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OX40L (mRNA-2416)

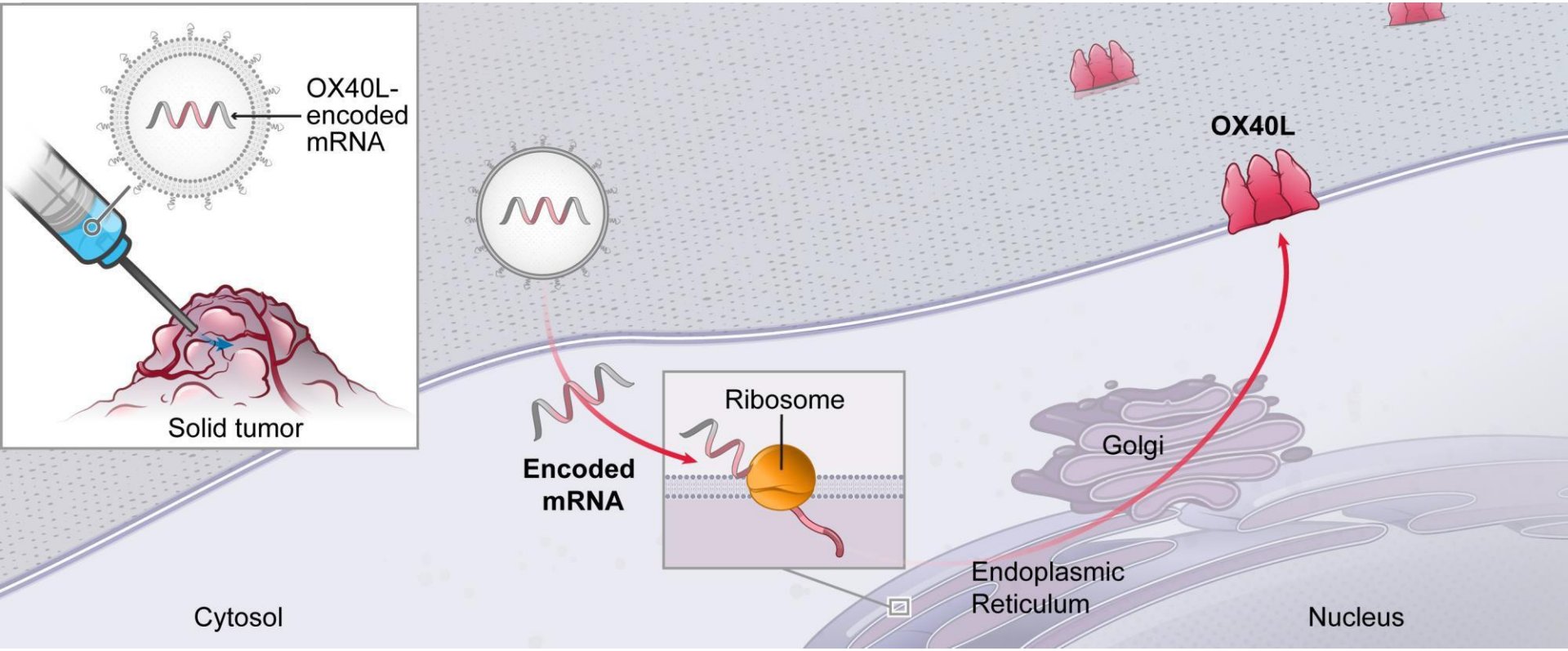
Last program update: June 10, 2020

Modality	ID #	Program *Indication*	Preclinical development	Phase 1	Phase 2	Phase 3 and commercial	Moderna rights
Intratumoral immuno-oncology	**mRNA-2416**	OX40L *Solid tumors/lymphoma* *Advanced ovarian cancer*	Solid tumors/ lymphoma	Ovarian			Worldwide
	mRNA-2752	OX40L/IL-23/IL-36γ (triplet) *Solid tumors/lymphoma*					Worldwide
	MEDI1191	IL-12 *Solid tumors*					50-50 U.S. profit sharing; AZ to pay royalties on ex-U.S. sales

mRNA encoding OX40L (mRNA-2416)

