Intratumoral electroporation of plasmid interleukin-12: efficacy and biomarker analyses from a phase 2 study in melanoma (OMS-1100)

Daud A¹, Algazi A¹, Ashworth M¹, Buljan M¹, Takamura KT², Diep T², Pierce RH² and Bhatia S³

¹ University of California, San Francisco – San Francisco, CA
² OncoSec Medical Inc. – San Diego, CA
³ University of Washington – Seattle, WA
Background: The Immunosuppressive Tumor Microenvironment

- Lack of immune stimulatory cytokines & chemokines
- Lack of co-stimulatory molecules
- Lack of tumor antigen processing & presentation
- High engagement of immune inhibitory molecules
- Low infiltration of cytotoxic T-cells (i.e. low TILs)
- High CD4 regulatory T-cell infiltration

Modified from Monjazeb et al. Front. Oncol., 26 July 2013
Intratumoral Plasmid IL-12 Electroporation

Local Treatment, Systemic Results

• Intratumoral plasmid IL-12 (pIL-12) Electroporation (EP) leads to local IL-12 expression

• IL-12 promotes anti-tumor immune response
  – Cytotoxicity via CD8+ T-cell and NK cell activation
  – Converts myeloid-derived suppressor cells (MDSC) into immunostimulatory antigen-presenting cells (APCs)

• Phase 1 Study: Intratumoral pIL-12 EP was well-tolerated and achieve some complete responses after one treatment cycle
Phase 2 Study Design and Treatment Schedule

Primary Objective:
- Overall Response Rate by modified “skin” RECIST within 180 days (ORR = CR + PR)

Secondary Objectives
- Disease Control Rate (DCR = CR + PR + SD)
- Distant Lesion Regression
- Duration of Response (DOR)
- Progression-Free Survival (PFS)
- Overall Survival (OS)
- Safety

1 Cycle = 90 days
Max 4 Treatment Cycles

Days

Phase 2 Study Design and Treatment Schedule

pIL-12 EP Cycle 1

pIL-12 EP Cycle 2

pIL-12 EP Cycle 3

pIL-12 EP Cycle 4

1 5 8 ... 90 1 5 8 ... 180 1 5 8 ... 270 1 5 8 ... 360
Why Modify RECIST for Skin Metastatic Melanoma?

Occurrence of new skin lesions does not always constitute clinical progression or worsening of disease status

Response to immunotherapy may be delayed

Patients with mainly cutaneous metastatic melanoma may not have RECIST 1.1 “measurable” disease
### Per Protocol Modifications to Standard RECIST Criteria

<table>
<thead>
<tr>
<th>Modified “Skin” RECIST</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measurable Disease</strong></td>
</tr>
<tr>
<td><strong>Maximum “target” lesion</strong></td>
</tr>
<tr>
<td><strong>New Lesions</strong></td>
</tr>
</tbody>
</table>
IL-12 EP is Safe and Well-Tolerated Across Multiple Treatment Cycles

<table>
<thead>
<tr>
<th>Adverse Event* (N=30)</th>
<th>All Grades N (%)</th>
<th>Grade 3 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>26 (87%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Inflammation</td>
<td>5 (17%)</td>
<td></td>
</tr>
<tr>
<td>Skin Discoloration</td>
<td>4 (13%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>3 (10%)</td>
<td></td>
</tr>
<tr>
<td>Erythema</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* treatment-related

No Treatment-Related SAEs
No Treatment-Related Grade 4 or 5 AEs

**PAIN SCORE SUMMARY**

<table>
<thead>
<tr>
<th>Median Score</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately after</td>
<td>3.00 (0-10)</td>
</tr>
<tr>
<td>5 minutes after</td>
<td>0.00 (0-8)</td>
</tr>
</tbody>
</table>

**Median Duration of Pain** 1 minute
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients (N = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>16 (53.3%)</td>
</tr>
<tr>
<td>Age</td>
<td>Median 67 yr (44-88 yr)</td>
</tr>
<tr>
<td>AJCC Stage</td>
<td></td>
</tr>
<tr>
<td>IIIB/C</td>
<td>19 (63.3%)</td>
</tr>
<tr>
<td>IVA</td>
<td>8 (26.7%)</td>
</tr>
<tr>
<td>IVB</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>IVC</td>
<td>1 (3.3%)</td>
</tr>
<tr>
<td>Prior Immunotherapy* (Yes)</td>
<td>16/29** (55.2%)</td>
</tr>
</tbody>
</table>

*Immunotherapies included ipilimumab, anti-PD1, interferon, IL-12 and GM-CSF

**Prior therapies data remain outstanding for 1 patient
pIL-12 EP Monotherapy Demonstrates Anti-tumor Activity in Advanced Melanoma

<table>
<thead>
<tr>
<th>Response Category*</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>**Stable Disease (SD)</td>
<td>5 (17%)</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>15 (52%)</td>
</tr>
<tr>
<td>Overall Response Rate (CR + PR)</td>
<td>9 (31%)</td>
</tr>
<tr>
<td>Disease Control Rate (CR + PR + SD)</td>
<td>14 (48%)</td>
</tr>
</tbody>
</table>

*by Modified “Skin” RECIST
**SD required to last for at least 90 days
pIL-12 EP Monotherapy Demonstrates Antitumor Activity in Advanced Melanoma

* = Patients with Clinical Progression

N=29
Intratumoral pIL-12 EP can lead to durable clinical responses
Complete Response with pIL-12 EP
**pIL-12 EP Promotes Local and Systemic Anti-Tumor Immunity**

<table>
<thead>
<tr>
<th>Distant Lesion Regression</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluable patients</td>
<td>26</td>
</tr>
<tr>
<td>Patients with distant lesion regression</td>
<td>13 (50%)</td>
</tr>
</tbody>
</table>

Distant Lesion Regression: not injected/electroporated, anatomically distinct
30 mice were injected with B16 cells in the left flank (7 days prior to first treatment) and again on the right flank (4 days prior to first treatment) to establish contralateral tumors.

