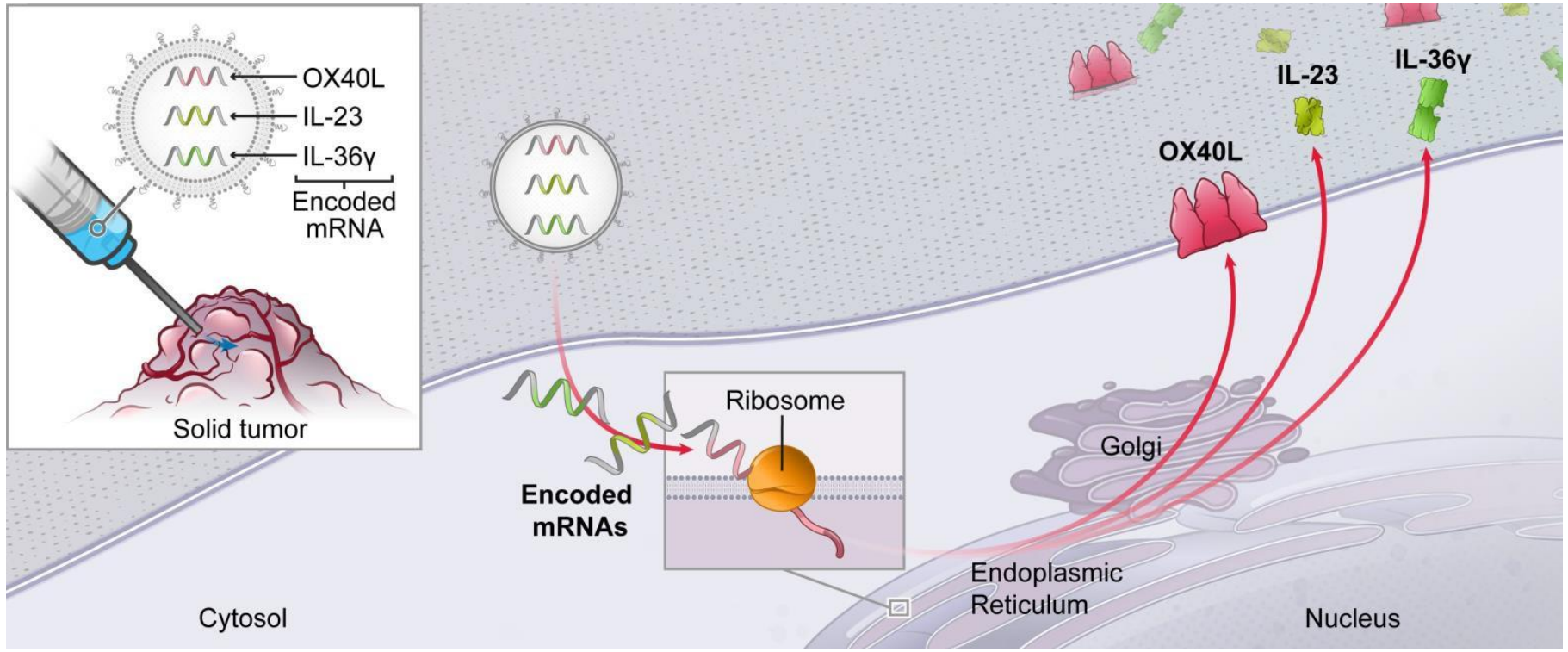
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Last updated: November 2nd, 2023

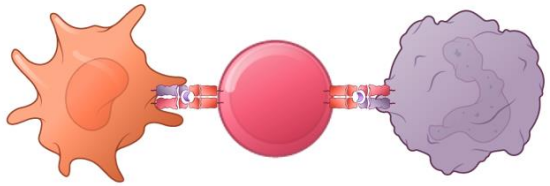
	Program	ID #	Preclinical development	Phase 1	Phase 2	Phase 3	Commercial	Moderna rights
Systemic secreted & cell surface therapeutics	Relaxin *Heart failure*	mRNA-0184						Worldwide
	PD-L1 *Autoimmune hepatitis*	mRNA-6981						Worldwide
Cancer vaccines & therapeutics	Individualized neoantigen therapy (INT)	mRNA-4157						50-50 global profit sharing with **Merck**
	KRAS vaccine	mRNA-5671						Worldwide
	Checkpoint vaccine	mRNA-4359						Worldwide
Intratumoral Immuno-oncology	OX40L/IL-23/IL-36γ (Triplet) *Solid tumors/lymphoma*	mRNA-2752						Worldwide
	Propionic acidemia (PA)	mRNA-3927						Worldwide
	Methylmalonic acidemia (MMA)	mRNA-3705						Worldwide
Systemic intracellular therapeutics	Glycogen storage disease type 1a (GSD1a)	mRNA-3745						Worldwide
	Ornithine transcarbamylase deficiency (OTC)	mRNA-3139						Worldwide
	Phenylketonuria (PKU)	mRNA-3210						Worldwide
Inhaled pulmonary therapeutics	Crigler-Najjar syndrome type 1 (CN-1)	mRNA-3351						Provided to **ILCM** free of charge
	Cystic fibrosis (CF)	VX-522						**Vertex** to pay milestones and royalties

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



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



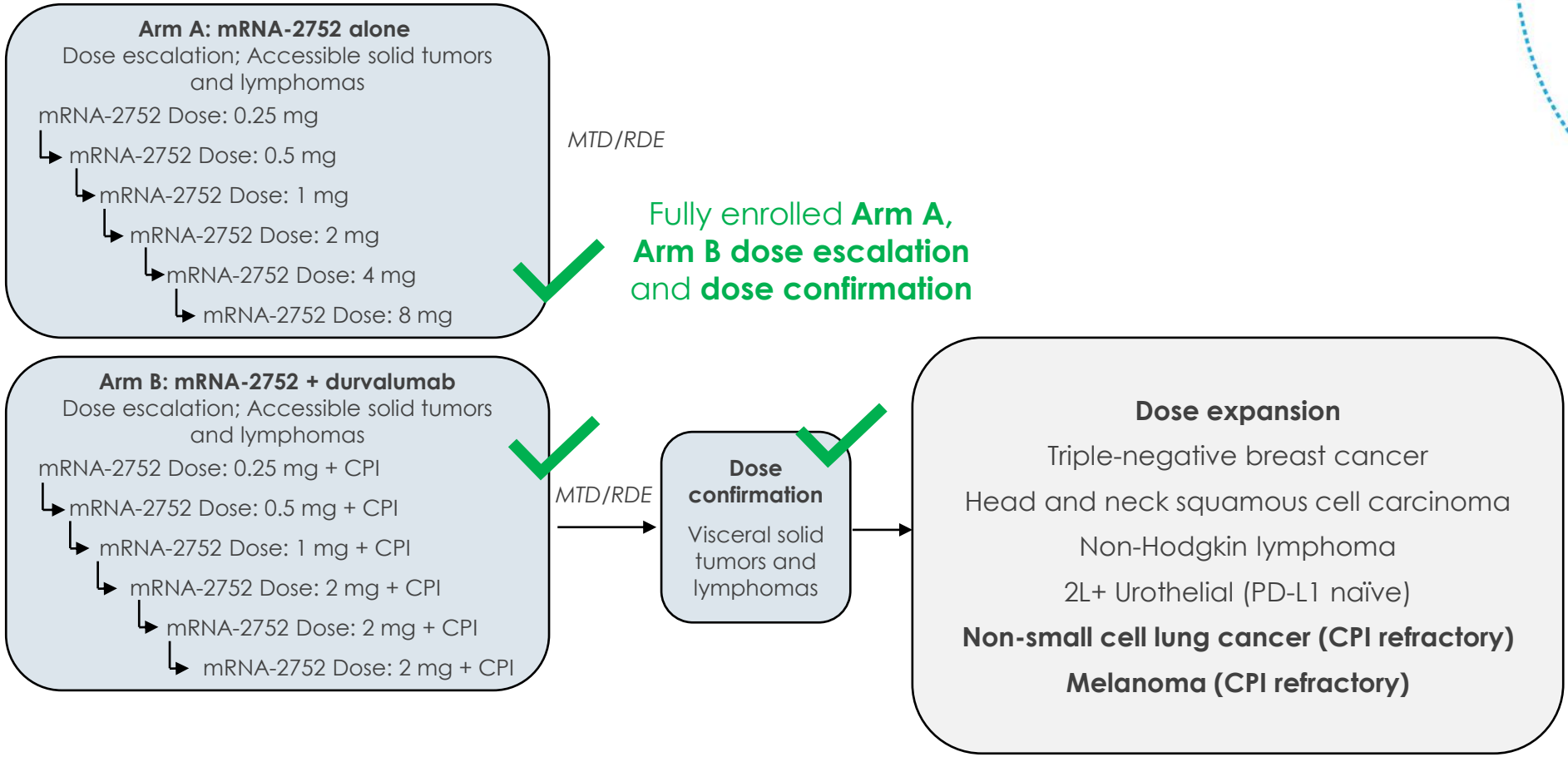
Dendritic Cell | T Cell | Cancer Cell

	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

Triplet (mRNA-2752) is ongoing in a Phase 1; 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