First program in the intratumoral immuno-oncology modality

- mRNA-2416 encodes for wild-type OX40L, which is a membrane protein that cannot be manufactured by recombinant technologies
- OX40L is a potent T cell co-stimulator, which promotes T cell proliferation and enhanced survival in the presence of a recognized antigen



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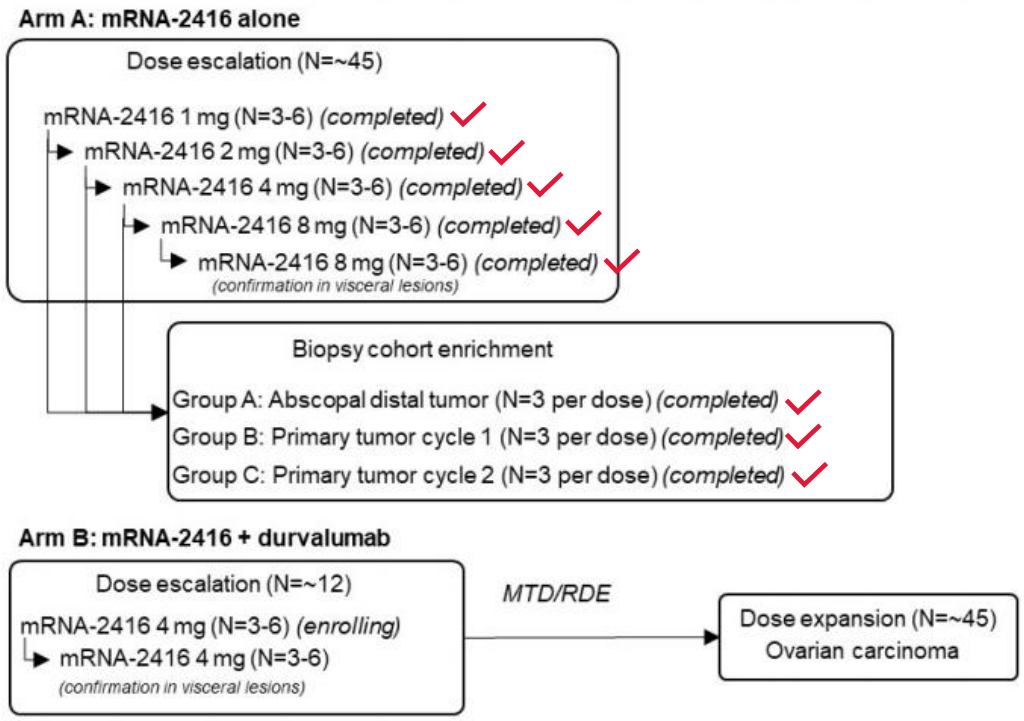
Phase 1 combination with durvalumab ongoing

Key Objectives

- Evaluate safety and tolerability of mRNA-2416 administered intratumorally
- Define the maximum tolerated dose and recommended dose for expansion
- Other endpoints include pharmacokinetic analyses as well as assessment of biomarkers of immunological response in tumor



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Data presented at AACR 2020

- 39 patients evaluated for safety and efficacy
- Overall mRNA-2416 monotherapy has been tolerable at all dose levels with no DLTs reported and majority of related AE's being grade 1 or grade 2

Related Adverse Events*		
	Arm A (monotherapy)	
	Grade 2	Grade 3
Back Pain	-	1
Chills	2	-
Decreased Appetite	2	-
Fatigue	7	1
Flushing	3	-
Hypersensitivity	2	-
Influenza Like Illness	-	1
Injection Related Reaction	5	1
Injection Site Pain	3	-
Injection Site Reaction	2	-
Myalgia	-	1
Nausea	1	1
Skin Ulcer	-	1

