MDNA11:2020 ASCO PRESENTATION
And Supplementary Results
Evolutionary Cytokines. Revolutionary Medicines.
In Vitro and In Vivo Characteristics of MDNA11: A Long-Acting “Beta-only” IL-2 Superkine in Syngeneic Mice Tumor Models and Non-human Primates

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Use of IL-2 (Proleukin) to treat cancer is limited by a short half-life, undesirable activation of Tregs, and adverse side effects.

MDNA11 is an IL-2 Superkine with the following features:

- Core mutations to increase affinity to CD122 (expressed by CD8+ T and NK cells) and diminish binding to CD25 (expressed by Tregs)
  - Designed to enhance therapeutic efficacy.

- Extended half-life by fusion to an albumin scaffold, known to also allow accumulation at tumor sites.
  - Designed to overcome the need for frequent administration at a high dose.
MDNA11: Enhanced Affinity for CD122; Does Not Bind CD25

**CD122 Binding**

**rhIL-2**  
($K_D = 210$ nM)

**MDNA11**  
($K_D = 6.6$ nM)

**CD25 Binding**

**rhIL-2**  
($K_D = 24$ nM)

**MDNA11**  
No Binding

Binding/affinity measured by BLI OCTET
Signaling in Naïve CD8⁺ T Cell  

<table>
<thead>
<tr>
<th>Naïve CD8⁺ T cells (EC₅₀, pM)</th>
<th>Treg (EC₅₀, pM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhIL-2</td>
<td>3390</td>
</tr>
<tr>
<td>MDNA11</td>
<td>460</td>
</tr>
</tbody>
</table>

pSTAT5 signaling in human PBMC. PBMC treated with increasing doses of rhIL-2 or MDNA11; pSTAT5 signals in different immune populations detected by flow cytometry.
**MDNA11 Has Longer Half-Life than MDNA19 In Mice and Non-human Primates**

<table>
<thead>
<tr>
<th></th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; in Mice (h)</th>
<th>T&lt;sub&gt;1/2&lt;/sub&gt; in NHP (h)</th>
<th>Cmax in NHP (ng/mL)</th>
<th>AUC in NHP (h.ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rhIL-2</td>
<td>0.28</td>
<td>1.4&lt;sup&gt;(a)&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDNA11</td>
<td>6.83</td>
<td>12.8 – 24.7&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>3,446&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>76,297&lt;sup&gt;(c)&lt;/sup&gt;</td>
</tr>
<tr>
<td>MDNA19</td>
<td>6.08</td>
<td>7.3 – 9.1&lt;sup&gt;(b)&lt;/sup&gt;</td>
<td>7,091&lt;sup&gt;(c)&lt;/sup&gt;</td>
<td>70,807&lt;sup&gt;(c)&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

(a) Measured in human  
(b) Data from repeat dosing (14-days apart) over the range of 0.01-0.6 mg/kg  
(c) Data based on first dosing at 0.3 mg/kg
MDNA11 Exhibits Superior Therapeutic Efficacy As Monotherapy Compared to MDNA19 in CT26 Tumor Model

- Mice implanted SQ with CT26 tumor cells and treatment initiated on Day 14
- Average tumor size at initiation of dosing = 90 mm³

<table>
<thead>
<tr>
<th>Dose</th>
<th>Tumor Volume (mm³)</th>
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<tr>
<td>Control</td>
<td></td>
</tr>
<tr>
<td>MDNA11 (5 mg/kg; once weekly for 2 weeks by IP)</td>
<td></td>
</tr>
<tr>
<td>MDNA19 (5 mg/kg; once weekly for 2 weeks by IP)</td>
<td></td>
</tr>
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</table>
MDNA11 Synergizes with Anti-CTLA4 to Induce 100% CT26 Tumor Regression

- Mice implanted SQ with CT26 tumor cells and treatment initiated on Day 14
- Average tumor size at initiation of dosing = 90 mm³
- MDNA11 & MDNA19: 5 mg/kg, 1x/wk for 2wks, IP
- αCTLA4 (4F10): 100 µg, 2x/wk for 2wks, IP

Control

αCTLA4 (4F10)

MDNA11 + αCTLA4 (4F10)

