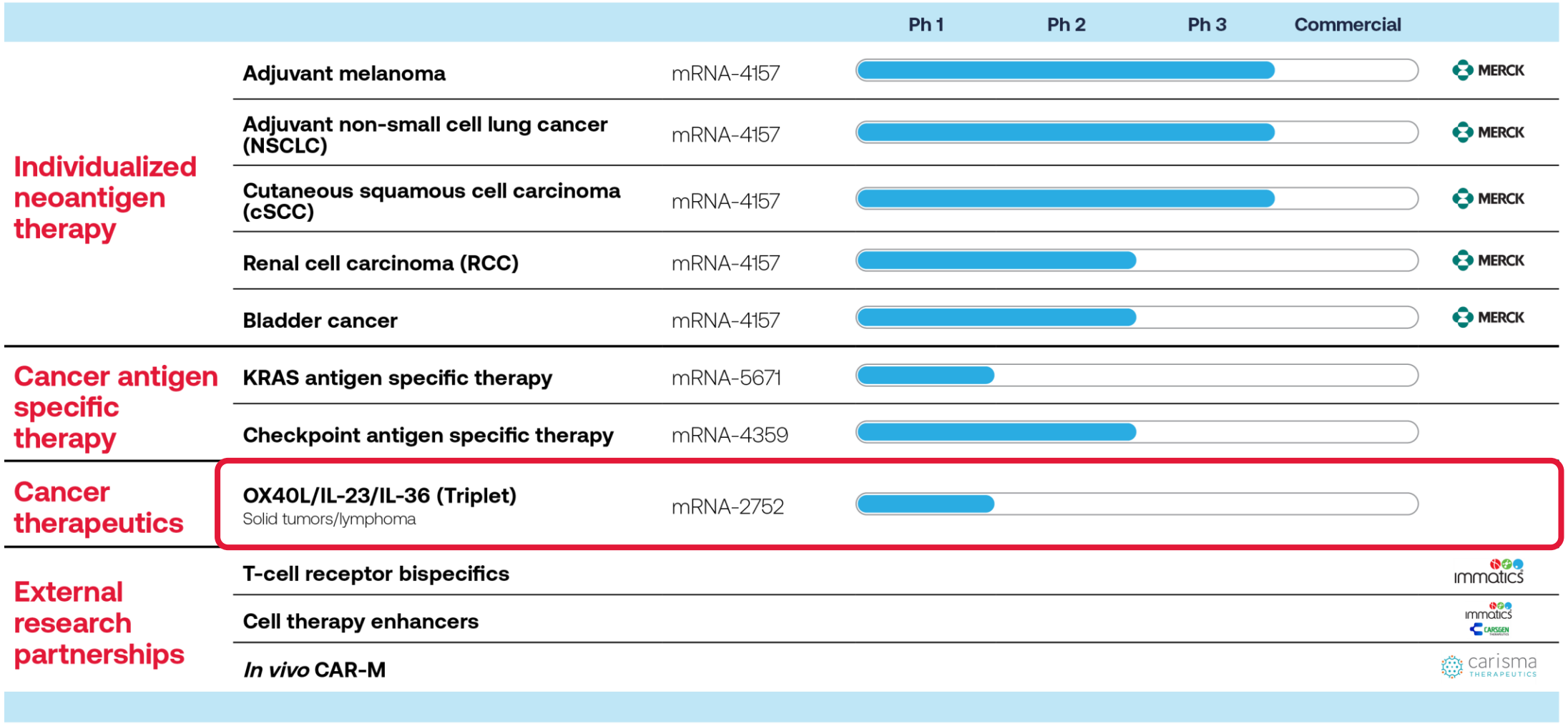
Checkpoint antigen specific therapy (mRNA-4359) is ongoing in a Phase 1/2 study; now enrolling Phase 2 cohort

Key Objectives

- Safety and tolerability of mRNA-4359 alone and in combination with pembrolizumab
- Antitumor activity of mRNA-4359 alone and in combination with pembrolizumab (ORR, DCR, DOR, PFS)
- T-cell profile changes (peripheral and tumor) after treatment of mRNA-4359 alone or in combination with pembrolizumab



