Primming response to anti-PD1/PDL1 blockade with intratumoral electroporation of plasmid IL-12 in advanced melanoma

Alain Algazi¹, Katy K. Tsai¹, Kathryn T. Takamura², Lawrence Chen¹, Chris Twitty², Mary Dwyer², Samantha Greaney¹, Tu T. Diep², Robert H. Pierce², Mai H. Le², Lawrence Fong¹, Adil Daud¹.

¹University of California San Francisco, San Francisco, CA;
²OncoSec Medical Incorporated, San Diego, CA
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**Industry**
- Acerta
- Amgen
- AstraZeneca
- Bristol Myers Squibb
- Genentech
- GlaxoSmithKline
- Lilly
- Medimmune
- OncoSec
- Merck
- Novartis
- Pfizer

**Foundations / Non-Profits / NCI**
- American Cancer Society
- CTEP/NCI
- Melanoma Research Alliance
- NCCN
- Southwest Oncology Group
- SWOG / Cold Spring Harbor Lab
**PD1/PDL1 Abs:**
Most effective in **inflamed** tumors populated with tumor-specific CD8+ TILs. Low TIL tumors are less likely to respond.

**IL-12:**
A key mediator of IFNγ-driven T\_H1 pro-inflammatory response

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**Hypothesis:** Intratumoral IL-12 will generate CD8\(^+\) TILs and prime response to PD1 blockade
INTRATUMORAL ELECTROPORATION OF DNA-ENCODED IMMUNOMODULATORY MOLECULES

1. DNA Injected
2. Electroporation
3. DNA Enters and Protein Expression
4. Local inflammation and T-cell Education
5. Systemic Anti-Tumor Immune Response
Prospective study of IT-pIL12-EP monotherapy in advanced melanoma

- **IT-pIL12-EP Schedule 1-5-8** (N=18)
  - Repeat cycle every 90 days
  - Day 1, Day 5, Day 8

- **IT-pIL12-EP Schedule 1-8-15** (N=16)
  - Repeat cycle every 6 weeks
  - Day 1, Day 8, Day 15

Retrospective analysis of IT-pIL12-EP-treated patients who received subsequent PD-1/PDL1 inhibitors

- Anti-PD1/PDL1 + Intervening Therapy N=6
- Anti-PD1/PDL1 Directly Following IT-pIL12-EP N=8

Followed for Response N=14

Pre- and post-IT-pIL12-EP PBMC and TIL were interrogated for phenotypic and functional anti-tumor responses
## PATIENT POPULATION

<table>
<thead>
<tr>
<th></th>
<th>All N=34</th>
<th>Anti-PD1/PDL1 Evaluable N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (years)</strong></td>
<td>69</td>
<td>74.5</td>
</tr>
<tr>
<td><strong>ECOG Performance Status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>34 (100%)</td>
<td>14 (100%)</td>
</tr>
<tr>
<td><strong>Therapies Prior to IT-pIL12-EP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEDI4736 (anti-PDL1)</td>
<td>1 (3%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Pembrolizumab (anti-PD1)</td>
<td>3 (9%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>5 (15%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Interferon</td>
<td>8 (24%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>9 (26%)</td>
<td>5 (35%)</td>
</tr>
<tr>
<td><strong>Best Overall Response (IT-pIL12-EP)</strong></td>
<td>(N=33)</td>
<td>(N=14)</td>
</tr>
<tr>
<td>CR</td>
<td>4 (12%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>6 (18%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>SD</td>
<td>5 (15%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>PD</td>
<td>18 (55%)</td>
<td>8 (57%)</td>
</tr>
</tbody>
</table>
STAGE OF DISEASE PRIOR TO IT-pIL12-EP AND PRIOR TO ANTI-PD1/PDL1

<table>
<thead>
<tr>
<th>Stage</th>
<th>All N=34</th>
<th>Anti-PD1/PDL1 Evaluable N=14</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prior to IT-pIL12-EP</td>
<td>Prior to IT-pIL12-EP</td>
</tr>
<tr>
<td>IIIB</td>
<td>8 (23%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>IIIC</td>
<td>13 (38%)</td>
<td>6 (43%)</td>
</tr>
<tr>
<td>IVA</td>
<td>5 (15%)</td>
<td>3 (21%)</td>
</tr>
<tr>
<td>IVB</td>
<td>5 (15%)</td>
<td>2 (14%)</td>
</tr>
<tr>
<td>IVC</td>
<td>3 (9%)</td>
<td>1 (7%)</td>
</tr>
</tbody>
</table>

A patient w/ stage IIIC melanoma prior to pIL12/EP
### Best Overall Response Rate to Anti-PD1/PDL1 Following IT-pIL12-EP

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>Without Intervening Therapy (N=8)</th>
<th>With Intervening Therapy (N=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4 (50%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>PR</td>
<td>2 (25%)</td>
<td>2 (33%)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (12.5%)</td>
<td>1 (17%)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (12.5%)</td>
<td>2 (33%)</td>
</tr>
</tbody>
</table>

