## OX40L/IL-23/IL-36γ (mRNA-2752)

_Last program update: September 17, 2020_

<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>
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<tbody>
<tr>
<td>Intratumoral immunology</td>
<td>mRNA-2416</td>
<td>OX40L</td>
<td>Solid tumors/lymphoma</td>
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<td>Ovarian</td>
<td>Worldwide</td>
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<td></td>
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<td>Solid tumors/lymphoma Advanced ovarian cancer</td>
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<tr>
<td></td>
<td>mRNA-2752</td>
<td>OX40L/IL-23/IL-36γ (triplet)</td>
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<td>Worldwide</td>
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<td>MEDI1191</td>
<td>IL-12</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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</tbody>
</table>
**Immune modulation with OX40L, IL-23, IL-36γ**

**OX40L**
- Transmembrane T cell co-stimulatory protein
- Promotes Th1, Th2, Th9; suppresses Treg
- Enhances expansion and survival of CD4 and CD8 T cells → promotes memory
- Preclinical monotherapy efficacy established and reported

**IL-23**
- Proinflammatory cytokine of the IL-12 family
- Expands and maintains Th17
- Acts on antigen experienced T cells
- Reported to prime DC
- Activates other cells that bridge innate to adaptive immunity (NKT, ILCs, γδ T cells)

**IL-36γ**
- Proinflammatory cytokine of the IL-1 family
- Acts on DCs to promote maturation and ↑ cytokine/chemokines
- Enhances T cell proliferation, Th1, Th9 differentiation
- Reported to preclinically enhance anti-cancer immunity
- Clear role in human barrier immunity and inflammatory disease

**Diagram**
- Dendritic T Cell
- Cancer Cell
- OX40L (molecule)
- IL-23 (molecule)
- IL-36γ (molecule)
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
**OX40L/IL-23/IL-36γ**

Preclinical data – combination of 3 targets demonstrates synergistic effects

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**Species:** Mouse

**Species:** Mouse

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**Cancer**

Durable anticancer immunity from intratumoral administration of IL-23, IL-36γ, and OX40L mRNAs

- Tumor volumes of both the treated and untreated tumors. Mice carrying bilateral MC38-S tumors received mRNA injected into the right flank tumor only.

- Local triplet mRNA treatment has global effects including on distal untreated tumors.

- 100% (n=20) complete responders with mouse OX40L/IL-23/IL-36γ in MC38 dual flank syngeneic mouse model study.

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1. Durable anticancer immunity from intratumoral administration of IL-12, IL-36γ and OX40L mRNA’s; Science Translation Medicine; Hewitt et al., 2019.

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Combination treatment of αPD-L1 Ab + OX40L/IL-23/IL-36γ mRNA iTu is synergistic in immunologically barren B16F10 model

- OX40L/IL-23/IL-36γ mRNA given iTu day 1 + mouse αPD-L1 Ab IP 10 mg/kg twice weekly x 2

- iTu OX40L/IL-23/IL-36γ mRNA-monotherapy can achieve CRs even in models that are completely refractory to systemic checkpoint inhibitor treatment
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
- Intended to assess: (1) Anti-tumor activity, (2) Protein expression in tumors and (3) Pharmacokinetics

Dosing

- mRNA-2752 Q2W for Cycle 1 and Q4W for Cycles 2-6 and durvalumab 1500 mg Q4W

**Arm A: mRNA-2752 alone**

- Dose escalation (N=~20)
  - Accessible solid tumors and lymphomas
    - mRNA-2752 0.25 mg
    - mRNA-2752 0.5 mg
    - mRNA-2752 1 mg
    - mRNA-2752 2 mg
    - mRNA-2752 4 mg
    - mRNA-2752 8 mg

**Arm B: mRNA-2752 + durvalumab**

- Dose escalation (N=~20)
  - Accessible solid tumors and lymphomas
    - mRNA-2752 0.25 mg + CPI
    - mRNA-2752 0.5 mg + CPI
    - mRNA-2752 1 mg + CPI
    - mRNA-2752 2 mg + CPI
    - mRNA-2752 4 mg + CPI
    - mRNA-2752 8 mg + CPI

**MTD/RDE**

- Ongoing

Dose confirmation (N=~3)
- Visceral Solid Tumors and Lymphomas

Dose expansion (N=~12 for each)
- Triple-negative breast cancer
- Head and neck squamous cell carcinoma
- Non-Hodgkin lymphoma
- 1L Urothelial (PD-L1 negative)
- 2L+ Urothelial (PD-L1 naïve)
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Data presented at ASCO 2020

- At ASCO 2020, we present findings from a first-in-human study of iTu mRNA-2752 in solid tumor patients as monotherapy or in combination with durvalumab. As of April 8, 2020, 29 patients were evaluable for safety and 23 patients evaluable for efficacy.