Moderna immuno-oncology pipeline: Triplet



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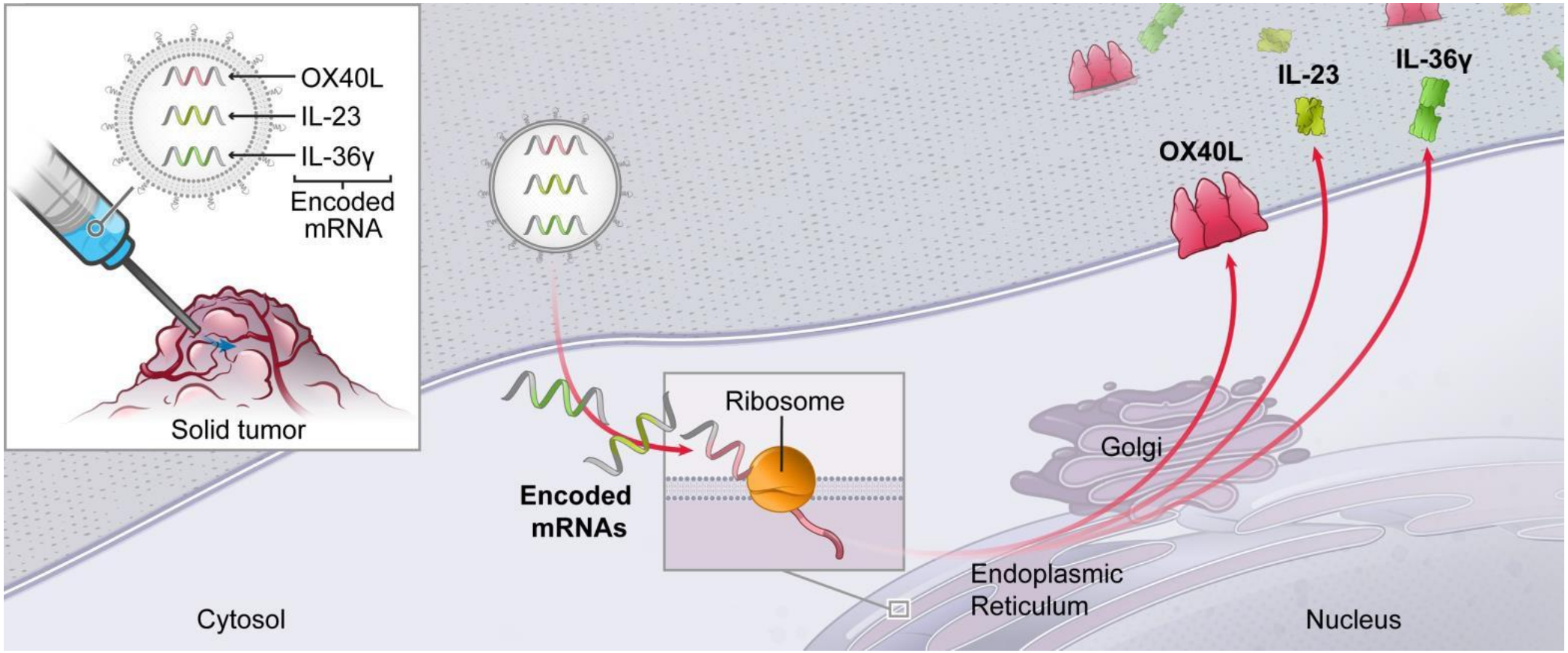
Triplet (OX40L/IL-23/IL-36γ) (mRNA-2752) overview

Moderna's technology enables novel combinations of targets



Intratumoral delivery may enable delivery of targets locally that are too toxic when administered systemically