Responses in patients (n=39)	
	Arm A (monotherapy)
Best Overall Response	
Complete Response (CR)	-
Partial Response (PR)	-
Stable Disease (SD)	14
Progressive Disease (PD)	15

AEs: ≥ 2 patients reporting treatment-related grade 2 events
AEs: ≥ 1 patient reporting treatment-related grade 3 events
No mRNA-2416 related grade 4/5 AEs were reported
* Related AEs of at least grade 2 highest grade reported once per patient

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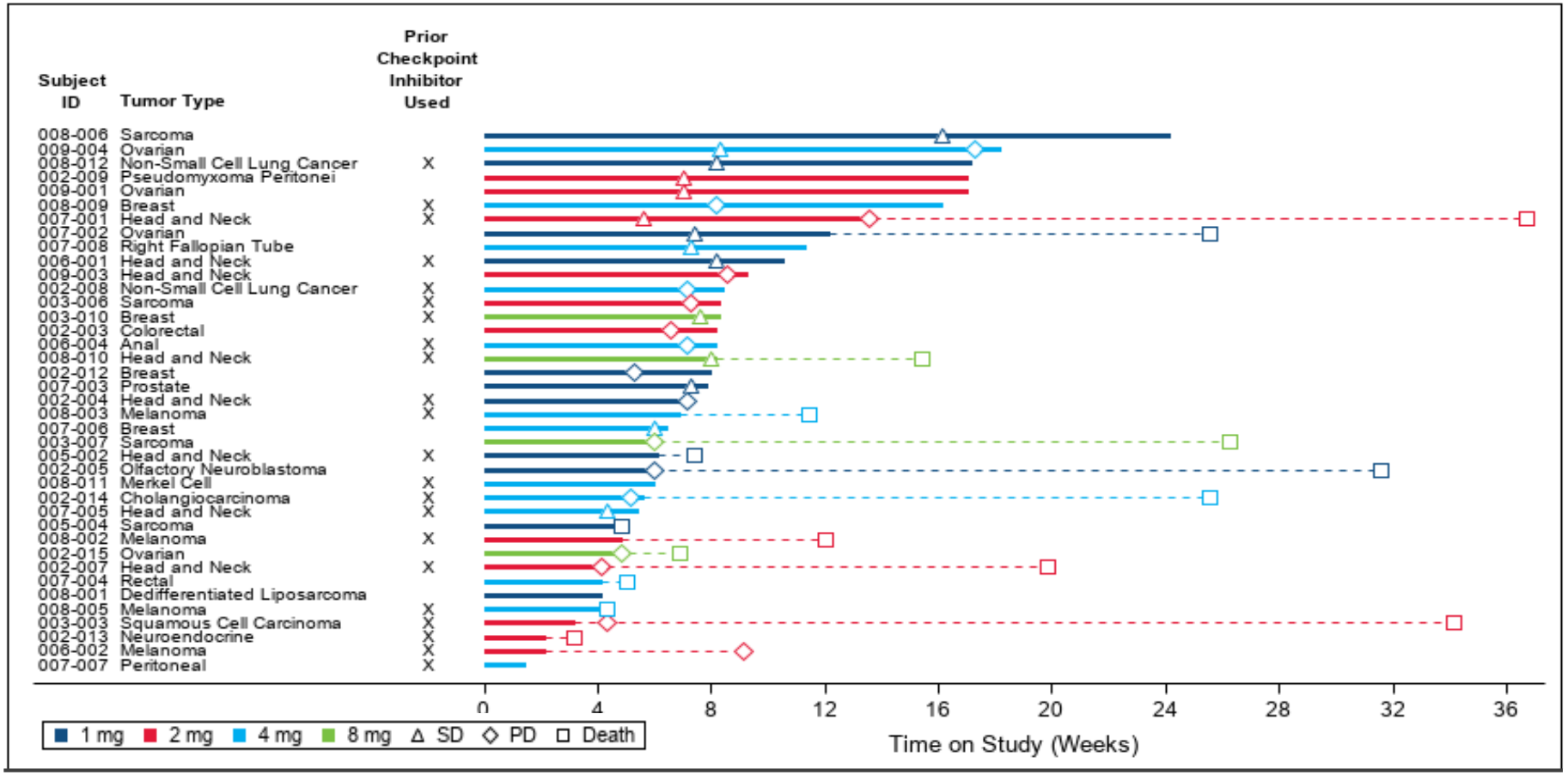
mRNA-2416-P101 Swimmer plot: ARM A monotherapy per RECIST 1.1