### Related Adverse Events*

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B</th>
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<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>6</td>
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<tr>
<td>Injection site pain</td>
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<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
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<td>1&quot;</td>
</tr>
<tr>
<td>Chills</td>
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<td>1&quot;</td>
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<tr>
<td>Fatigue</td>
<td>3</td>
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<tr>
<td>Alanine aminotransferase increased</td>
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<td>-</td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
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<td>-</td>
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<tr>
<td>Back pain</td>
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<td>-</td>
</tr>
<tr>
<td>Rash maculo-popular</td>
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<td>-</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>-</td>
<td>1&quot;</td>
</tr>
<tr>
<td>Malaise</td>
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### Responses in evaluable patients per RECIST 1.1

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Arm A (n=15)</th>
<th>Arm B (N=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Partial Response</td>
<td>-</td>
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</tr>
<tr>
<td>Stable Disease (SD)</td>
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<td>4</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

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

Data presented at ASCO 2020

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

Data presented at ASCO 2020

mRNA-2752-P101 Waterfall Plot of Maximum %Change from Baseline in Sum of Diameters of Target Lesions Based on Investigator Assessment per RECIST 1.1

Tumor shrinkage in both injected and un-injected target lesions in both monotherapy and in combination
Phase 1 dosing & biopsy collection schedule from arms A and B (mRNA-2752 +/- durvalumab)

**Dose Escalation/Confirmation**

**Arm A: mRNA-2752 monotherapy**

- Collection of newly obtained tumor samples during screening and at 1 other time point

**Arm B: mRNA-2752 + Durvalumab Combo**

- Collection of newly obtained tumor samples during screening and at 1 other time point
PD-L1 expression is increased after mRNA-2752 treatment

- %PD-L1+ in tumor-associated immune cells is shown at baseline versus C1D2 (Arm A monotherapy), C1D15 (Arm B combination), and C2D1 (Arms A and B).

- Elevated PD-L1 and T cell populations post-treatment in patient with PR. Representative pre- and post- treatment biopsies from squamous-cell bladder cancer patient with partial response by RECIST 1.1.
Elevated IL-23, IL-36γ, IFN-γ and TNF-α after treatment with mRNA-2572 +/- durvalumab

A) IL-23 and IL-36γ introduced cytokines are increased after treatment

B) Levels of cytokines downstream of IL-23 and IL-36γ are also elevated

C) Treatment leads to enhanced expression of IFNγ and TNFα

Plasma and/or tissue protein levels from (A) introduced IL-23 and IL-36γ, (B) their respective downstream cytokines IL-22 and IL-6, and (C) the anti-tumor cytokines IFNγ and TNFα were assessed at baseline and post-treatment. * Greatest plasma IL-23 levels were measured from samples at the highest dose level (4 mg) tested thus far and were transiently within autoimmune disease ranges (e.g. psoriasis, rheumatoid arthritis), subsiding by day 8. Due to variability in plasma IL-36γ levels across samples, fold changes from baseline were calculated; highest magnitude of changes were seen in the highest dose levels assessed (2 and 4 mg). Significant increase and similar kinetics post-treatment were observed in plasma MIP3α, IL-27, IL-10, IL-8; plasma IL-2 did not exceed 4 pg/mL at evaluated doses (not shown).
OX40L/IL-23/IL-36γ (Triplet) (mRNA-2752)

Conclusions from ASCO 2020 presentation

- iTu mRNA-2752 given as monotherapy and in combination with durvalumab is tolerable at all dose levels studied with no DLTs reported and the majority of related AE's being grade 1 or 2

- Administration of iTu mRNA-2752 is associated with tumor shrinkage in both injected and non-injected lesions in both monotherapy and in combination, with 1 PR in a PD-L1 low squamous-cell bladder patient

- Increased IL-23 and IL-36γ protein expression after 6-24 hours in tumor and/or plasma

- Analyses of tumor and plasma biomarkers suggest a sustained immunomodulatory effect of treatment that includes elevated PD-L1, IFN-γ, TNF-α and levels

- Plasma IFN-γ and TNF-α levels were well below what has been suggested as clinically toxic levels

- These data support the ongoing testing of the mRNA-2752/durvalumab combination in Arm B of the Phase I study
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