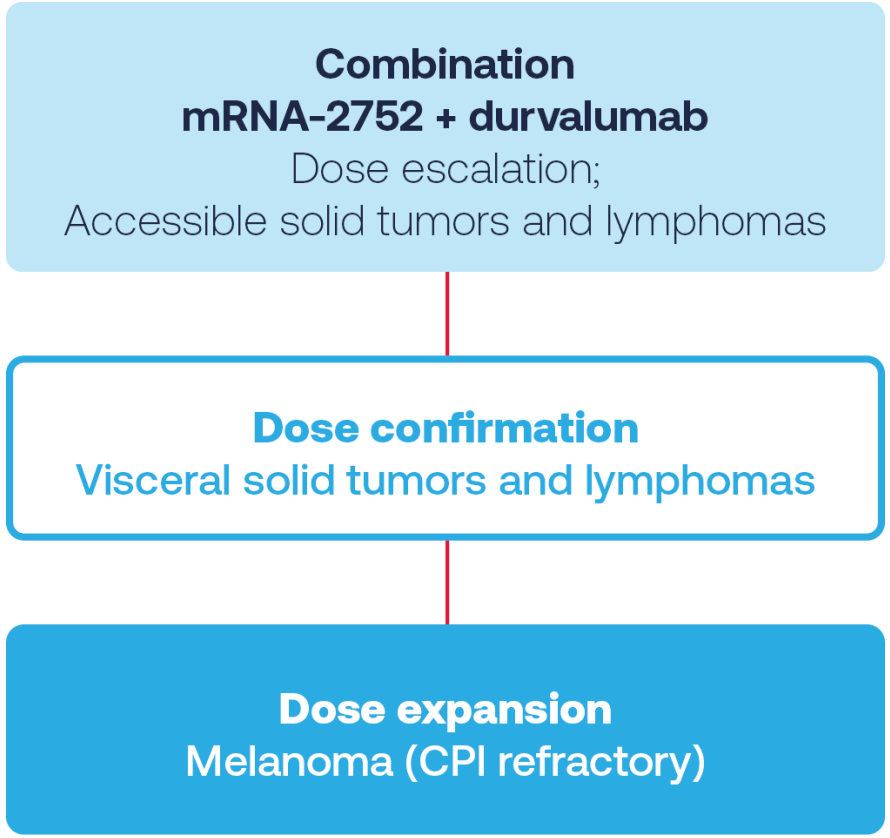
Triplet (mRNA-2752) is ongoing in a Phase 1 study; patients dosed in combination with durvalumab