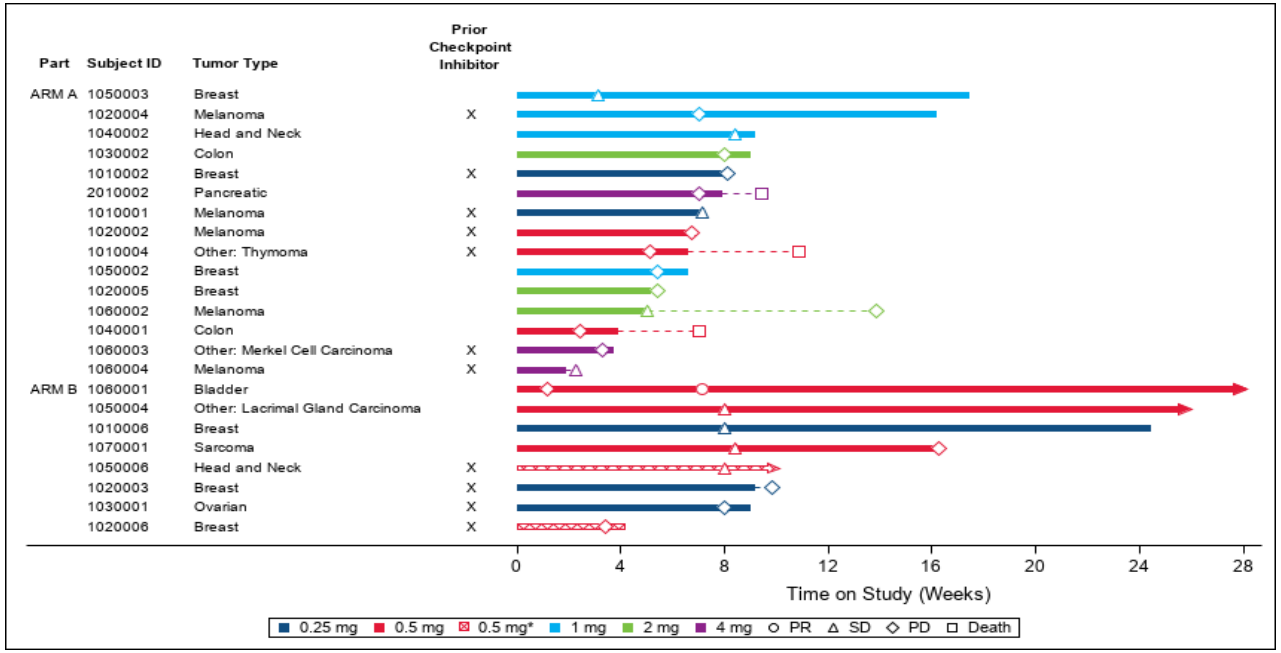
Triplet (mRNA-2752): Preliminary safety and efficacy data (ASCO 2020)

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**		

*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

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.

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

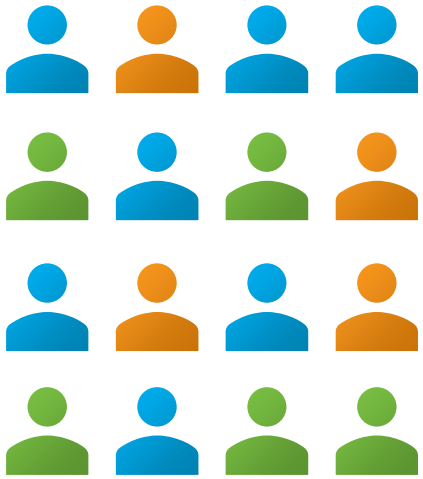
- Primary CPI resistance: estimated ~40-65% pts
- Secondary acquired resistance: 39-43% pts at 3 years

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

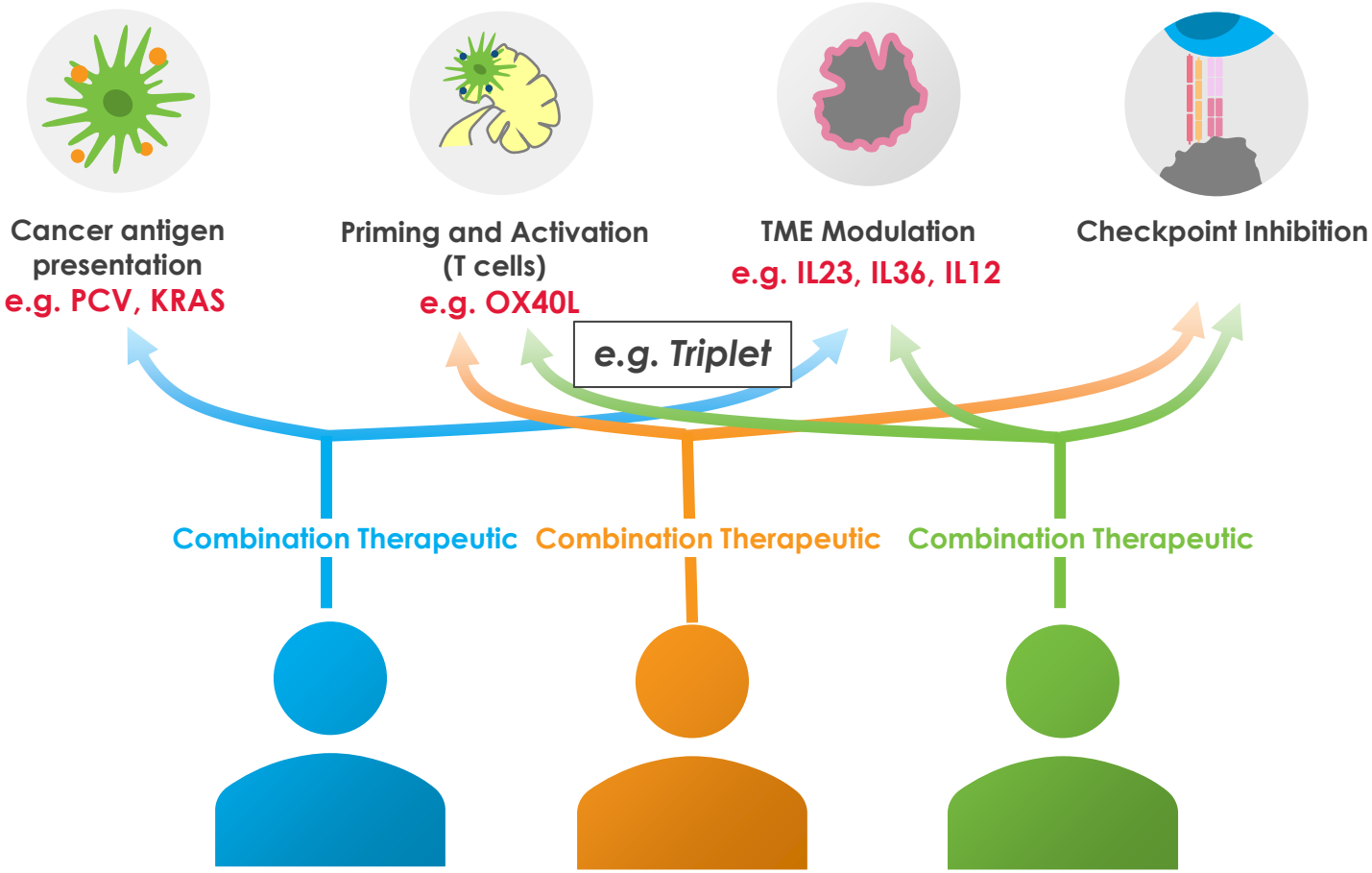
- ✓ iTu mRNA-2752 as monotherapy and in combination with durvalumab is tolerable at all dose levels studied
- ✓ mRNA-2752 is associated with tumor shrinkage in both injected and non-injected lesions in both monotherapy and in combination
- ✓ These data support the ongoing testing of the mRNA-2752/durvalumab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

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



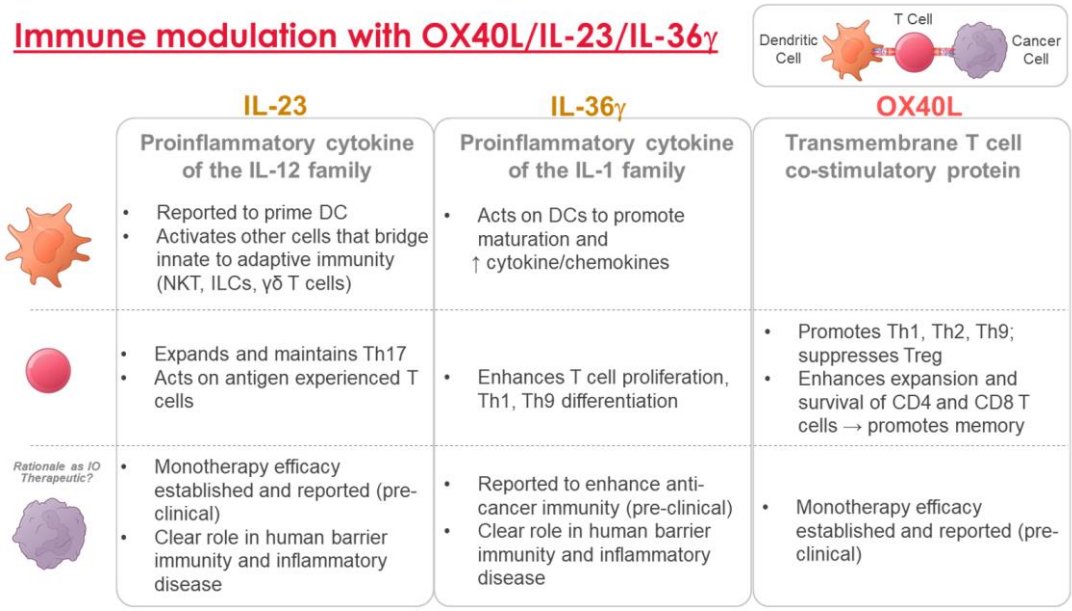
Tailored treatment

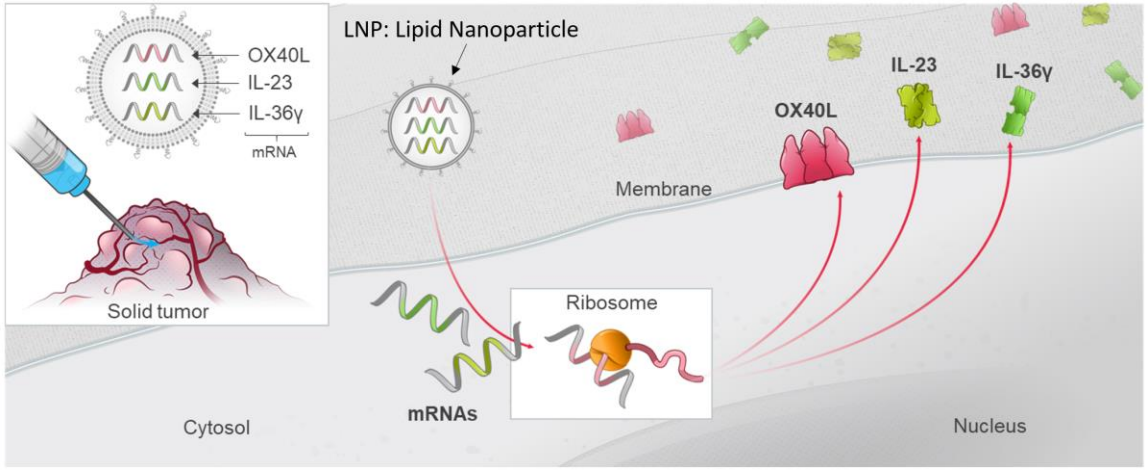
Phase 1 Study of mRNA-2752, a Lipid Nanoparticle Encapsulating mRNAs Encoding huOX40L, IL-23, and IL-36γ Intratumoral (iTu) Injection +/- Durvalumab in Advanced Solid Tumors and Lymphoma