- 14/39 had stable disease (SD), of these patients 6 had SD for ≥14 weeks
- 4/6 ovarian patients on study had SD; 1 patient with sarcoma on drug for entire study (24 weeks)

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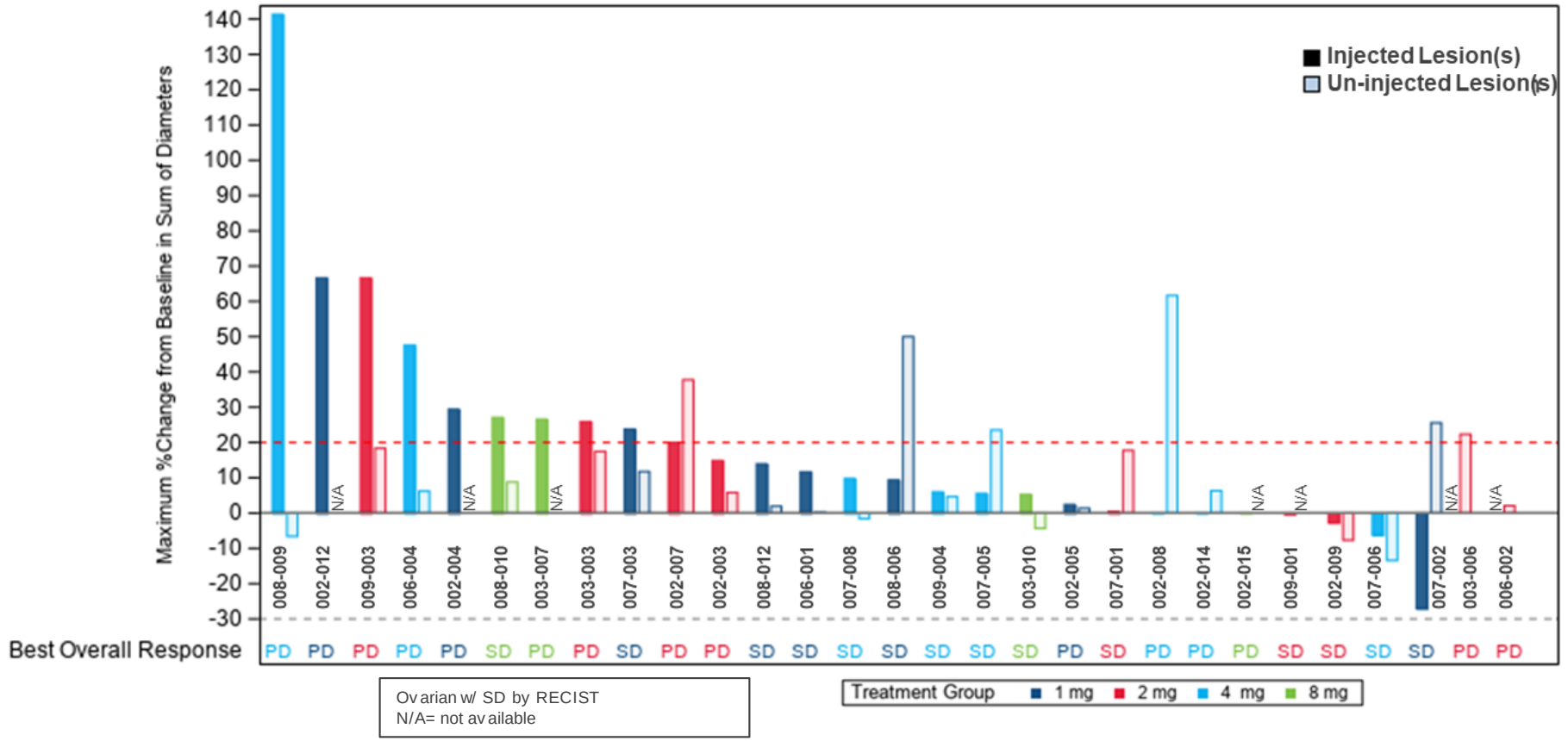
Data presented at AACR 2020