![Bar chart showing best overall response rates for anti-PD1/PDL1 therapy with and without intervening therapy.](chart.png)
DEPTH OF RESPONSE TO IT-pIL12-EP AND ANTI-PD1/PDL1 FOLLOWING IT-pIL12-EP

Intervening therapy

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>% change from baseline (prior to therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-100</td>
</tr>
<tr>
<td>112</td>
<td>-75</td>
</tr>
<tr>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>102</td>
<td>25</td>
</tr>
<tr>
<td>14</td>
<td>-25</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
</tr>
</tbody>
</table>

No intervening therapy

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>% change from baseline (prior to therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>110</td>
<td>-100</td>
</tr>
<tr>
<td>109</td>
<td>-75</td>
</tr>
<tr>
<td>111</td>
<td>25</td>
</tr>
<tr>
<td>106</td>
<td>25</td>
</tr>
<tr>
<td>113</td>
<td>-75</td>
</tr>
<tr>
<td>13</td>
<td>-25</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>15</td>
<td>25</td>
</tr>
</tbody>
</table>

* Progression of non-targets
** SUV decrease
DURATION OF RESPONSE TO IT-pIL12-EP AND ANTI-PD1/PDL1 FOLLOWING IT-pIL12-EP

- Duration on IT-pIL12-EP
- Duration on Intervening Therapy
- Duration on Anti-PD1/PDL1 (color by BOR-CR/ PR/ SD/ PD)

- CR-IT-pIL12-EP
- PR-IT-pIL12-EP
- SD-IT-pIL12-EP
- PD-IT-pIL12-EP
- Continue to be followed
PATIENT CASE STUDIES – CLINICAL RESPONSE PROFILE

CASE STUDY #1
Stage IVB
PR-IT-pIL12-EP
PR-Pembrolizumab

CASE STUDY #2
Stage IVB
SD-IT-pIL12-EP
CR-Pembrolizumab

CASE STUDY #3
Stage IIIC
PD-IT-pIL12-EP
CR-Pembrolizumab
PATIENT CASE STUDY #1

Clinical and radiographic response to therapy

NanoString© demonstrates differential expression of immune activating genes 4 weeks post-IT-pIL12-EP

Clinical and radiographic response to therapy

NanoString© demonstrates differential expression of immune activating genes 4 weeks post-IT-pIL12-EP
PATIENT CASE STUDY #2

Chromogenic IHC

Pre-IT-pIL12-EP
Day 11
Day 39

Multispectral fluorescent IHC

A brisk tumor infiltrate before treatment is further increased with IT-pIL12-EP therapy

Disease stabilization after one cycle of IT-pIL12-EP

Received 3 additional cycles of IT-pIL12-EP over one year until PD

Initiated Pembrolizumab without intervening therapy (10 month durable CR)
PATIENT CASE STUDY #3

Chromogenic IHC

Pre-IT-pIL12-EP  Day 11  Day 39
CD3+CD8+ % of nucleated cells

PD-L1 /CD3/ CD8/ FoxP3  CD163 /DAPI

Immune Ratios
CD8:PD-L1 = 0.13
CD8:FoxP3 = 1
CD8:PD-L1 = 0.014
CD8:FoxP3 = 13
CD8:PD-L1 = 0.32
CD8:FoxP3 = 41

Minimal change in lesion size from baseline to Day 39
PATIENT CASE STUDY #3 CONT.

IT-pIL12-EP is associated with increased frequency of circulating tumor antigen-specific CD8 T cells

- Patient only received one cycle of IT-pIL12-EP
- 49% CTLA4+/PD1+ in non-IT-pIL12-EP treated tumor observed prior to initiating Pembrolizumab (CD45+CD3+CD8+ gate)
- Ongoing complete response (1 year+) to Pembrolizumab despite overall non-response to IT-pIL12-EP
CONCLUSIONS

- IT-pIL-12 therapy can promote the generation of CD8+ TILs, triggering the PD-1 immune checkpoint (i.e. ‘adaptive immune resistance’) and providing the ‘substrate’ for effective anti-PD1/PD-L1 therapy.

- Patients who received IT-pIL12-EP and later went on to receive a PD1/PDL1 inhibitor demonstrated a high PD1/PDL1-associated response rate (n=14; 64% BORR), and those who did not have an intervening therapy had a BORR of 75% (n=8).

- A prospective clinical trial combining IT-pIL12-EP and Pembrolizumab in advanced melanoma is ongoing at the University of California, San Francisco and the Huntsman Cancer Center at The University of Utah (NCT02493361).
Prospective Trial Ongoing
pIL-12/EP with pembrolizumab in Metastatic Melanoma (NCT02493361)

Stage IIib to IVc melanoma with accessible lesions

TIL < 25% (N = 41)
Stratified by TIL % (flow cytometry)

TIL ≥ 25% (N = 41)
Expansion to include high TIL tumors under review

Cycle Odd (21 days)
Day 1
Day 5
Day 8
Repeat every 42 days

Cycle Even (21 days)
Day 1

Plasmid IL-12 with Electroporation
Pembrolizumab

Accruing
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