**OX40L (mRNA-2416)**

*Last program update: May 6, 2021*

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

Intratumoral immunology
mRNA-2416 Encodes OX40L and is Injected Directly into a Tumor

OX40L:
- Homotrimeric protein normally expressed on professional antigen presenting cells (APCs)
- T cell co-stimulator which promotes effector T cell proliferation and enhanced survival in the presence of a recognized antigen
- Can inhibit suppressive activity of T-regs

• When mRNA-2416 is delivered into a tumor, cells in the tumor are directed to express OX40L protein in its native membrane-bound form, which in turn, may lead to a stronger T cell attack against the tumor and promote abscopal effects
Preclinical models demonstrate synergistic effect of combination OX40L and aPD-L1

MC38

- mOX40L single dose at 6.25 µg intratumorally (MC38-S) or 0.5 mg/kg intraperitoneally (ID8), on day 11 or 15 post tumor implantation, respectively
- αPD-L1 at 10 mg/kg, twice per week
- Control: non-translating mRNA. Log-rank test (Mantel-Cox), all animals included

ID8

- mOX40L single dose at 6.25 µg intratumorally (MC38-S) or 0.5 mg/kg intraperitoneally (ID8), on day 11 or 15 post tumor implantation, respectively
- αPD-L1 at 10 mg/kg, twice per week
- Control: non-translating mRNA. Log-rank test (Mantel-Cox), all animals included

Anti-tumor efficacy in MC38-S and ID8 mouse syngeneic colon and ovarian carcinoma tumor models
OX40L (mRNA-2416)
Phase 1/2 combination with durvalumab fully enrolled; Phase 2 dose expansion has dosed first patients

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

Dosing
Arm A:
• mRNA-2416 up to 8 mg iTu q2W x 2, then up to qmonthly x 5

Arm B and Dose expansion arm:
• mRNA-2416 up to 8 mg iTu q2W x 2, then up to qmonthly x 5
• Durvalumab 1500 mg IV qmonthly x 6
OX40L (mRNA-2416)
Data presented at AACR 2020

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

### Related Adverse Events*

<table>
<thead>
<tr>
<th>Arm A (monotherapy)</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back Pain</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Flushing</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Influenza Like Illness</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Injection Related Reaction</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Injection Site Pain</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Injection Site Reaction</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Myalgia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Skin Ulcer</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

### Responses in patients (n=39)

<table>
<thead>
<tr>
<th>Arm A (monotherapy)</th>
<th>Best Overall Response</th>
<th>Complete Response (CR)</th>
<th>Partial Response (PR)</th>
<th>Stable Disease (SD)</th>
<th>Progressive Disease (PD)</th>
</tr>
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</tbody>
</table>

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
OX40L (mRNA-2416)
Data presented at AACR 2020

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)
OX40L (mRNA-2416)
Data presented at AACR 2020

- 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
Phase 1 dosing & biopsy collection schedule and biomarker readouts from arm A (monotherapy mRNA-2416)

Biomarker Readouts from FFPE Biopsies
- Multiplexed Quantitative Immunofluorescence (QIF)
  - OX40L protein expression
  - T cell abundance, activation
- Whole transcriptome (RNAseq) for assessing baseline and post-treatment inflammatory states
  - PD-L1 / PD-1 axis
  - T cell-inflamed/activation signatures

FFPE = formalin-fixed, paraffin embedded
Protein expression by QIF 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, 007-002 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)

Slide 9
Increased PD-L1 ranked score in 5/9 patients post-treatment

- 5 of 9 Group B/C cases (injected lesions) with increased quartile ranking of PD-L1
  - PD-L1 at transcript level reported to have high positive predictive value for response to anti-PD-1/PD-L1 Abs (Conroy et al., 2019)

<table>
<thead>
<tr>
<th>Patient ID (dose level, cohort, tumor type)</th>
<th>PD-L1 (TPM)</th>
<th>Fold change</th>
<th>Quartile (TCGA)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>008-006 (1C, SARC)</td>
<td>1.80</td>
<td>45.70</td>
<td>25.42</td>
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<tr>
<td>007-002 (1B, OVCA)</td>
<td>7.68</td>
<td>37.81</td>
<td>4.92</td>
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<tr>
<td>007-006 (3B, BRCA)</td>
<td>4.92</td>
<td>17.26</td>
<td>3.51</td>
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<tr>
<td>002-004 (1C, HNSCC)</td>
<td>2.41</td>
<td>7.11</td>
<td>2.95</td>
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<td>007-007 (3B, PC)</td>
<td>30.99</td>
<td>79.98</td>
<td>2.58</td>
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<tr>
<td>007-003 (1B, PRAD)</td>
<td>2.98</td>
<td>3.81</td>
<td>1.28</td>
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<tr>
<td>009-004 (3C, OVCA)</td>
<td>16.82</td>
<td>21.38</td>
<td>1.27</td>
</tr>
<tr>
<td>002-007 (2B, HNSCC)</td>
<td>10.54</td>
<td>11.35</td>
<td>1.08</td>
</tr>
<tr>
<td>006-001 (1B, HNSCC)</td>
<td>36.10</td>
<td>35.32</td>
<td>0.98</td>
</tr>
</tbody>
</table>

Quartile rankings defined using PD-L1 transcript levels across TCGA dataset (RNAseq data, 9654 samples across 33 tumor types)

TPM = Transcripts Per Million
Increased T cell-inflamed GEP ranked score in 6/9 patients after mRNA-2416 treatment

- 6 of 9 Group B/C cases (injected lesions) with increased quartile ranking of T-cell inflamed GEP scores
  - Cases without increased GEP ranking post-treatment had elevated GEP scores at baseline (e.g., 007-007 and 006-001)

**GEP score:**
- GEP = Gene Expression Profile; 18-gene signature; predictive of pembro response (Ayers et al., 2017; Cristescu et al., 2018)
- GEP Quartile rankings determined across TCGA
OX40L (mRNA-2416)

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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