mRNA-2416-P101 Waterfall of BOR (RECIST) by Lesion Injection Status



- 14 patients with best overall response of stable disease by RECIST
- 4 patients with tumor shrinkage in injected lesions
- 5 patients overall had reduction in un-injected lesions
- Overall 2 patients had tumor shrinkage in both injected and un-injected lesions, 2 patients had tumor shrinkage in their injected lesions only (Ovarian), while 3 patients had tumor shrinkage in their un-injected lesions only

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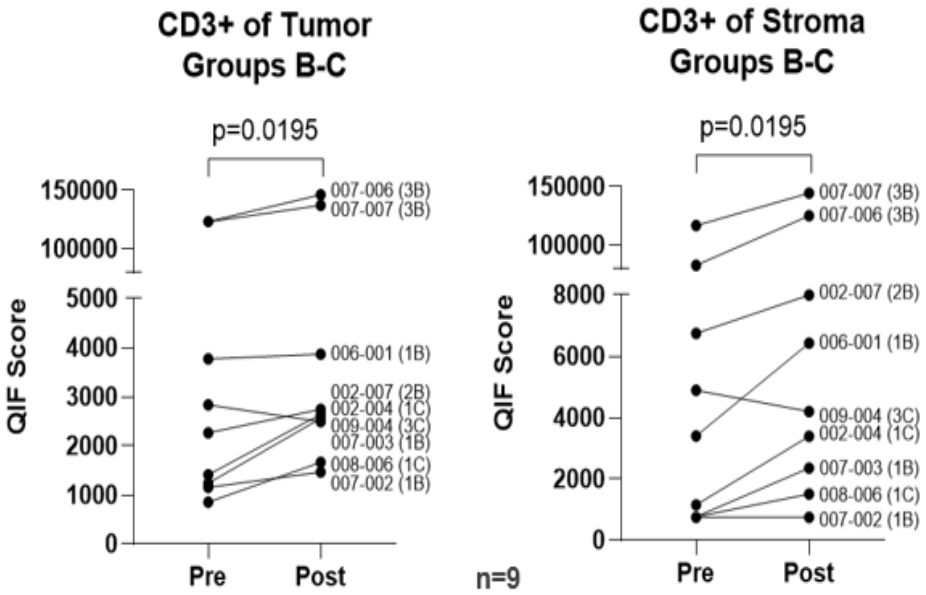
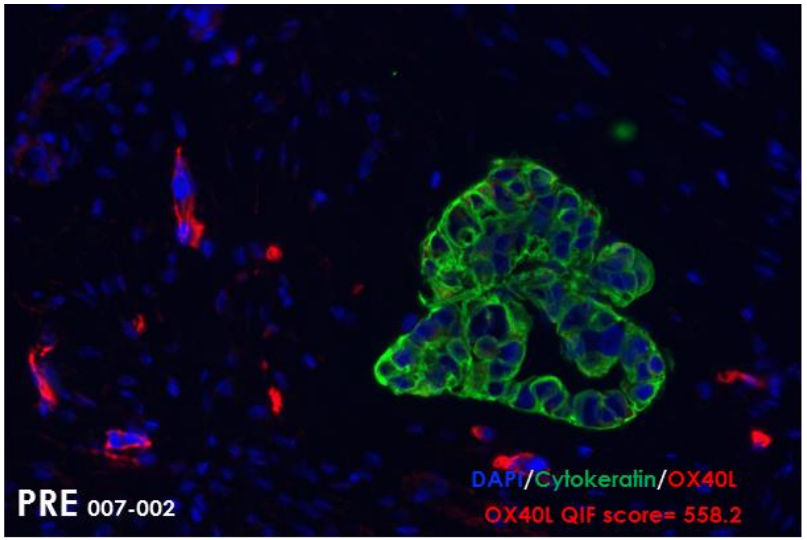
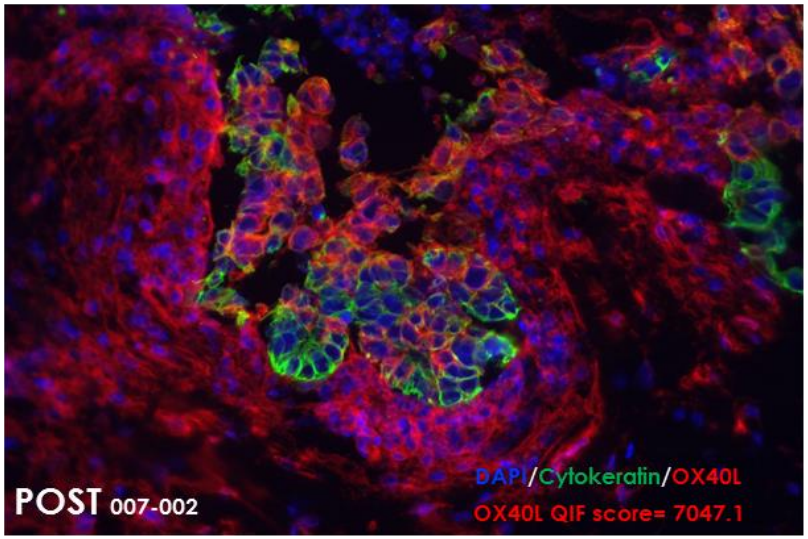
Protein expression by mQIF of OX40L & T cell scores post-mRNA-2416 in injected lesions

