Moderna's therapeutics: OX40L/IL-23/IL-36γ (Triplet)

Last program update: November 4, 2021

Modality	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	IL-2 *Autoimmune disorders*	mRNA-6231						Worldwide
	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines	Personalized cancer vaccine (PCV)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						50-50 global profit sharing with **Merck**
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	IL-12 *Solid tumors*	MEDI1191						50-50 U.S. profit sharing; **AZ** to pay royalties on ex-U.S. sales
Localized Regenerative Therapeutics	VEGF-A *Myocardial ischemia*	AZD8601						**AZ** to pay milestones and royalties
	Propionic acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic acidemia (MMA)	mRNA-3705						Worldwide
Systemic Intracellular Therapeutics	Glycogen storage disease type 1a (GSD1a)	mRNA-3745	Open IND					Worldwide
	Phenylketonuria (PKU)	mRNA-3283						Worldwide
	Crigler-Najjar syndrome type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge
Inhaled Pulmonary Therapeutics	Cystic fibrosis (CF)	VXc-522						**Vertex** to pay milestones and royalties

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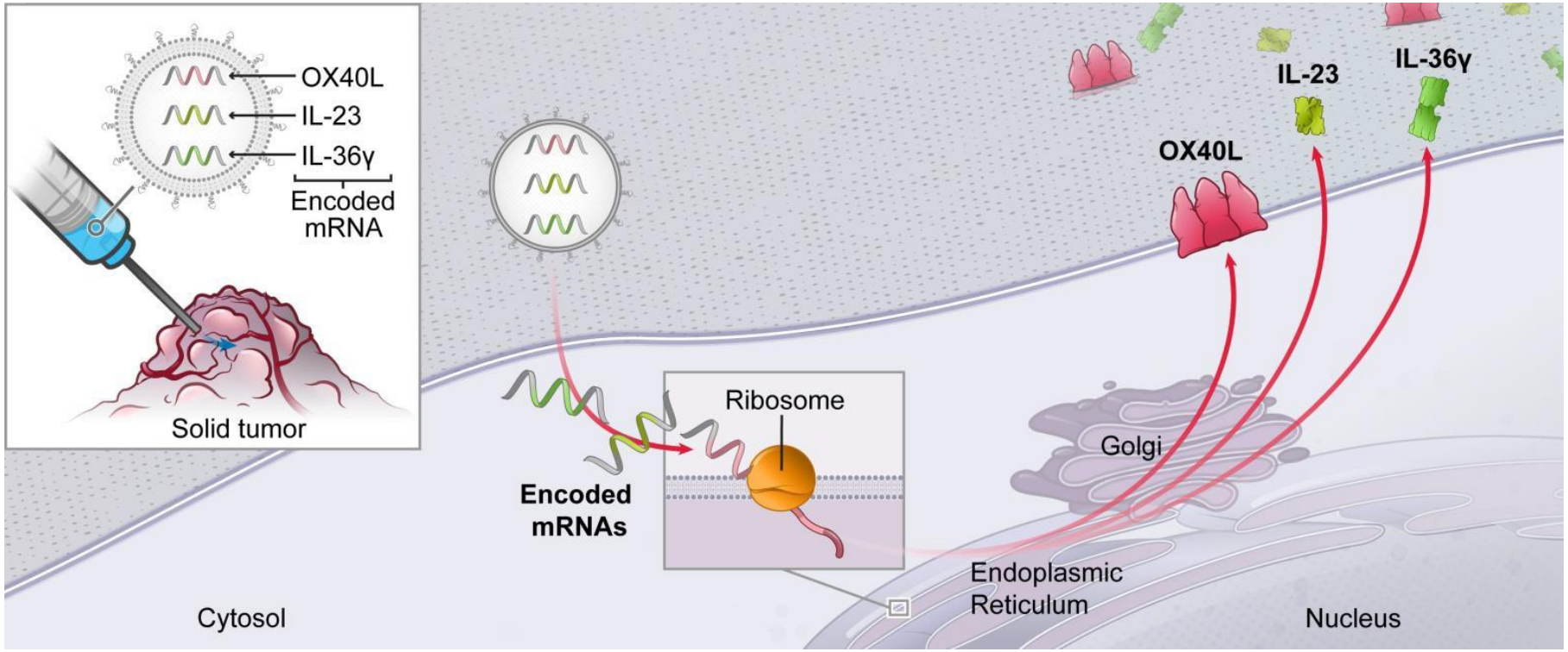
OX40L/IL-23/IL-36γ (mRNA-2752) overview