Key Objectives

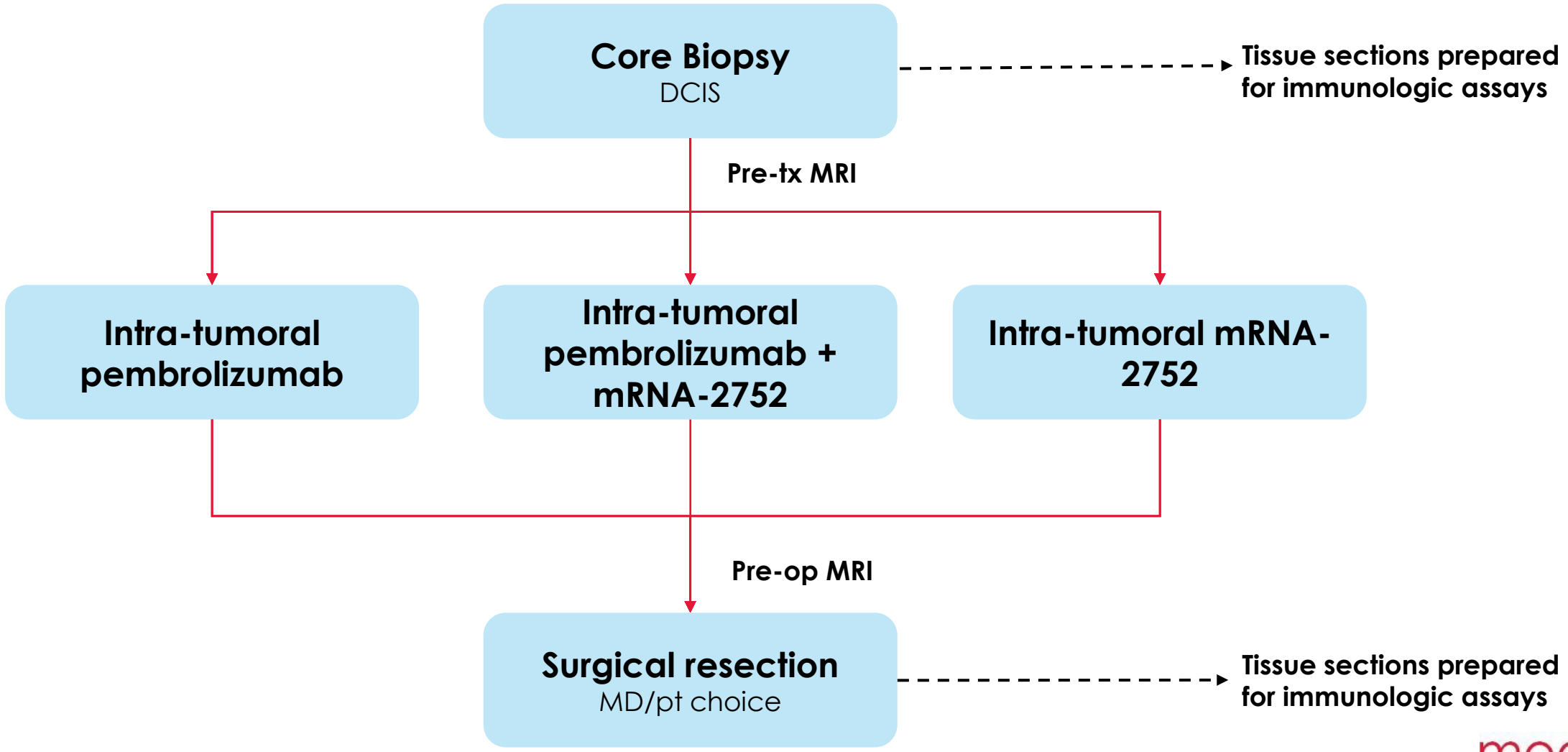
Evaluate safety and tolerability of mRNA-2752 administered alone and in combination with PD-L1 inhibitor

Define maximum tolerated dose (MTD) and recommended dose for expansion for mRNA-2752 alone and in combination with durvalumab

Secondary Objectives: (1) Anti-tumor activity, (2) Protein expression in tumors and (3) Pharmacokinetics



Investigator sponsored ductal carcinoma in situ (DCIS) study with Triplet (OX40L/IL-23/IL-36γ) (mRNA-2752)