- Increased OX40L protein expression observed in the tumor microenvironment (TME) in several cases, including in an ovarian patient, with the most marked increase, as shown here
- Increased CD3+ T cells in the TME, in both tumor and stromal compartments



Data points labeled with patient ID (dose level + cohort; dose levels: 1= 1mg; 2= 2mg; 3= 4mg; cohorts: B= bx at C1D2-3; C=bx at C2D2-3)





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Conclusions from AACR 2020 presentation

- mRNA-2416 is well tolerated when given as monotherapy at all dose levels studied with no DLTs reported
  - The majority of TEAEs reported were grade 1/2, and no grade 3 TEAEs > 3%
- 14/39 patients achieved a best overall response (BOR) of stable disease (SD), of these patients 6 had SD for ≥14 weeks.
- 4/6 Ovarian Patients achieved a best overall response (BOR) of stable disease (SD) along with noted clinical observation of tumor regression in injected as well as un-injected lesions supporting further investigation of this histology
- **Patients treated with mRNA-2416 displayed increased OX40L protein and T-cell infiltration in the TME, upregulation of PD-L1 transcript, and activation of a pro-inflammatory gene expression response, while murine studies combining mRNA-2416 with PD-L1 blockade resulted in synergistic anti-tumoral efficacy**
- The observations of broad pro-inflammatory activity and beneficial changes in the TME with upregulation of PD-L1 support the evaluation of combination intratumoral mRNA-2416 with the anti-PD-L1 inhibitor durvalumab in solid tumors, which is ongoing in Part B of this study with a focus on advanced Ovarian carcinoma

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