Moderna's technology enables novel combinations of targets
Intratumoral delivery may enable delivery of targets locally that are too toxic systemically



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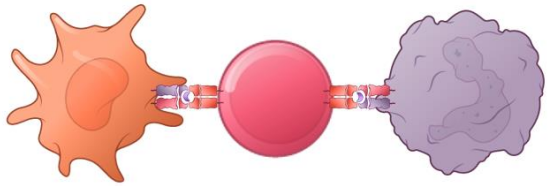
Immune modulation with OX40L, IL-23, IL-36γ



Dendritic Cell | T Cell | Cancer Cell

	OX40L	IL-23	IL-36γ
	Transmembrane T cell co-stimulatory protein	**Proinflammatory cytokine of the IL-12 family** • Reported to prime DC • Activates other cells that bridge innate to adaptive immunity (NKT, ILCs, gd T cells)	**Proinflammatory cytokine of the IL-1 family** • Acts on DCs to promote maturation and ↑ cytokine/chemokines
	• Promotes Th1, Th2, Th9; suppresses Treg • Enhances expansion and survival of CD4 and CD8 T cells → promotes memory	• Expands and maintains Th17 • Acts on antigen experienced T cells	• Enhances T cell proliferation, Th1, Th9 differentiation
	• Preclinical monotherapy efficacy established and reported	• Preclinical monotherapy efficacy established and reported • Clear role in human barrier immunity and inflammatory disease	• Reported to preclinically enhance anti-cancer immunity • Clear role in human barrier immunity and inflammatory disease