External Oncology Research Partnerships

Rose Loughlin

Senior Vice President,
Research and Early Development

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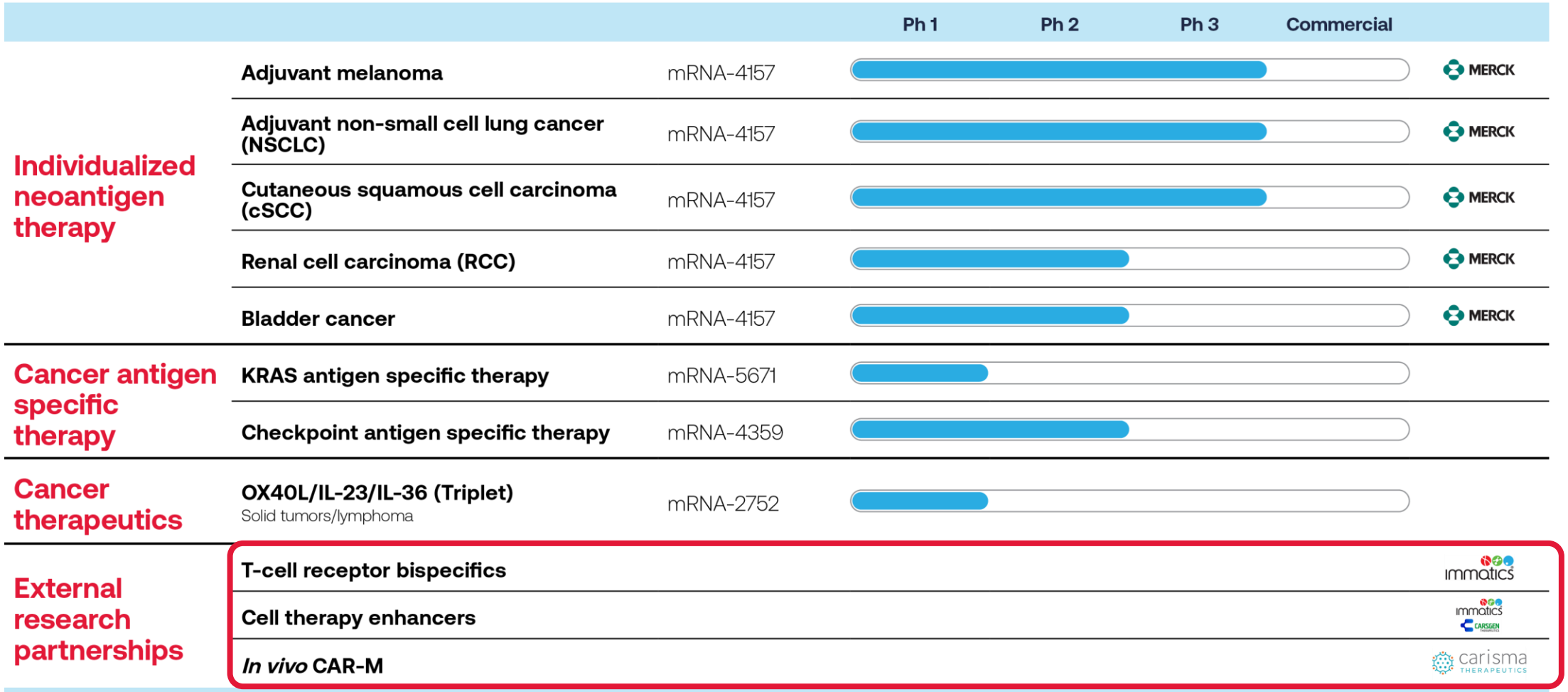
Moderna immuno-oncology pipeline: partnerships