SITC 2021 November 10-14

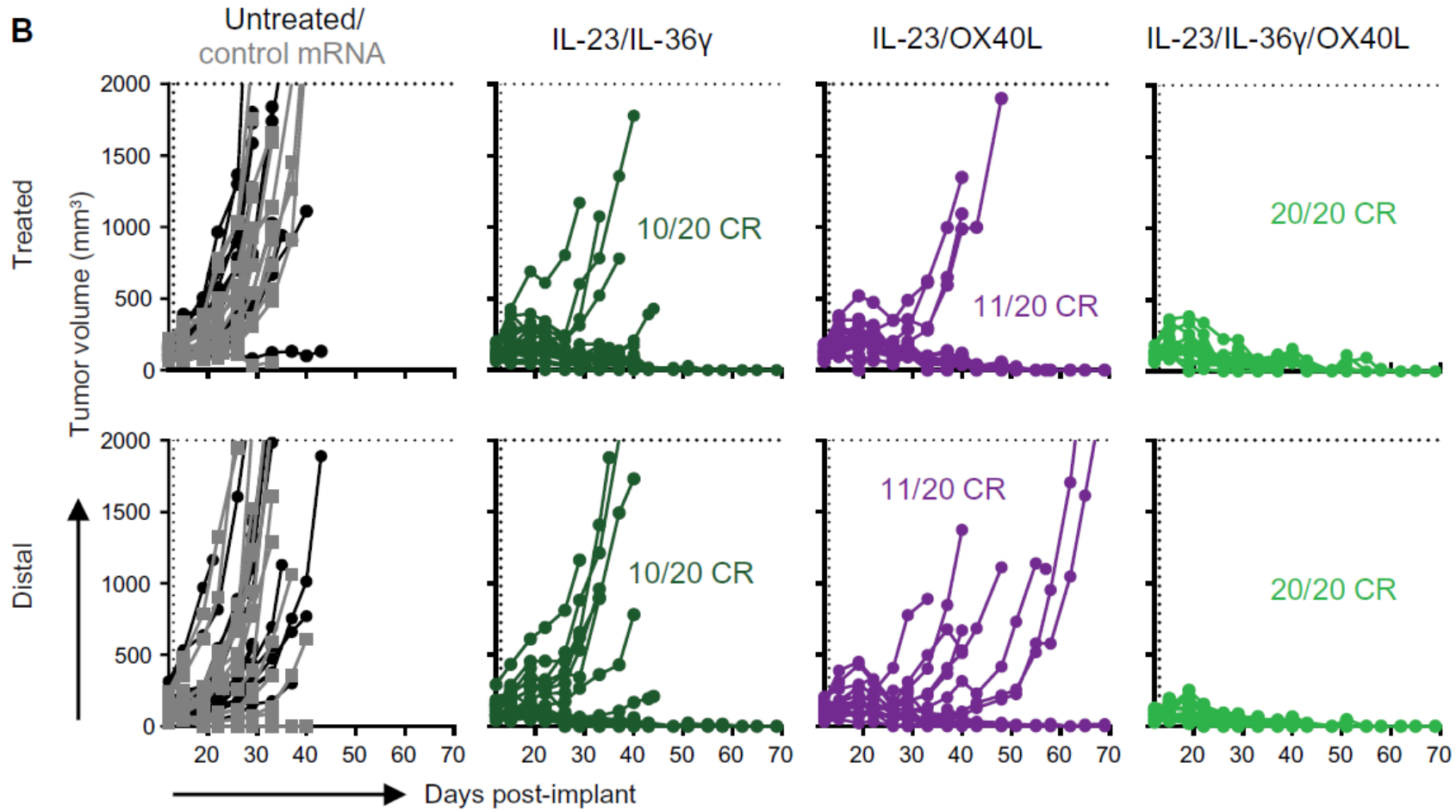
Background

- mRNA-2752 is a novel mRNA-based therapeutic that encodes the T cell co-stimulator OX40L and the pro-inflammatory cytokines IL-23 and IL-36γ
- The induction of pro-inflammatory cytokines along with T-cell co-stimulation directly in the tumor serves to ignite a response or transform an otherwise suppressive tumor microenvironment (TME) into one permissive of a more productive immune response
- Prior preclinical studies showed robust anti-tumor activity in mouse as a single agent and in combination with PD-L1 blockade, with regressions in both injected and un-injected lesions
- Here we present follow-up data from our first-in-human study of intratumoral mRNA-2752 in solid tumors as monotherapy and in combination with the anti-PD-L1 blocking antibody durvalumab





Treated and abscopal responses in MC-38 models treated with 5 μg mRNA



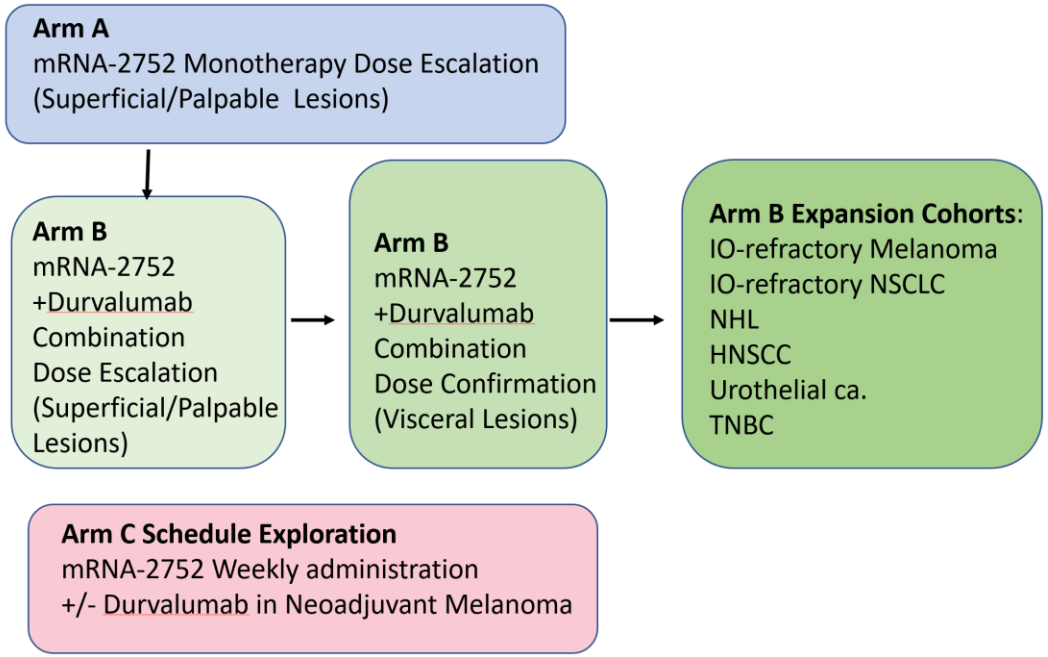
Hewitt et al. Sci Transl Med 2019.

Methods

- iTu mRNA-2752 was administered every 2 weeks for the first cycle, followed by every 28 days for up to 7 doses in combination with durva in patients with advanced solid malignancy or lymphoma

- Biomarker analyses include measurement of IL-23, IL-36γ and pro-inflammatory cytokine proteins in pre- and post-treatment tumor biopsies and plasma

- Immunohistochemistry for PD-L1 and T cell markers, transcriptional scores (T cell-inflamed and dendritic cell signatures) were used to further characterize baseline status and changes to the TME with treatment



Objectives:

- Assess the safety and tolerability of mRNA-2752 +/- durvalumab
- Characterize the pharmacokinetics of mRNA-2752 +/- durvalumab
- Characterize protein expression from introduced mRNAs and biomarkers of immune response
- Assess preliminary anti-tumor activity in select expansion cohorts of TNBC, HNSCC, NHL, urothelial carcinoma, and immune checkpoint refractory-melanoma and -NSCLC

Safety

- As of this reporting, 51 solid tumor patients have been treated either with mRNA-2752 alone (n = 19) or in combination (n = 32)
- Of the 45 evaluable patients evaluated per RECIST, there have been 2 PRs and 15 SD
- Safety profile shows mRNA-2752 given in combination with durvalumab is tolerable at all dose levels evaluated
- Most common TEAEs included pyrexia, fatigue, injection site erythema/pain/swelling/and edema and the majority were grade 1/2
- There were no treatment related Grade 4/5 events
- 1 DLT of grade 2 CRS occurred in a patient at the 8 mg dose confirmation cohort in combination with durvalumab