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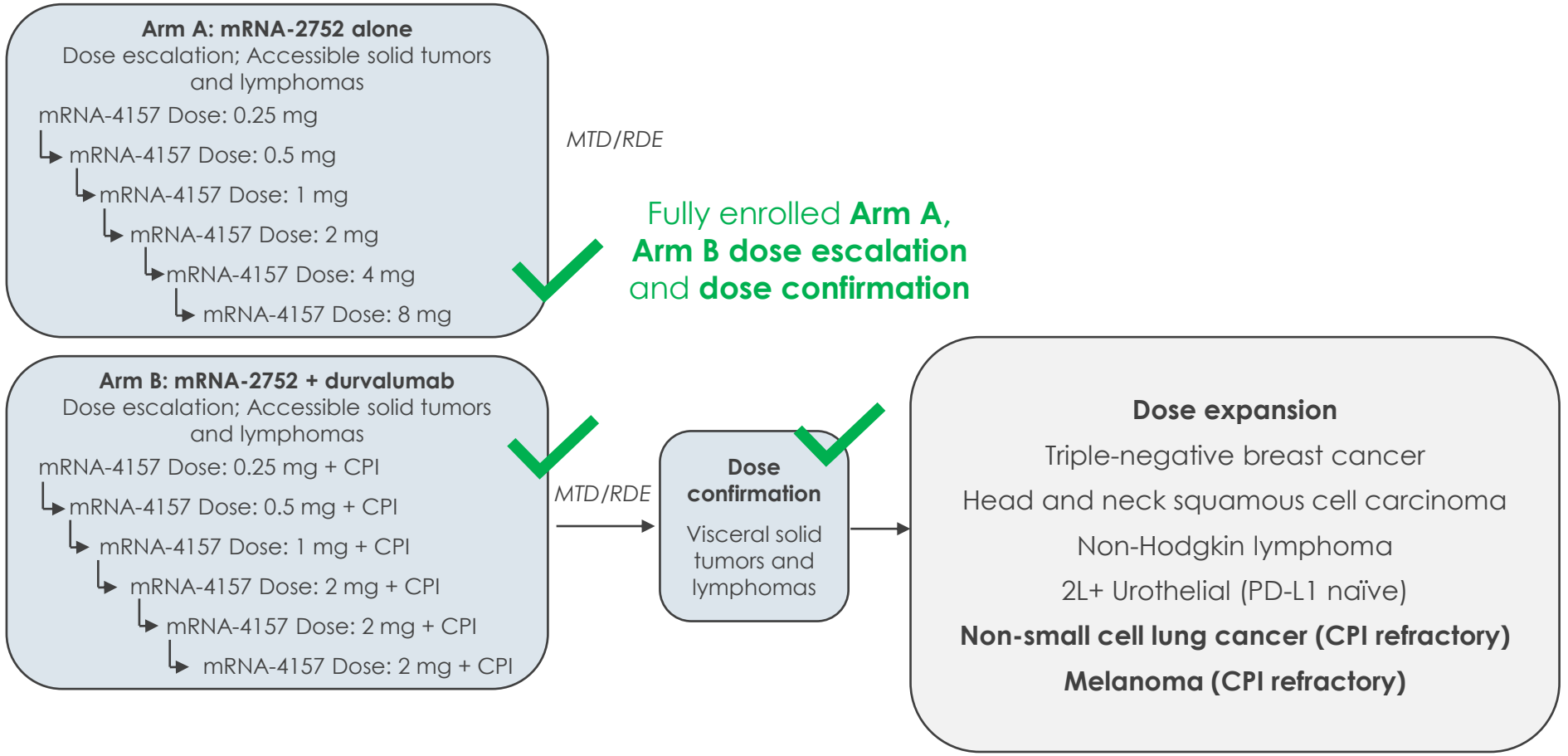
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Phase 1 ongoing; 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

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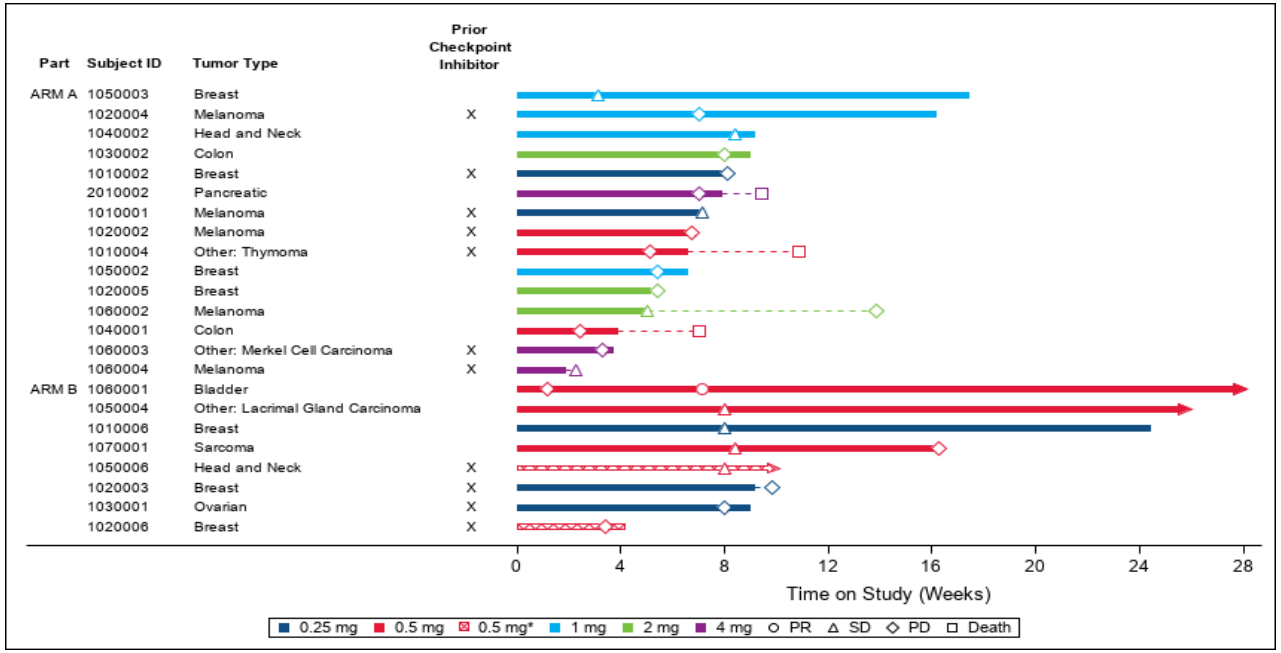
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Preliminary Safety and Efficacy Data(ASCO 2020)