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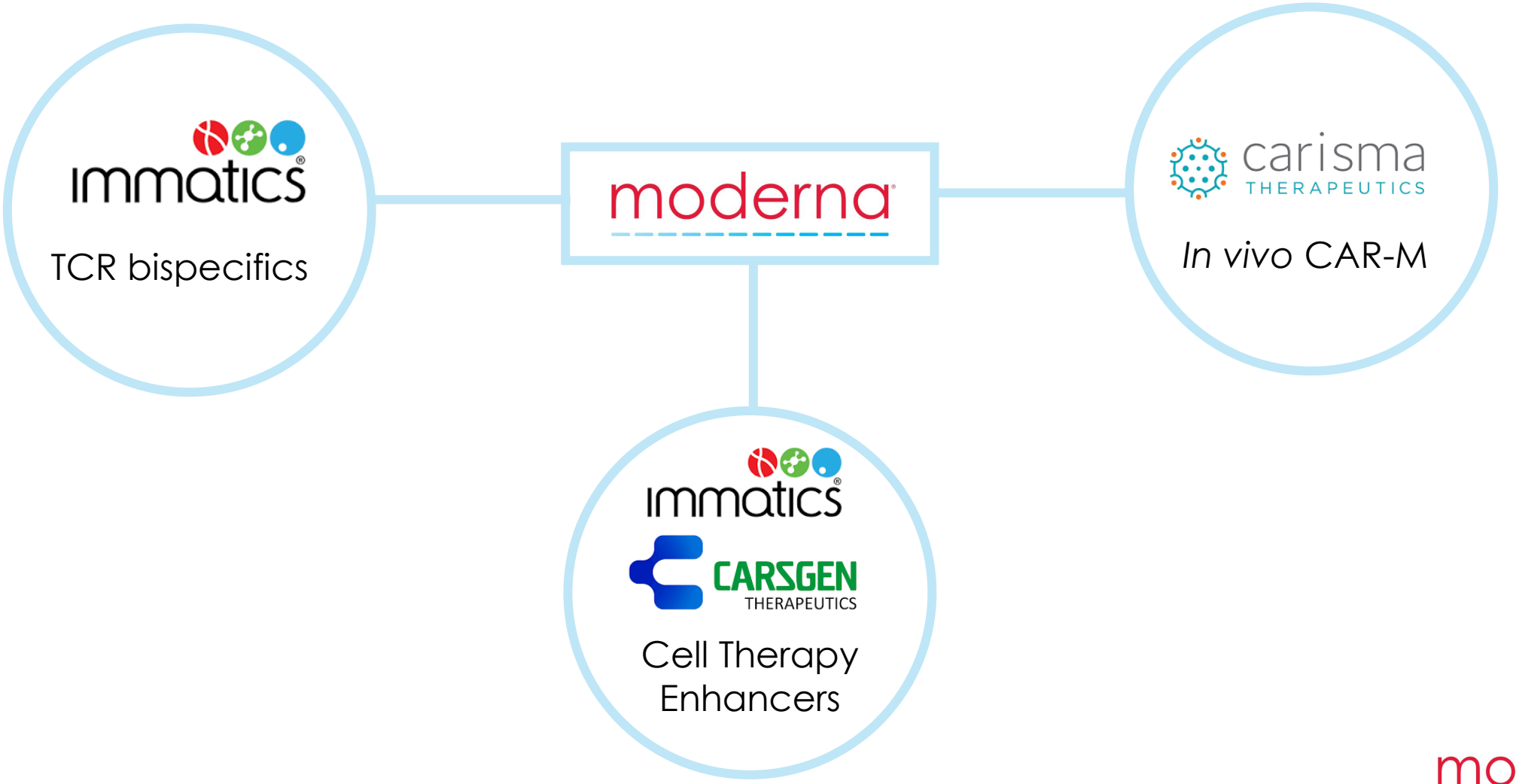
We established partnerships to extend the reach of our mRNA oncology franchise



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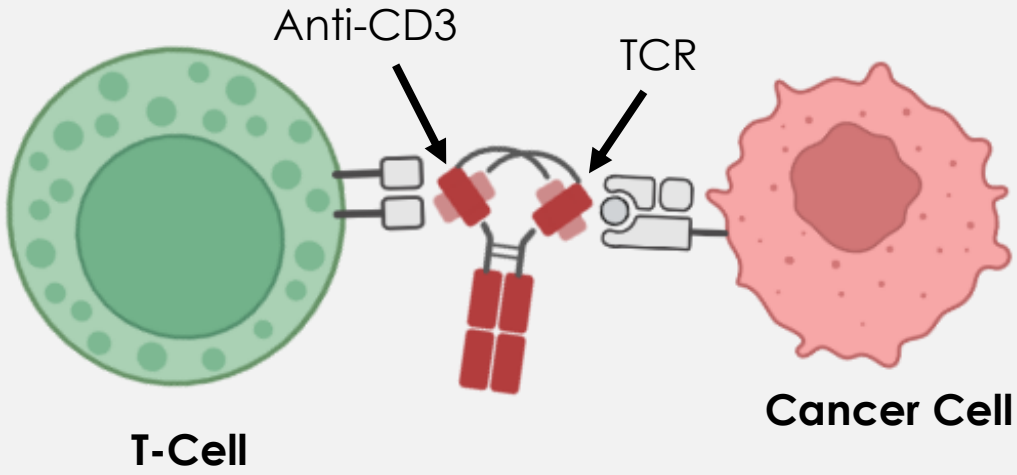
In vivo expression of TCR bispecifics with mRNA technology