Related Treatment Emergent Adverse Events*

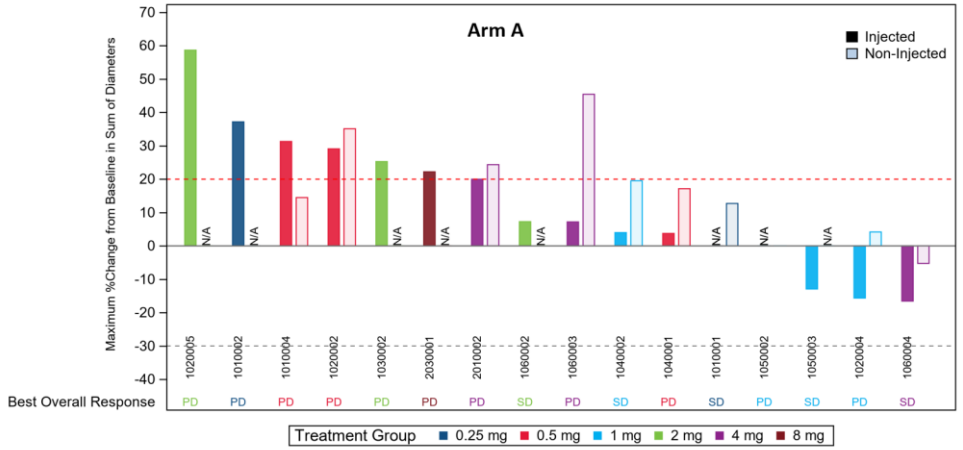
	Arm A (N=19)			Arm B (N=32)		
	Gr 1 (%)	Gr 2 (%)	Gr 3 (%)	Gr 1 (%)	Gr 2 (%)	Gr 3 (%)
Pyrexia	5 (26.3)	-	1**	7 (21.9)	2 (6.3)	-
Fatigue	1 (5.3)	1 (5.3)	1**	6 (18.8)	3 (9.4)	-
Chills	2 (10.5)	-	1**	4 (12.5)	1 (3.1)	-
Injection site erythema	5 (26.3)	2 (10.5)	-	6 (18.8)	2 (6.3)	-
Injection site pain	7 (36.8)	-	1 (5.3)	2 (6.3)	4 (12.5)	1 (3.1)
Injection site swelling/edema	1 (5.3)	1 (5.3)	-	4 (12.5)	3 (9.4)	-
Injection related reaction	-	-	1**	-	3 (9.4)	-
Flushing	0	1 (5.3)	-	2 (6.3)	1 (3.1)	-
Nausea	-	-	-	2 (6.3)	1 (3.1)	-
Vomiting	-	-	-	1 (3.1)	1 (3.1)	-
Diarrhea	1 (5.3)	-	-	2 (6.3)	1 (3.1)	-
ALT increase	1 (5.3)	1 (5.3)	-	-	-	-
AST increase	2 (10.5)	-	-	1 (3.1)	-	-
Back pain	1 (5.3)	1 (5.3)	-	-	-	-
Rash	1 (5.3)	1 (5.3)	-	3 (9.4)	-	-
Tumor pain	-	-	-	2 (6.3)	-	-
Peripheral edema	-	-	-	2 (6.3)	1 (3.1)	-
Syncope†	-	-	-	-	-	2 (6.3)
Asthenia	-	1 (5.3)	-	2 (6.3)	-	-

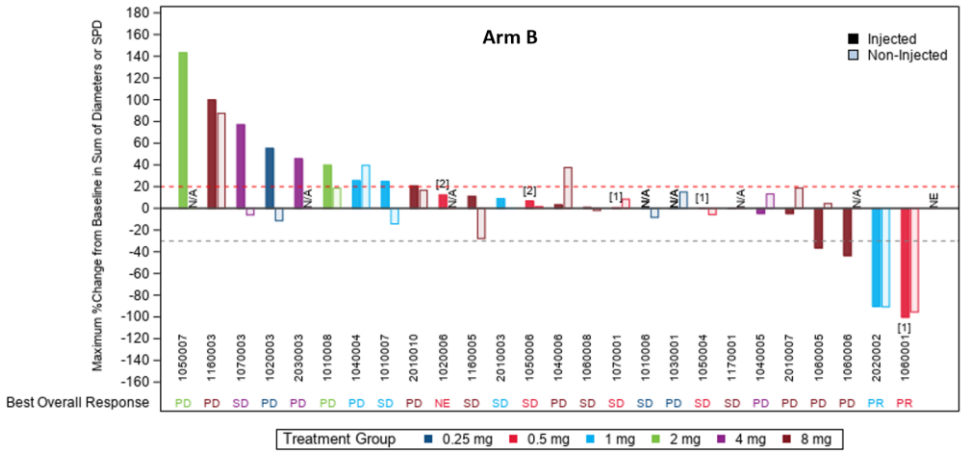
*Treatment-related AEs reported once per patient, occurring in > 5% of patients
**All Gr 3 events observed in 1 patient @ 4mg dose
No Gr 4 or 5 AEs were reported
1 DLT of Gr 2 Cytokine Release Syndrome occurred in a patient @ 8mg in dose confirmation cohort
†No grade below Gr3 for syncope in CTCAE v5.0

Clinical Efficacy

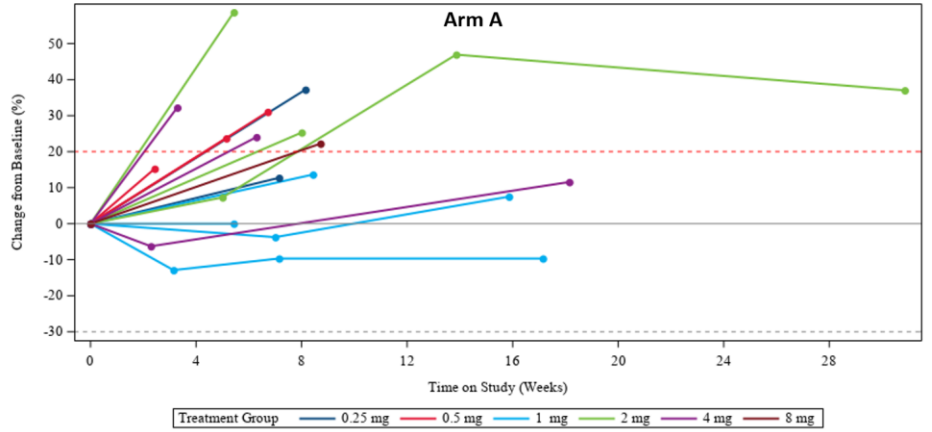
- Tumor shrinkage was observed in both injected and/or un-injected lesions in both monotherapy and combination
- Of the 45 evaluable patients evaluated per RECIST, there have been 2 PRs and 15 SD

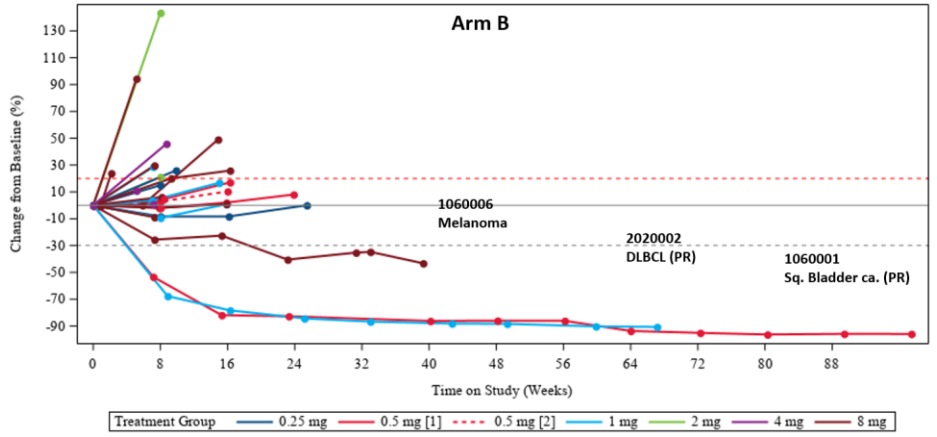
Maximum %Change from Baseline in Sum of Diameters of Target Lesions by Injection Status
Based on Investigator Assessment per RECIST 1.1 /Cheson



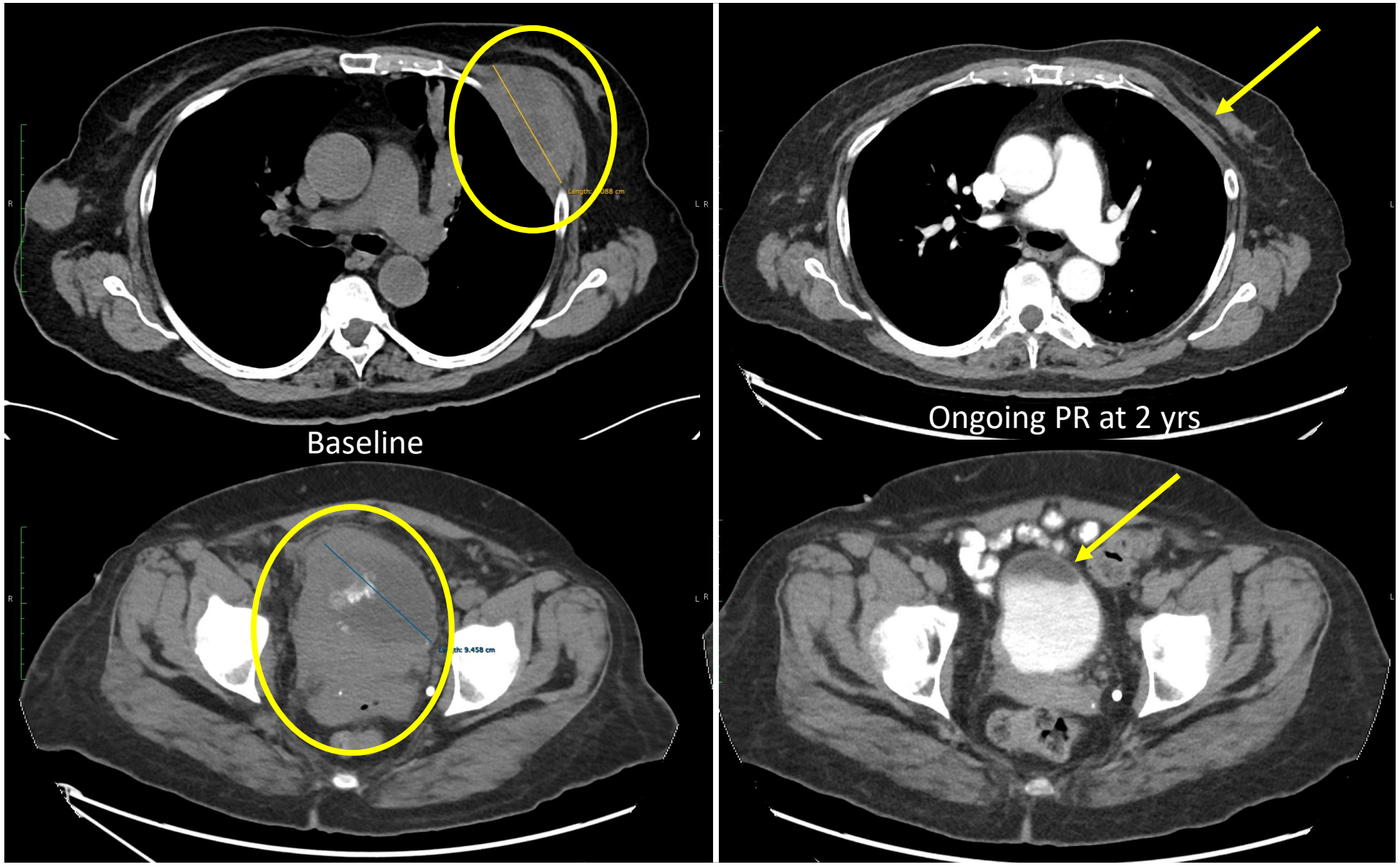


Percent Change from Baseline in Sum of Diameters of Target Lesions Over Time
Based on Investigator Assessment per RECIST 1.1 /Cheson