MDNA19 + αCTLA4 (4F10)

CR = Complete Regression
MDNA11 Inhibits Tumor Growth and Induces A Strong Memory Response As Monotherapy & In Combination with αCTLA4 in CT26 Tumor Model

CT26 tumor (~60 mm³) bearing Balb/c mice were treated with MDNA11 (5 mg/kg 1x/week, 2 weeks) or Anti-CTLA4 (200 µg 2x/week, 2 weeks) by IP injection. Re-challenge experiment performed by implanting 2 x 10⁶ CT26 cells in opposite flank (Day 49, Day 116 and Day 165), without further treatment.
MDNA11 Has Stronger Effect On Lymphocyte Expansion Than MDNA19 In NHP

- Fold increase in lymphocytes compared to pre-treatment.
- No expansion of eosinophils, responsible for VLS.

**N = 1 per dose**
MDNA11 Induces Proliferation & Expansion of CD4^+ T, CD8^+ T and NK Cells But Not Tregs in NHP
MDNA11 Induces Durable Proliferation and Expansion of CD8⁺ T Cells in NHP
MDNA11 & MDNA19 Induce CD8 T-cell Proliferation But Not Tregs in NHP

- Adult male cynomolgus monkeys (8-12 years) received repeat dose (14 days apart) of MDNA11 or MDNA19 by slow IV bolus.
- Percentage of Ki67-positive circulating CD8 T-cells at different time points were quantified by flow cytometry.
- N = 1 per dose level.
MDNA11 Exhibits a Stronger Effect on Non-Treg CD4 T-cell Expansion than MDNA19

- Adult male cynomologus monkeys (8-12 years) received repeat dose (14 days apart) of MDNA11 or MDNA19 by slow IV bolus.
- Circulating CD4 T-cells at different time points were quantified by flow cytometry.
- Post-dose data were normalized to base-line (Day -1)
- N = 1 per dose level.
# MDNA11 and MDNA19 Compared

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<th>Phenotype/Parameter</th>
<th>Comparison</th>
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<tr>
<td>Activity in Human PBMC P-STAT5 Assay</td>
<td>MDNA11 ~ MDNA19</td>
</tr>
<tr>
<td>Receptor Selectivity Based on Affinity Studies</td>
<td>MDNA11 ~ MDNA19</td>
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<tr>
<td>Efficacy: Monotherapy in CT26 Tumor Model</td>
<td>MDNA11 &gt; MDNA19</td>
</tr>
<tr>
<td>Efficacy: Combination with Anti-CTLA4 in CT26 Tumor Model</td>
<td>MDNA11 &gt;&gt; MDNA19</td>
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<tr>
<td>Half-Life in Mice</td>
<td>MDNA11 ≥ MDNA19</td>
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<td>Half-Life in NHP</td>
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<tr>
<td>Effect on Lymphocyte Expansion in NHP</td>
<td>MDNA11 ≥ MDNA19</td>
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<tr>
<td>Effect on CD8 T-cell vs. Treg Proliferation in NHP</td>
<td>MDNA11 ~ MDNA19</td>
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<td>Effect on CD4 T-cell Expansion in NHP</td>
<td>MDNA11 ≥ MDNA19</td>
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<td>Low Immunogenicity (ADA response) in NHP</td>
<td>MDNA11 ~ MDNA19</td>
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<td>Overall Safety Profile in NHP</td>
<td>MDNA11 ~ MDNA19</td>
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</table>
Key Features of **MDNA11**:

- **Increased affinity to CD122**: no binding to CD25
- **Increased potency towards CD8\(^+\) T cells** with diminishing activity on Tregs
- Potential to **accumulate in tumor micro-environment**
- **Enhanced PK** in mice and NHP
- Potent and durable tumor control as **monotherapy with strong memory response** in mouse CT26 model; strong synergy with anti-CTLA4

In NHP:
- Induces expansion of lymphocytes and not eosinophils (associated with VLS)
- Induces durable proliferation and expansion of CD8\(^+\) T and NK cells but not Tregs
- Transient weight loss and diarrhea at higher dose (0.3 - 0.6 mg/kg).
- **Safety profile**: No cytokine storm; No ADA response; No change in liver and kidney function; No hypotension; No VLS