mRNA-2752-P101 Safety Data

Related Adverse Events*				
	Arm A		Arm B	
	Grade 1-2	Grade 3	Grade 1-2	Grade 3
Injection site erythema	6	-	3	-
Injection site pain	6	-	2	-
Pyrexia	5	1**		
Chills	3	1**		
Fatigue	3	1**		
Alanine aminotransferase increased	2	-		
Aspartate aminotransferase increased	2	-		
Back pain	2	-		
Rash maculo-popular	2	-		
Injection site reaction	-	1**		
Malaise	-	1**		

mRNA-2752-P101 Swimmer plot: per RECIST 1.1



17 patients on Arm A with duration on study up to 16 weeks. 12 patients on Arm B up to 28 weeks on study and continuing at time of data cutoff.

*Treatment-related AEs reported once per patient. **All Gr 3 events observed in 1 patient @ 4mg dose
AEs: ≥ 2 patients (grade 1-2), ≥ 1 patient (grade 3), No Gr 4 or 5 AEs were reported

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High unmet medical need in checkpoint inhibitor (CPI) refractory melanoma

CPI refractory melanoma presents a **high unmet medical need with low survival rates**

- 8000 patients/year and no approved treatment
- mPFS 2-4.7 months

	ORR	Median PFS
KEYNOTE-002 (Pembro)	**22%**	2.9 months
CheckMate-037 (Nivo)	**27%**	3.1 months
Ipi/Nivo post Pembro (Zimmer et al. 2017)	**16%**	2.0 months
Low-dose Ipi + Pembro (n=70) (Olson et al, 2020, ASCO#10004)	**31%**	4.7 months

Target Population: Both primary refractory and secondary acquired resistance with progression on prior CPI as most recent treatment

- Primary CPI resistance: estimated ~40-65% pts
- Secondary acquired resistance: 39-43% pts at 3 years

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

- ✓ iTu mRNA-2752 as monotherapy and in combination with durvalumab is **tolerable at all dose levels studied**
- ✓ mRNA-2752 is associated with **tumor shrinkage** in **both injected** and **non-injected lesions** in both monotherapy and in combination
- ✓ These data **support the ongoing testing** of the mRNA-2752/durvalumab combination in Arm B of the Phase I study
  - Update to be shared at SITC 2021