Partial Response in sq. bladder patient at 0.5 mg mRNA-2752 + durvalumab with 81% shrinkage of target lesions ongoing at 2 years (ASCO 2020)



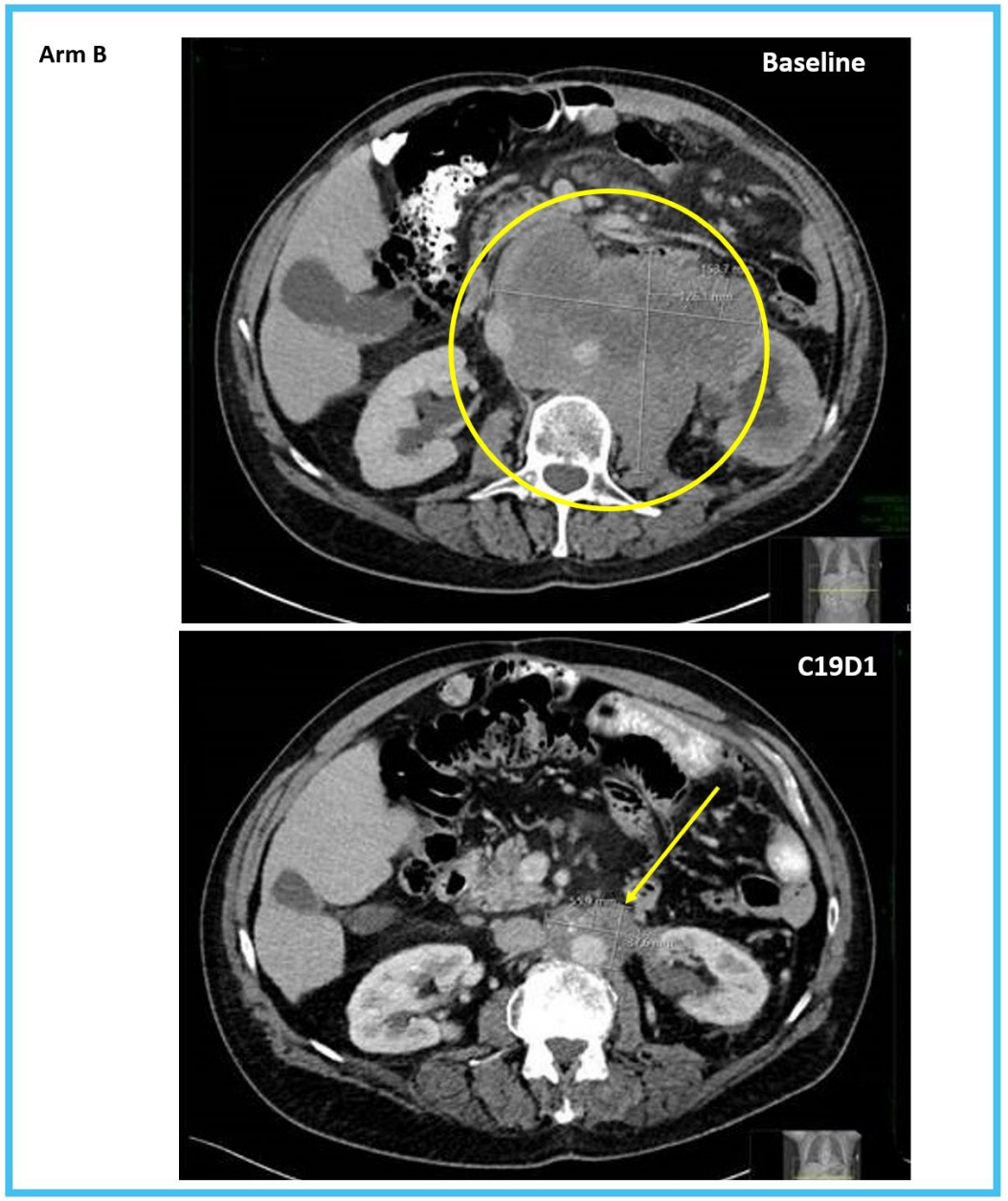
Partial Response in DLBCL

- Shown here are CT scan images for Subject 2020002, a DLBCL pt, previously progressed on R-CHOP, R-DHAX, CAR-T, and BR/polatuzumab with ongoing response of injected lesion at 75 weeks

*a second PR occurred in a squamous-cell bladder carcinoma (PD-1/L1 naïve) patient that received 0.5 mg mRNA-2752 with durva, and showed an 81% reduction of target lesions

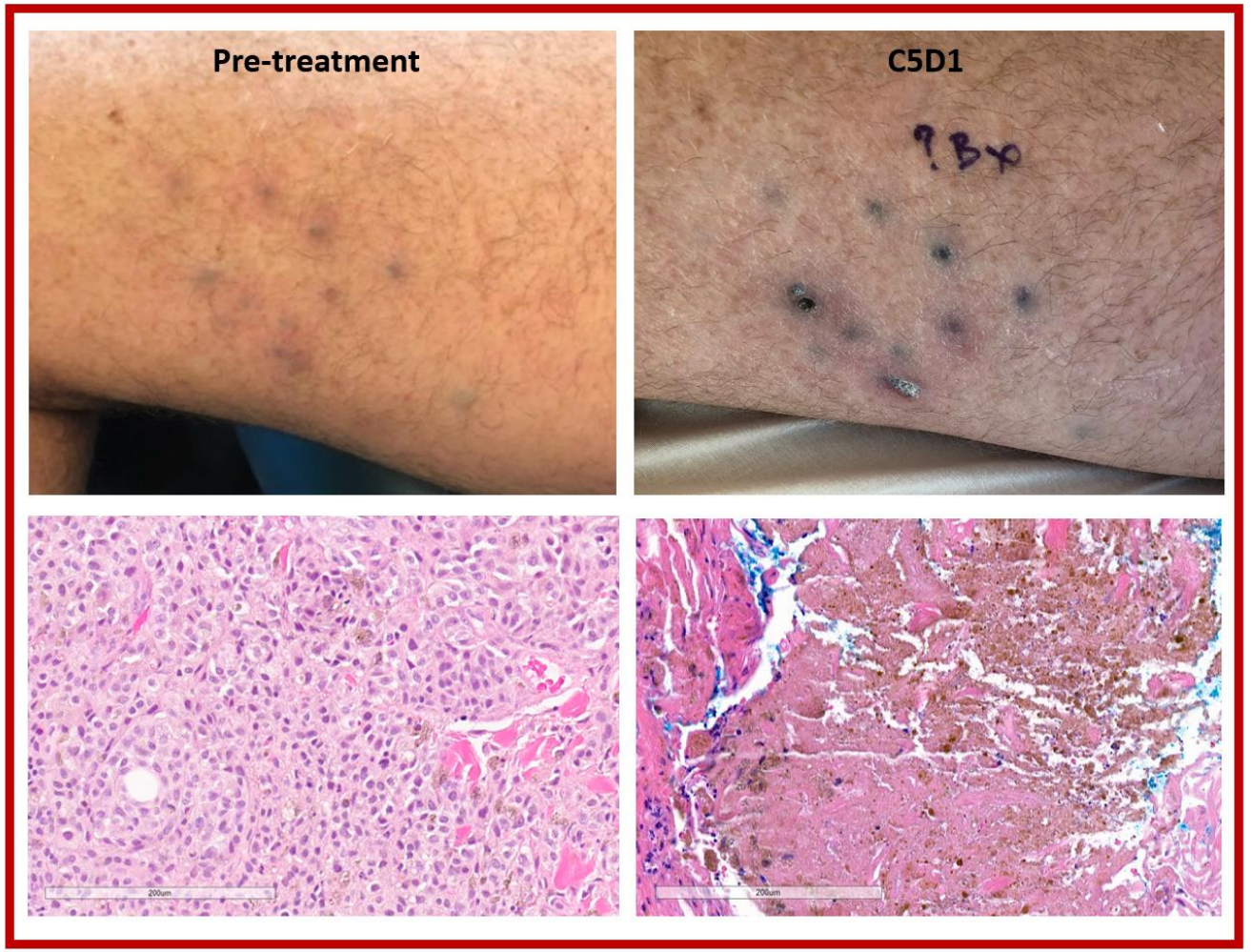
- These results were previously reported at ASCO 2020
- This patient maintained a PR for 24 cycles and is now receiving Durvalumab monotherapy off study

CT scan images for Patient 2020002: a DLBCL with ongoing Partial Response of the injected lesion at 75 weeks. Previous therapies included R-CHOP, R-DHAX, CAR-T, and BR/polatuzumab (**BELOW**).



Clinical Benefit in Melanoma

- Skin examination for Patient 1060006: a melanoma patient, progressed on TVEC and pembrolizumab, demonstrating response in injected lesion
- Subcutaneous nodules became flattened on exam with necrosis apparent in some lesions
- Shown here are Pre-treatment (left) and at C5D1 (right) with corresponding H&E biopsy results below photographs
- Pretreatment biopsy shows melanoma invasion into dermis (bottom left); on-treatment biopsy shows minimal viable tissue with pigment laden macrophages (bottom right)



Skin examination for Patient 1060006: in a melanoma patient, progressed on TVEC and pembrolizumab, demonstrating response in injected lesion. Subcutaneous nodules became flattened on exam with necrosis apparent in some lesions. Pre-treatment (left) and at C5D1(right) with corresponding H&E biopsy results below photographs. Pretreatment biopsy shows melanoma invasion into dermis (bottom left); on-treatment biopsy shows minimal viable tissue with pigment laden macrophages (bottom right).