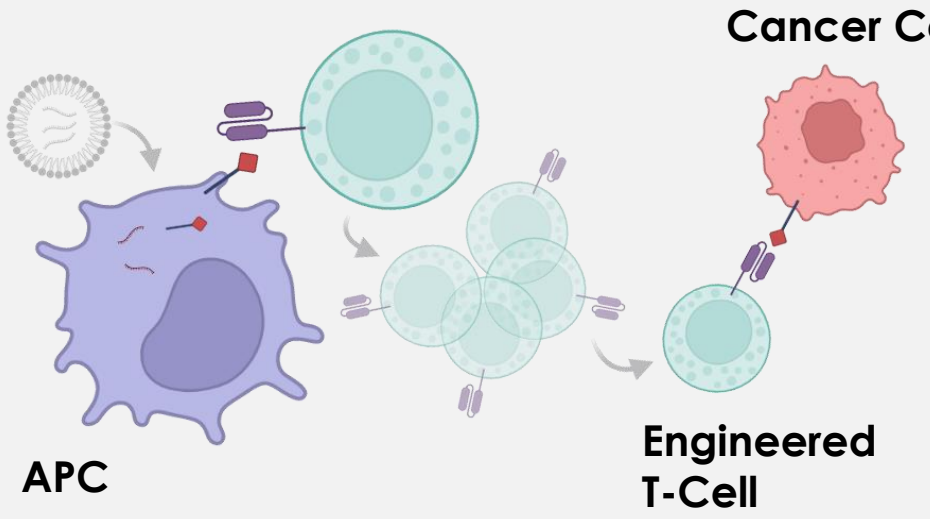
TCR-based therapies unlock the entire proteome, including intracellular antigens

TCR bispecifics direct T cells to recognize and kill cancer cells that display target antigen

Collaboration leverages Moderna's mRNA technology for in vivo expression of Immatics' half-life extended TCR bispecifics TCER®

Two of Immatics' TCR bispecifics are currently in Phase 1 clinical trials

mRNA enhancers to boost ex vivo T cell therapies



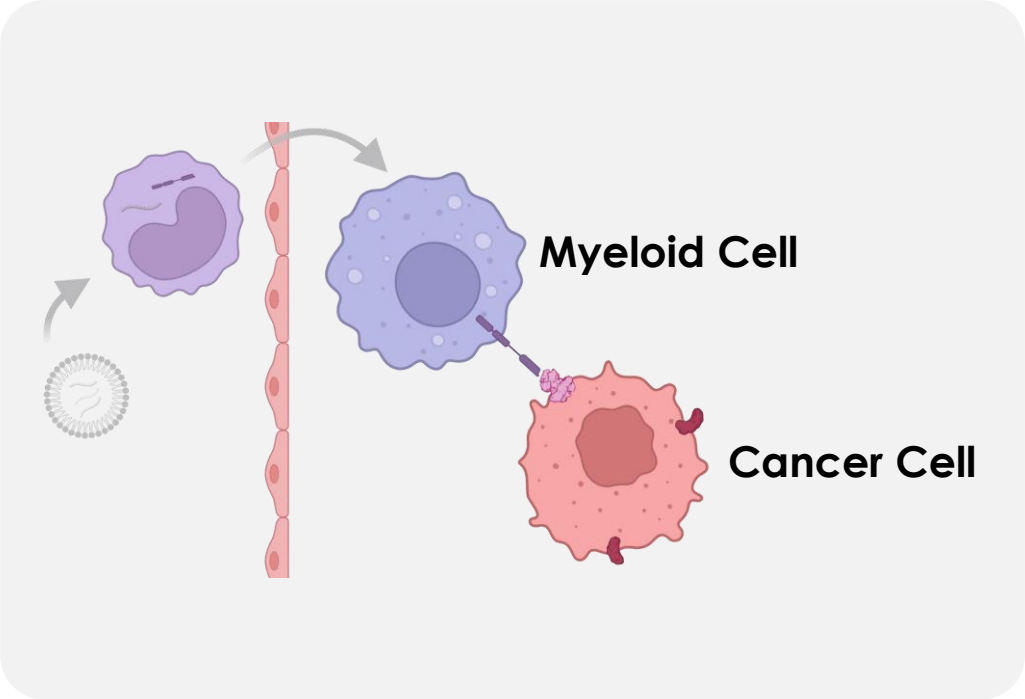
We have established collaborations to combine mRNA enhancers with ex vivo T cell therapies