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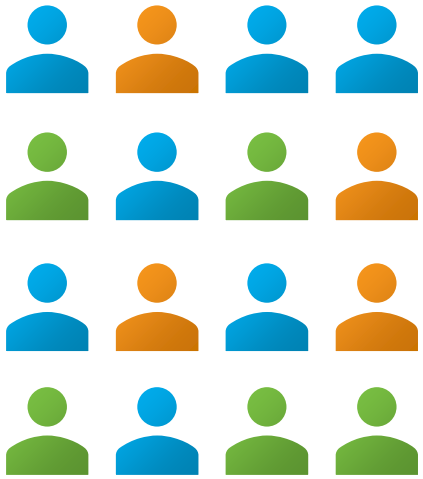
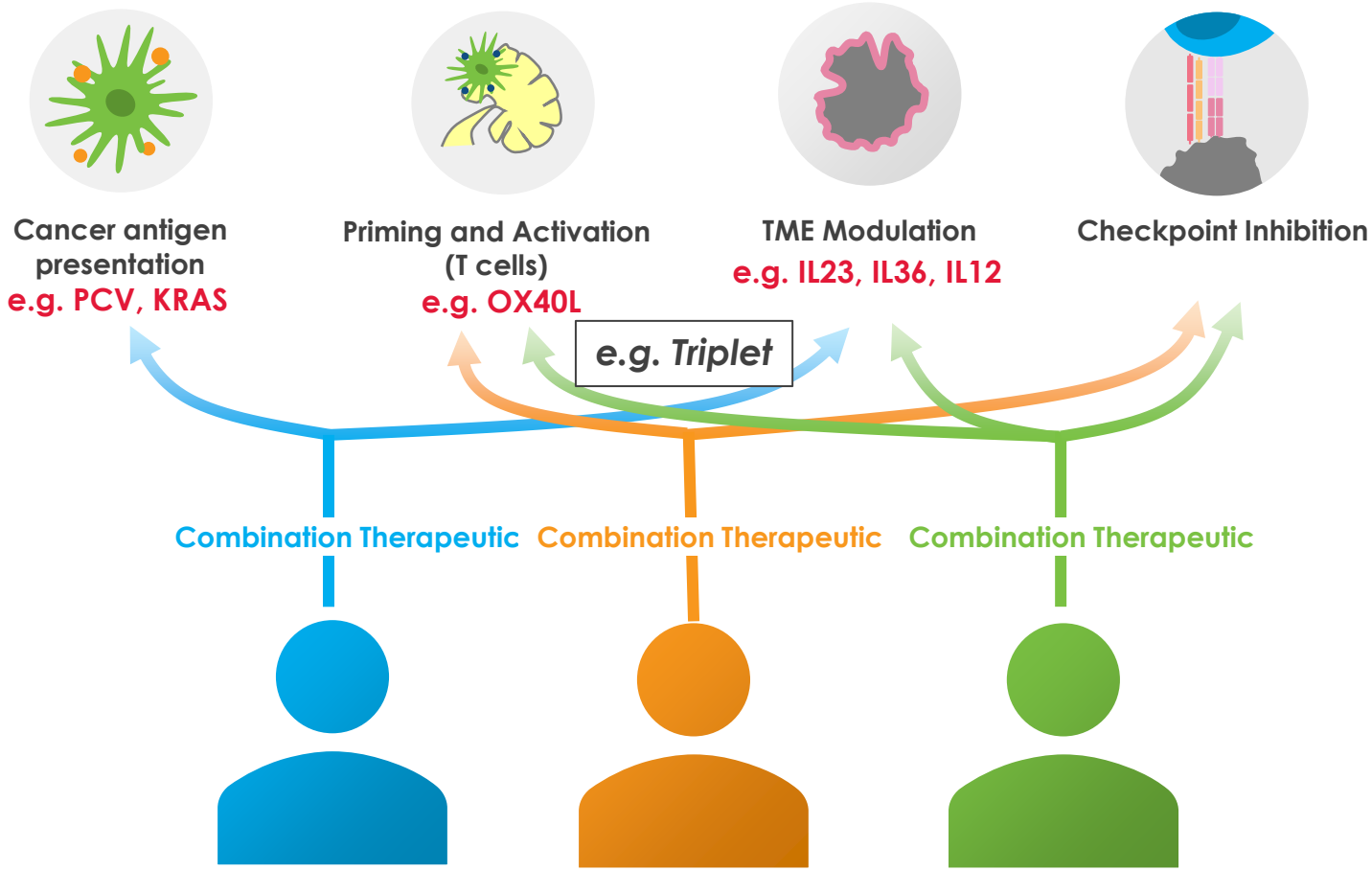
We believe mRNA will enable combination therapies personalized for individual tumors and patients

Response prediction based on immune signatures…



…is expected to lead to a rational combination of multiple IO approaches



Tailored treatment

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