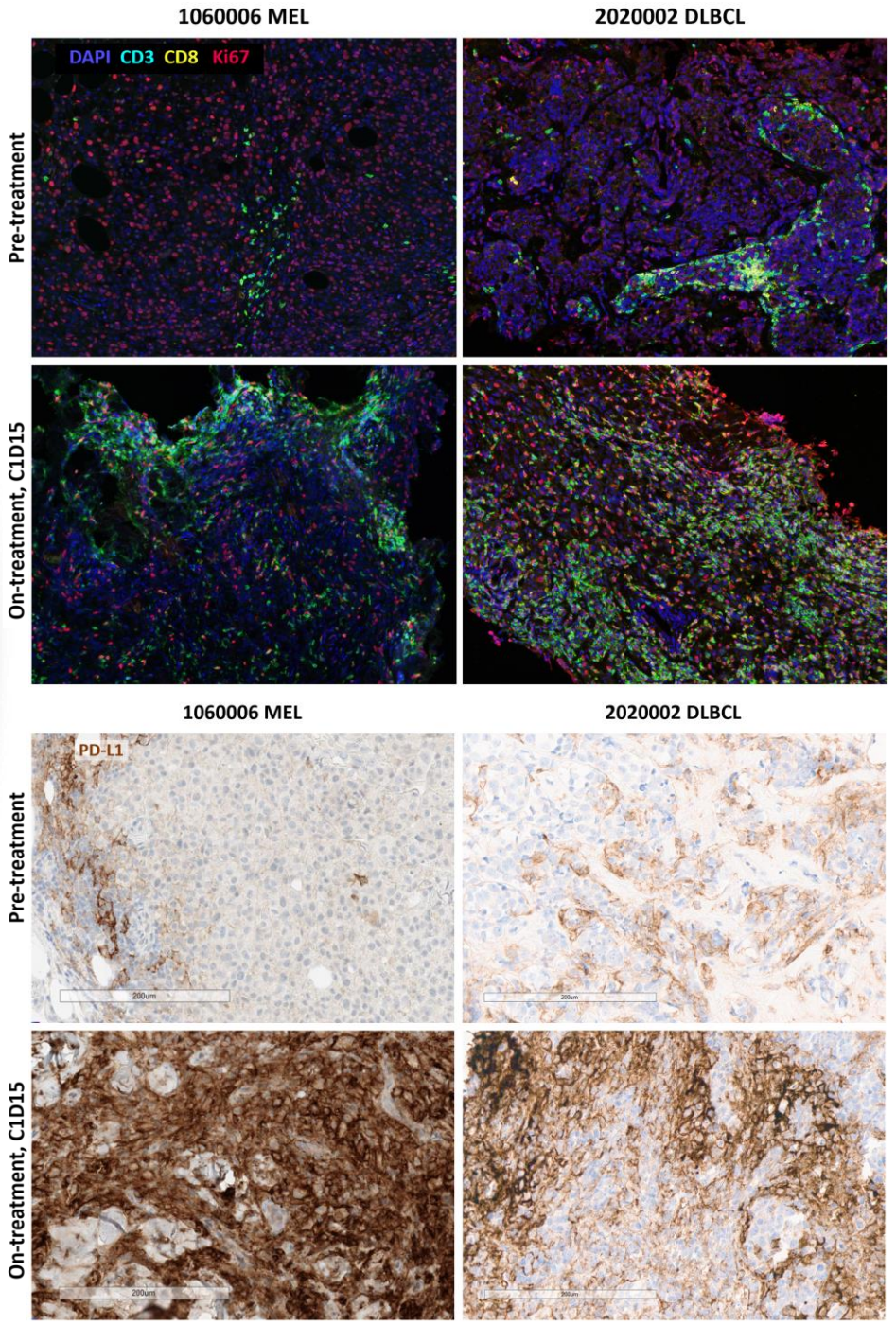
Modulation of the tumor microenvironment (TME) with treatment

- Representative T cell panel by Fluorescence-IHC (CD3, cyan; CD8, yellow; Ki67, red; DAPI, blue) and PD-L1 IHC (SP263 Ventana) at baseline and C1D15 for the melanoma and DLBCL patient (Fig A)

- Analyses of tumor and plasma biomarkers demonstrate increased IL-23 and IL-36γ protein expression post-treatment (ASCO 2020, next slide), and suggest a sustained immunomodulatory effect that includes elevated systemic IFN-γ, TNF-α (next slide), intra-tumoral PD-L1 (marker of interferon signaling; Figs A, C), proliferating (activated) T cells (Figs A, B), and T cell-inflamed (GEP) and DC transcriptional signature scores (Fig D)

- Greatest changes in pharmacodynamic markers (e.g. PD-L1 [Figs A, B], TILs [Fig A], transcriptional scores [Fig D]) observed in patients with clinical benefit

A



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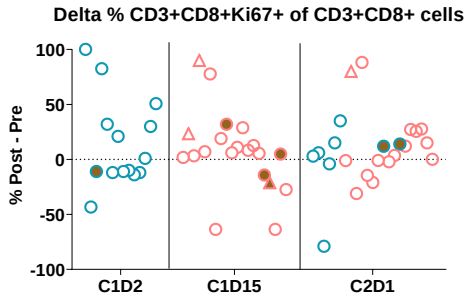

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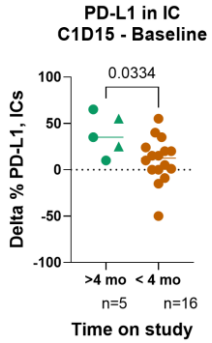

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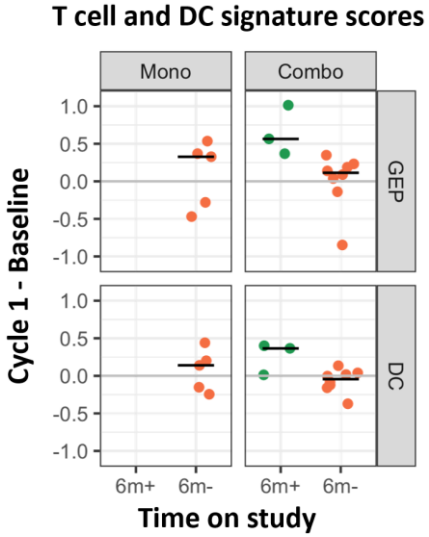
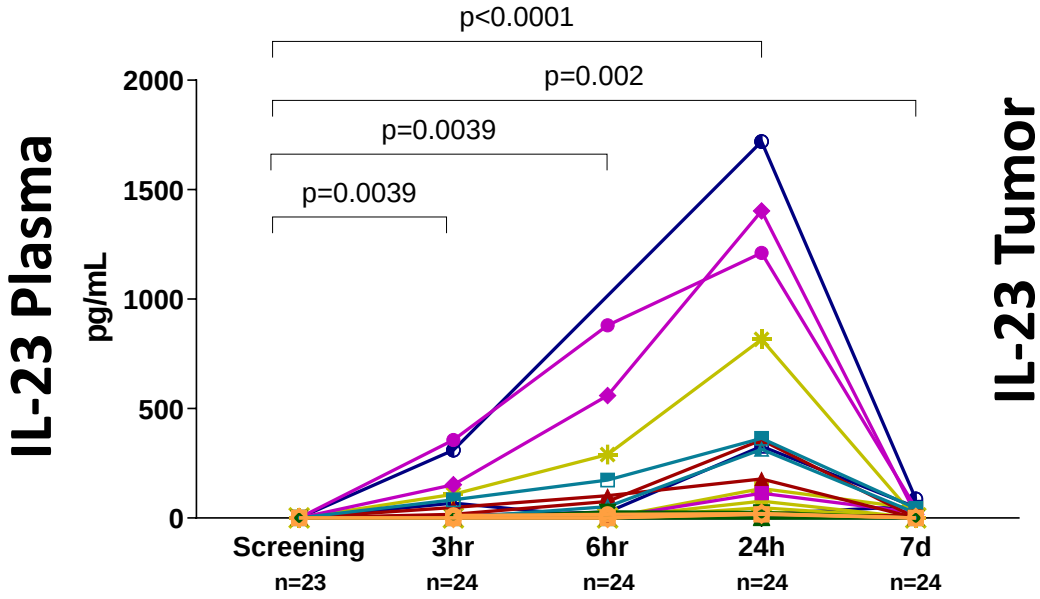
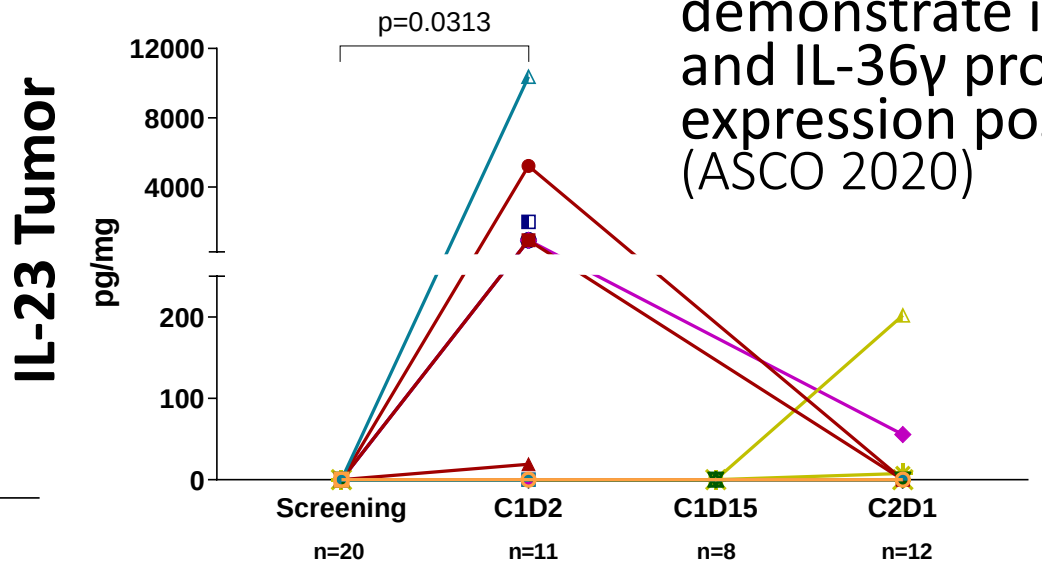
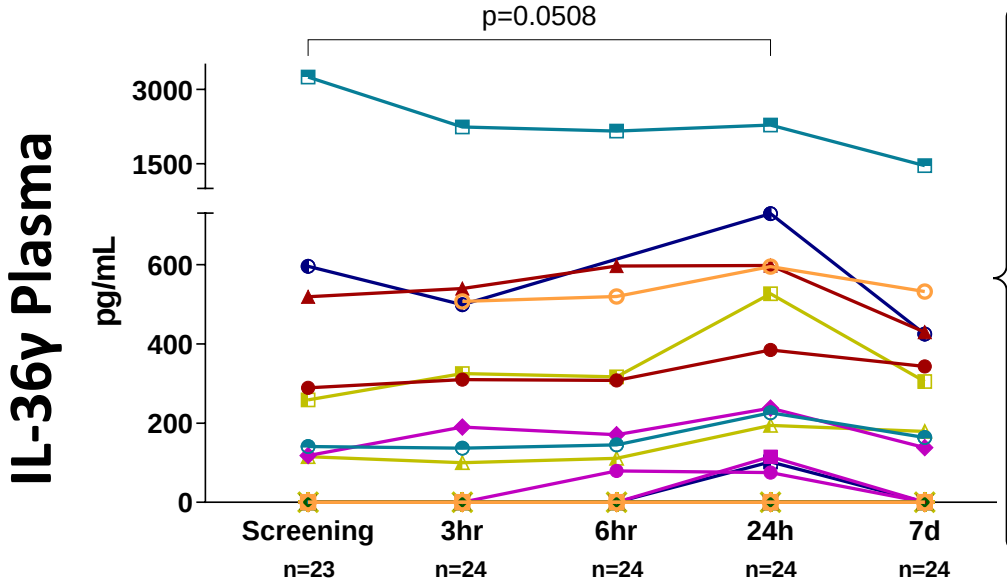
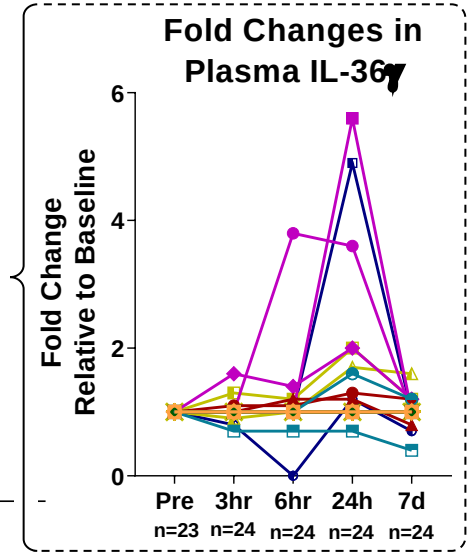