Immatics: Evaluation of Immatics' IMA203 TCR-T therapy targeting PRAME in combination with Moderna's PRAME mRNA enhancer

CARsgen: Evaluation of CARsgen's CT041 CAR-T therapy targeting CLDN18.2 in combination with Moderna's CLDN18.2 mRNA enhancer

In vivo CAR-M: redirecting endogenous myeloid cells with mRNA technology

carisma THERAPEUTICS



In vivo cell therapy approach to engineer chimeric antigen receptors (CARs) in myeloid cells

Combines Carisma's expertise in engineered myeloid cell biology and Moderna's mRNA technology platform

CAR-M aims to direct myeloid cells to overcome barriers to successful immunotherapy, particularly for solid tumors

Ex vivo CAR-M (HER2) CT-0508 was well tolerated and demonstrated MOA (trafficking, immune activation and T cell clonal expansion in TME) in Phase 1 trial

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Q & A

Appendix

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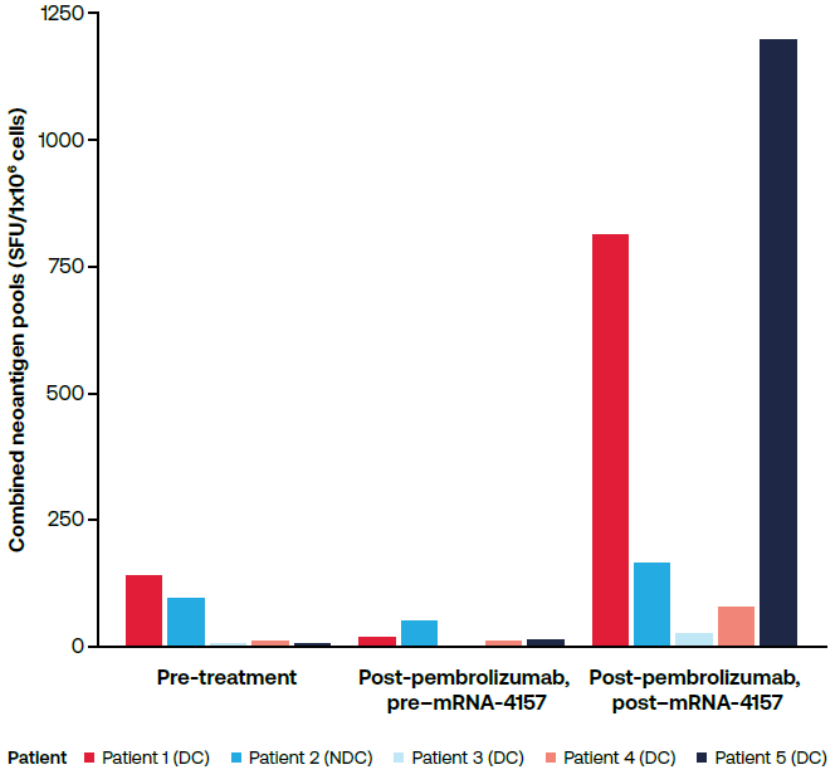
INT: Phase 1 Head & Neck immunogenicity data

Biomarkers

Sustained de novo T cell induction to targeted neoantigens was seen in 5/5 available patient samples (Figure 3); IFN-° responses were higher post mRNA-4157 + pembrolizumab compared with baseline

Neoantigen-reactive T cell response to neoantigen peptide pools



Immunogenicity was evaluable in 5/22 (22.7%) patients with all 3 timepoints; 7 patients had insufficient sample quantity or quality. Data are plotted as sum of responses to mRNA-4157–specific neoantigen peptide pools (mix of individualized neoantigen peptides) at indicated timepoints during treatment. Patients with CR, PR, or SD were classified as 'disease control' and patients with PD were classified as 'no disease control'.
DC, disease control; NDC, no disease control; SFU, spot forming unit