30 mice were treated in the left flank on days 1, 5 and 8.

Treated and untreated tumors were harvested in 5 mice from each of 6 cohorts (baseline and 5 post-treatment time points).

Endpoints: “Clinical” and pathologic assessment & transcriptional analysis (Nanostring).
B16 contralateral 2-tumor model:
Clinical and Pathologic Observations

• By Day 11, all treated tumors were complete clinical responders with no pathologic evidence of tumor.

• By Day 18, clinical and pathologic response in non-injected tumors was observed with 3/5 mice (partial response accompanied by significant TIL infiltrate in the non-injected tumor).

• By Day 22, 1/5 mice harvested showed persistent TILs and a complete response in the non-injected tumor; non-injected tumors in 4 out of 5 mice had no significant increase in TILS.
IL-12 Expression is Associated with Increased Tumor-Associated Inflammatory Cell Infiltrate in Electroporated Lesions in Patients and Mouse Model

Patient Paired Biopsies, baseline versus Day 11 (N=10)

B16.F10 Mouse Melanoma Model
IL-12 Expression Results in Increased Expression of Co-Stimulatory Genes in Treated Lesions in Patients

Patient Paired Biopsies, baseline versus Day 11 (N=10)
IL-12 Expression Results in Increased Expression of Co-Stimulatory Genes in Treated Lesions in B16.F10 Mice
Induction of ‘Adaptive Resistance’ may limit systemic immune response induced by intratumoral pIL-12 electroporation.
Intratumoral IL-12 and the Induction of Systemic Anti-Tumor Immunity
‘Adaptive Resistance’ phenotype predicts response to anti-PD-1 in melanoma

- pIL-12-induced TIL generation provides rationale for combination with PD-1/PD-L1 mAb
- UCSF Investigators to study combination of intratumoral pIL-12 and pembrolizumab in low TIL patients

Conclusions

• Intratumoral EP of pIL-12 demonstrates monotherapy activity in advanced cutaneous & in-transit melanoma
  – ORR 31% & DCR 48% & CR 14%

• Intratumoral EP of pIL-12 is safe and well-tolerated across multiple treatment cycles
  – No treatment-related Serious Adverse Events Reported
  – No treatment-related Grade 4 or 5 treatment-related AEs Reported

• Local intratumoral treatment with pIL-12 EP achieves systemic tumor regression
  – 50% patients have regression of a distant lesion

• Preliminary data suggests that intratumoral pIL-12 EP drives tumor immunogenicity and is predicted to synergize with anti-PD1/PD-L1 therapies
Acknowledgements

**UCSF**
- Michael Buljan
- Neharika Khurana
- Jade Yen

**Univ. of Washington**
- Nicole A. Real

**John Wayne Cancer Center**
- Kelly Garver
- Holly Hou
- Madonna Johnson

**Lakeland Regional Cancer Center**
- Robin Stewart

**Oncosec Medical Inc**
- Mai H. Le, MD
- Victoria Leonidova
- Angel Nguyen
- Poorva Nemlekar
- Olivia Yang

Thank you to all of the patients
Additional Slides
### Potential Advantages of Intratumoral Electroporation over Viral Vectors

<table>
<thead>
<tr>
<th>Intratumoral Electroporation</th>
<th>Intratumoral Viral Vectors</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neutralizing anti-drug immune response; allows for retreatment</td>
<td>Patients develop antibodies to the viral vector; retreatment may not be effective or toxic</td>
</tr>
<tr>
<td>No need for separate quarantining of centers</td>
<td>May Require separate quarantining of centers</td>
</tr>
<tr>
<td>No risk of insertional mutagenesis</td>
<td>Potential risk of insertional mutagenesis; need very long term safety follow-up</td>
</tr>
<tr>
<td>No DNA payload limits</td>
<td>DNA payload constrained by viral “packaging” limits</td>
</tr>
<tr>
<td>Relatively low manufacturing costs</td>
<td>Significantly higher manufacturing costs</td>
</tr>
</tbody>
</table>
Duration On Study

![Graph showing the duration on study over time (months). The y-axis represents duration on study (%) and the x-axis represents time (months). The graph indicates a decrease in duration on study with increasing time.](image-url)
Median Progression-Free Survival (PFS)

Median PFS: 3.1 mos
Median Duration of Response and Disease Control

Duration of Response (CR and PR)

Median = 3.2 mo
Range (2.1-16.6 mo)

N = 9

Duration of Disease Control
(CR, PR and SD)

Median = 5.9 mo
Range (2.7-16.6 mo)

N = 14