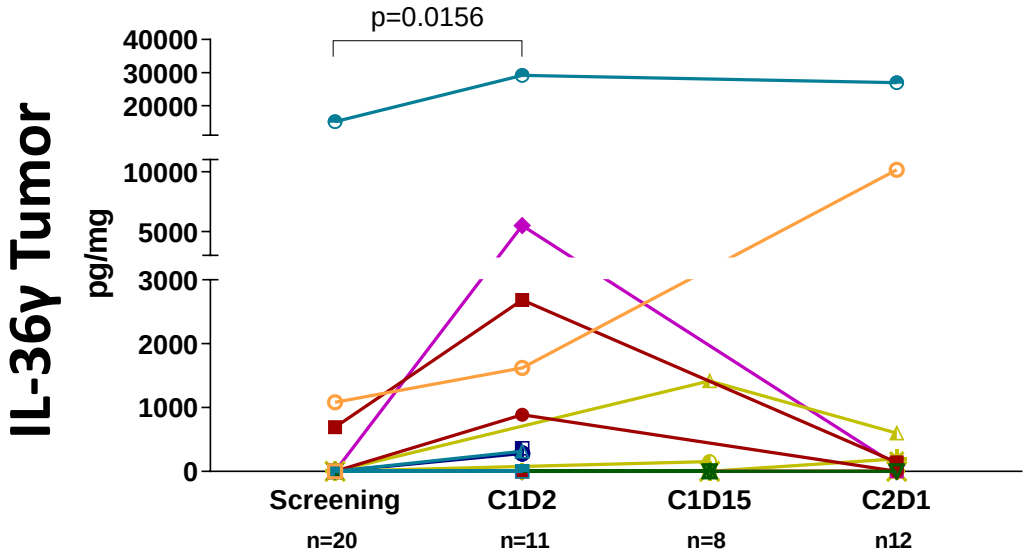
Analyses of tumor and plasma biomarkers demonstrate increased IL-23 and IL-36γ protein expression post-treatment (ASCO 2020)











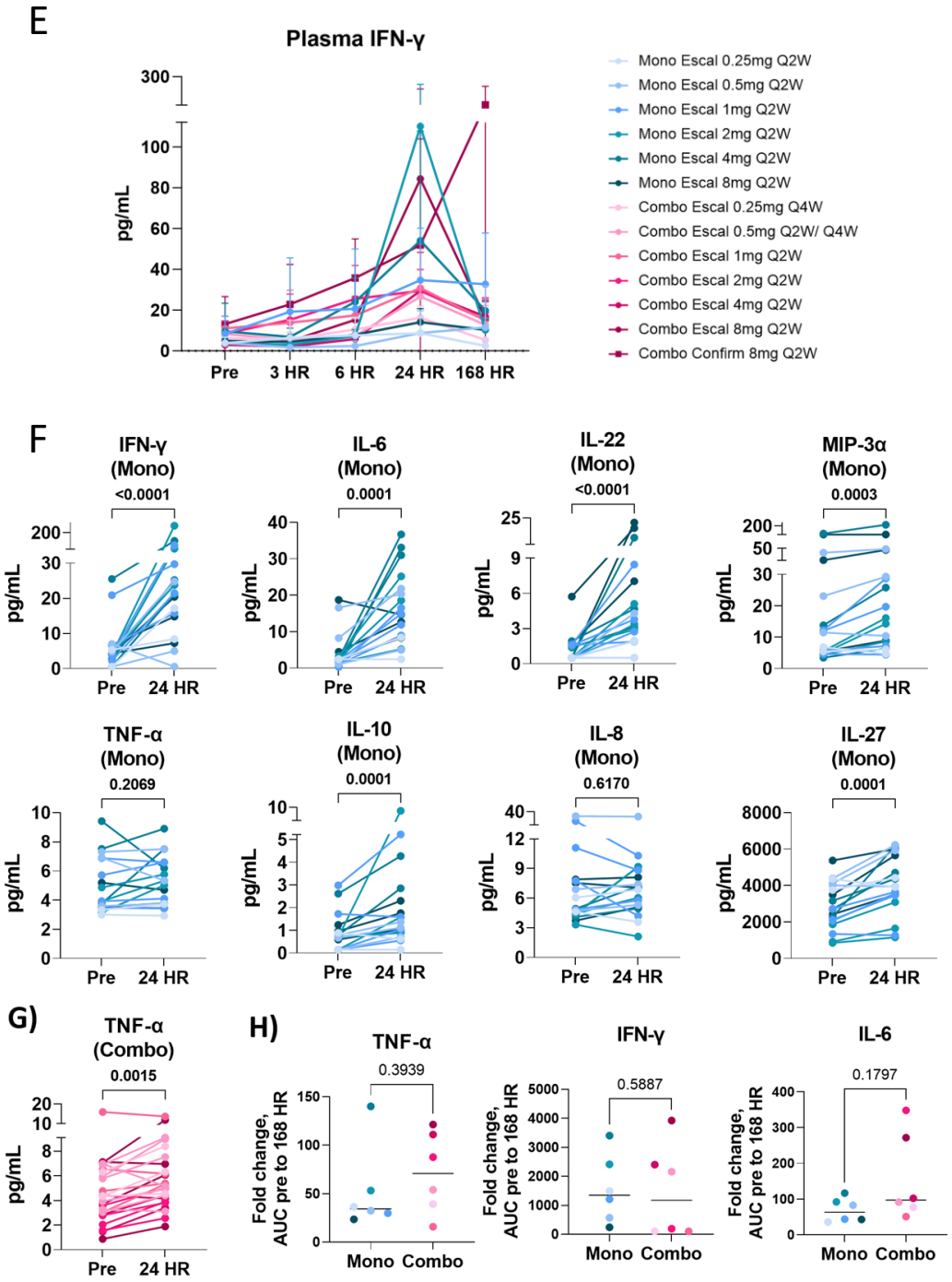
Expression of systemic cytokines with treatment

- Increases in plasma IFN-γ levels relative to baseline were observed at 3, 6, 24, and 168 hours post- first dose, with peak expression at 24 hours (samples averaged per dose and treatment groups; Fig E)

- Significantly increased levels of several other pro-inflammatory cytokines, including IL-6, IL-22, MIP-3α, IL-10, and IL-27 observed in patients on mRNA-2752 monotherapy treatment (Fig F)

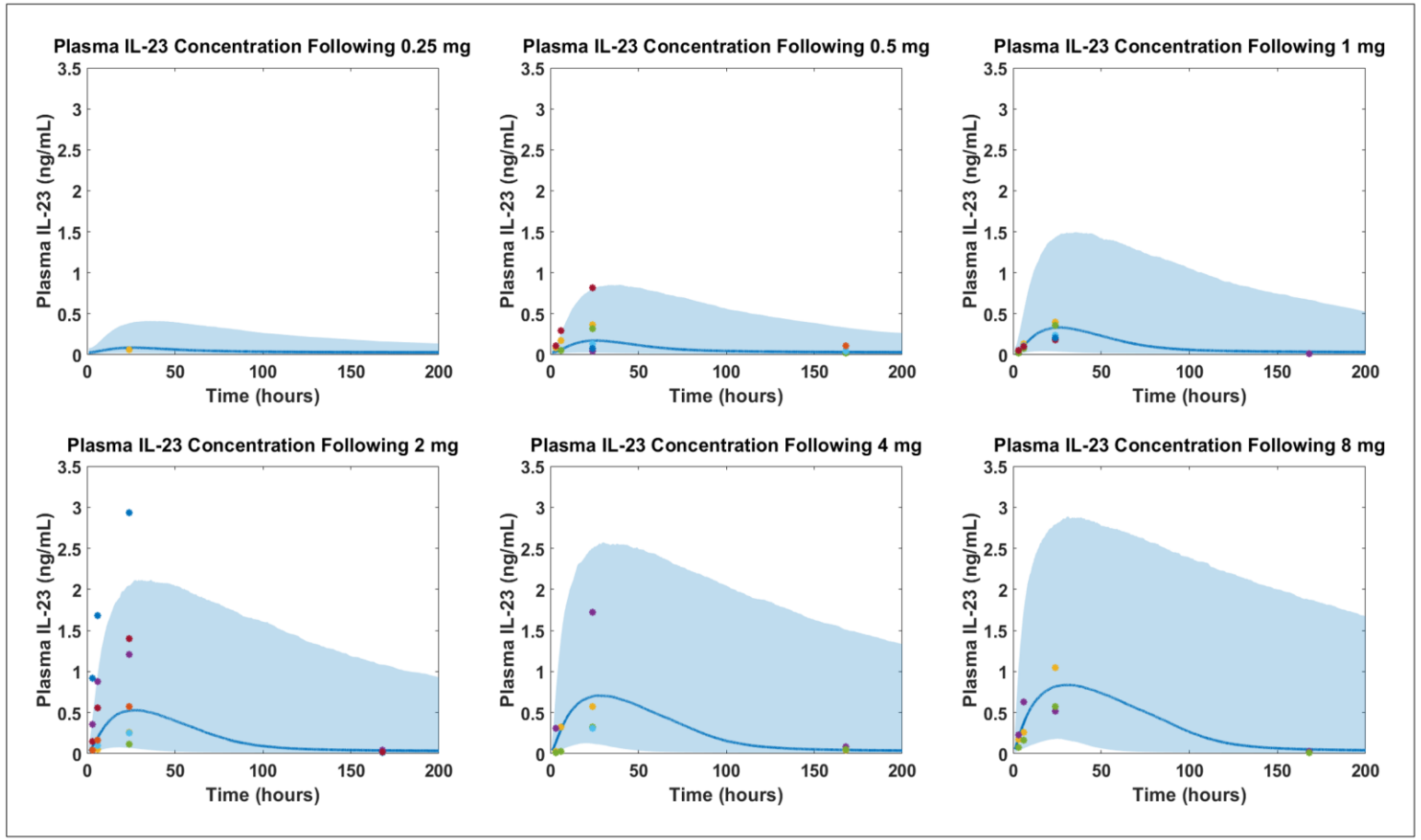
- Trend toward increased TNF-α levels at 24 hours post-dose with monotherapy, and significant increase observed in combination cohort at this timepoint (Fig G)

- While some cytokines trended toward increased levels with combination relative to monotherapy treatment, when overall measurements (via Area Under the Curve for baseline through 168 hour) were assessed, differences were not significantly different (all p>0.05), suggesting that mRNA-2752 is a key driver in modulating systemic cytokine levels (Fig H)



Pharmacokinetic-Pharmacodynamic Modeling

- Shown are the plasma IL-23 concentrations at all dose levels evaluated; shaded regions indicate 90% prediction intervals
- Median IL-23 plasma levels remain below 1ng/mL at dose ranges up to 8mg, supporting the therapeutic goal of Itu therapy to limit systemic exposure and toxicity, thereby increasing potency
- Model simulations of Q2W dosing vs. QW dosing suggest that increasing dose density may have a greater effect on IL-23 levels than increasing the dose
- This is being further explored in a cohort of melanoma patients in the neoadjuvant setting

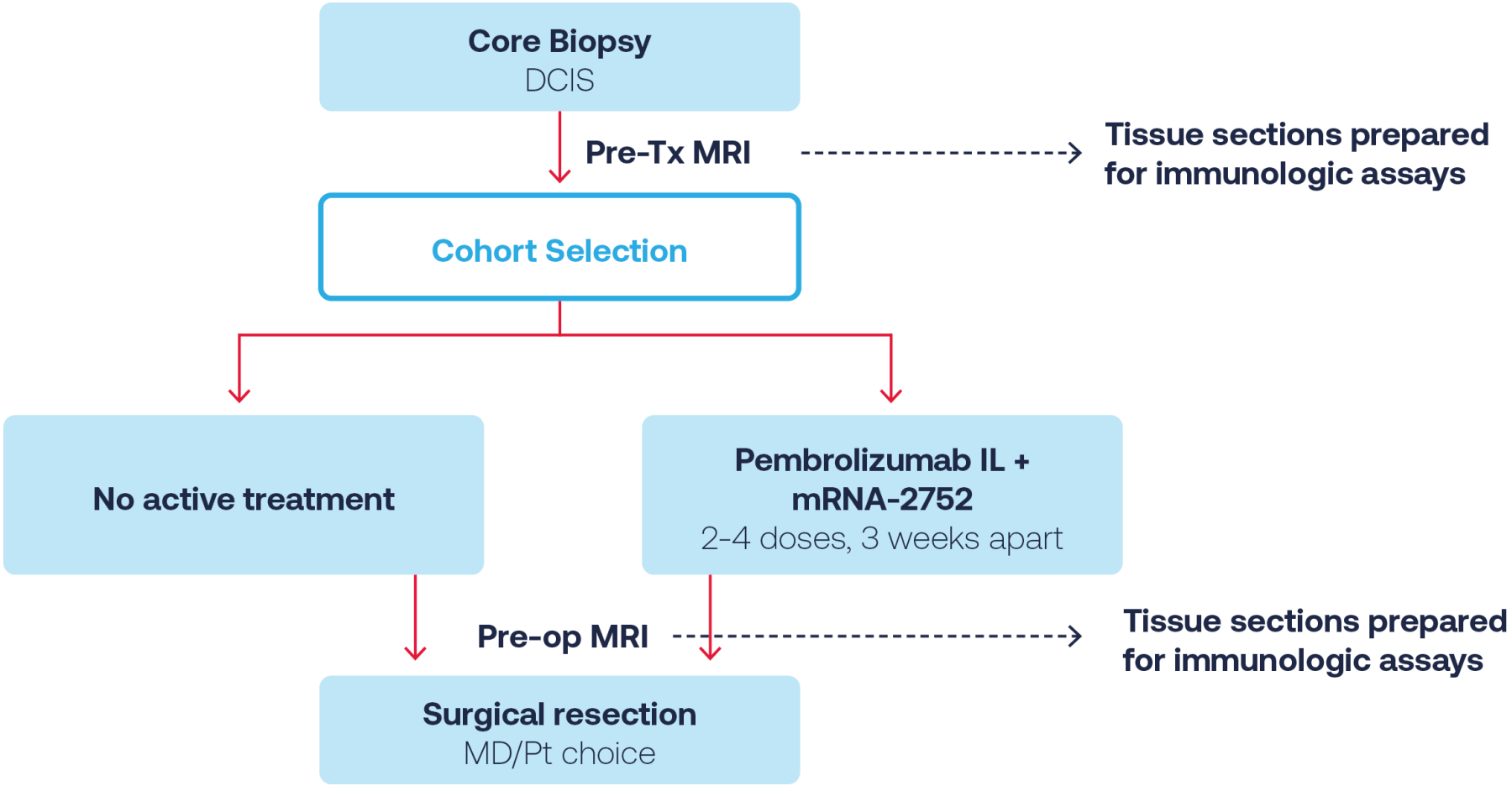


Model fit of IL-23 protein concentrations in plasma from mono and combo doses of 0.25mg to 8mg delivered by intra-tumoral injection.
Shaded regions: 90% prediction intervals. Solid dark lines: medians. Dots relate to individual patient data, with each patient within a plot defined by one color. Prediction intervals are defined by 3000 Monte Carlo simulations, including both fixed and random effects in model outputs.

Conclusions

- iTu mRNA-2752 given as monotherapy and in combination with durvalumab is tolerable at all dose levels studied; the recommended dose for expansion (RDE) is up to 8mg mRNA-2752 + durvalumab
- Median IL-23 plasma levels maintained at < 1ng/mL with dose ranges up to 8mg supports the therapeutic goal of ITu therapy to limit systemic exposure and toxicity
- Administration of iTu mRNA-2752 is associated with tumor shrinkage in both injected and un-injected lesions as monotherapy and in combination with durvalumab
- Durable PRs seen in a PD-L1-low squamous-cell bladder cancer patient, and a DLBCL after progression on CAR-T
- Treatment response of the injected lesion was seen in a melanoma patient progressed on pembrolizumab and T-VEC
- Evidence of immunomodulation/ expected pharmacodynamics in the TME of both injected and un-injected lesions, in both monotherapy and combination cases, as indicated by increases in proliferating (activated) T cells, PD-L1 levels (marker of interferon signaling), and T cell-inflamed (GEP) and DC transcriptional signature score, with greatest changes observed in patients with clinical benefit
- Pro-inflammatory cytokines, including IFN-γ, are predominantly transiently elevated post- monotherapy treatment, peaking at 24 hours post-treatment; trend toward further elevated levels of a subset of cytokines, including TNF-α, in combination with durvalumab
- PK/PD modeling supports QW dosing which is being explored in cutaneous melanoma in the neoadjuvant setting
- Enrollment is ongoing in expansion cohorts of TNBC, urothelial carcinoma, lymphoma, and immune checkpoint inhibitor-refractory melanoma and NSCLC

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



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Forward-looking statements

This presentation contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, as amended, including regarding: clinical trials; the potential for intratumoral delivery to enable delivery of targets locally that are too toxic systemically; potential market size; and potential for mRNA to enable combination therapies personalized for individual tumors and patients. In some cases, forward-looking statements can be identified by terminology such as "may," "should," "expects," "intends," "plans," "aims," "anticipates," "believes," "estimates," "predicts," "potential," "continue," or the negative of these terms or other comparable terminology, although not all forward -looking statements contain these words. The forward-looking statements in this presentation are neither promises nor guarantees, and you should not place undue reliance on these forward-looking statements because they involve known and unknown risks, uncertainties and other factors, many of which are beyond Moderna's control and which could cause actual results to differ materially from those expressed or implied by these forward-looking statements. These risks, uncertainties and other factors include those described in Moderna's most recent Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission (SEC) and in subsequent filings made by Moderna with SEC, which are available on the SEC's website at www.sec.gov. Except as required by law, Moderna disclaims any intention or responsibility for updating or revising any forward-looking statements in this presentation in the event of new information, future developments or otherwise. These forward-looking statements are based on Moderna's current expectations and speak only as of the date referenced on the first page.