Reactivating the anti-tumor immune response by targeting innate and adaptive immunity in a phase I/II study of intratumoral IMO-2125 in combination with systemic ipilimumab in patients with anti-PD-1 refractory metastatic melanoma

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Presenter Disclosure Information

Cara Haymaker

The following relationships exist related to this presentation:

\(< \text{ENTER EITHER}> \)
\(< \text{No Relationships to Disclose}> \)
\(< \text{OR}> \)
\(< \text{COMPANY X, Received, Role (i.e. BMS, Honorarium, Speaker)}> \)
\(< \text{COMPANY Y, Received, Role (i.e. Pfizer, Salary, Employee)}> \)
Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125

1. Intratumoral administration of IMO-2125

2. Draining Lymph node

3. Primed T-cells migrate to distant tumor sites

4. Increased TIL Infiltration

Metastases are targeted by primed T-cells

Dendritic Cell  Tumor specific antigens  NK cell  CD8+ T cell
Arm 1 Trial Design (NCT02644967)

- i.t. IMO-2125 alone
- i.t. IMO-2125 + Ipilimumab

**Intratumoral IMO-2125**

**Ipilimumab**

**Weeks:** 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13

**Cycles:**
- Cycle 1
- Cycle 2
- Cycle 3
- Cycle 4
Key Enrollment Criteria

**Inclusion Criteria**

- Diagnosis of metastatic melanoma with stage III (in transit lesions), IVA, IVB, or IVC disease
- **Progressive disease after treatment with PD-1 inhibitor**
- \( \geq 2 \) measurable tumor lesions \( \geq 1.0 \) cm
- \( \geq 18 \) years
- ECOG \( \leq 2 \)
- Adequate renal, bone marrow, liver and cardiac function

**Exclusion Criteria**

- Received therapy with prior TLR agonist therapy
- Symptomatic, unstable or progressing CNS, meningeal, or epidural disease
- Concurrent systemic steroid therapy higher than physiologic dose (7.5 mg/day of prednisone)
- Active autoimmune disease requiring disease-modifying therapy
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs.)</td>
<td>55 (39-76)</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (60%)</td>
</tr>
<tr>
<td>Female</td>
<td>4 (40%)</td>
</tr>
<tr>
<td>BRAF V600E (+)</td>
<td>3 (30%)</td>
</tr>
<tr>
<td>Mucosal Melanoma</td>
<td>2 (20%)</td>
</tr>
<tr>
<td>Visceral Disease</td>
<td>8 (80%)</td>
</tr>
<tr>
<td>Brain Metastases (treated)</td>
<td>1 (10%)</td>
</tr>
<tr>
<td>Received anti-PD-1</td>
<td>10 (100%)</td>
</tr>
<tr>
<td>Received anti-CTLA-4</td>
<td>5 (50%)</td>
</tr>
<tr>
<td>Duration on anti-PD-1 therapy</td>
<td>8-63 weeks</td>
</tr>
</tbody>
</table>
### Most Frequent Adverse Events

<table>
<thead>
<tr>
<th>AE Preferred Term</th>
<th>All, N (%)</th>
<th>Grade III, N (%)</th>
<th>Grade IV, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>10 (100)</td>
<td>5 (50)</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (60)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (50)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anemia</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (40)</td>
<td>2 (20)</td>
<td>-</td>
</tr>
<tr>
<td>ALT increase</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>AST increase</td>
<td>3 (30)</td>
<td>-</td>
<td>1 (10)</td>
</tr>
<tr>
<td>Triglycerides increase</td>
<td>3 (30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (30)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (30)</td>
<td>1 (10)</td>
<td>-</td>
</tr>
<tr>
<td>Decreased WBC</td>
<td>3 (30)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Data cut off: Oct 07, 2016
Safety Summary (N=10)

IMO-2125 dosing cohort (ipi 3 mg/kg x 4 doses)

<table>
<thead>
<tr>
<th>N subjects with...</th>
<th>4 mg (N=3)</th>
<th>8 mg (N=4)</th>
<th>16 mg (N=3)</th>
<th>Total (N=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 TEAE</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>3 (100)</td>
<td>10 (100)</td>
</tr>
<tr>
<td>Related TEAE</td>
<td>2 (67)</td>
<td>4 (100)</td>
<td>2 (67)</td>
<td>8 (80)</td>
</tr>
<tr>
<td>≥ 1 SAE</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>2 (67)</td>
<td>6 (60)^</td>
</tr>
<tr>
<td>Discontinue for AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death from AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DLT</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

^related SAE (IMO or ipi): hypophysitis (2), fever, elevated LFT’s, diarrhea, nausea

Data cut off: Oct 07, 2016
Early response data to IMO-2125 + Ipilimumab

IMO-2125 Dose Assigned
- 4 mg
- 8 mg
- 16 mg

- M Start of Response
- PR Ongoing
- Mucosal melanoma
- * Confirmed PR followed by unconfirmed CR

Weeks

Data cut off: Nov. 7, 2016
Tumor Imaging of Patient with a Complete Response:
Ipilimumab 3mg plus i.t. IMO-2125 8 mg
Study 2125-204: Immune response monitoring to correlate with mechanism of action

- **DNA and RNA** (TCRseq and gene expression)
- **Tumor Core Needle biopsy**
- **Pre-dose**
- **24 hours post i.t. IMO-2125 injection**
- **Ipilimumab**
- **Week 8**
  - 5 doses of IMO-2125 and 3 doses of Ipi

**Injected** = Injected lesion
**Distant** = Un-injected lesion

- **= collection of biopsy**
- **= collection of PBMCs**

**C1W2**
**C2W5**
**C4W11**

**Formalin - IHC**
**Fresh flow cytometry**
- DC subsets and maturation
- Immune infiltrate changes
- T cell activation/functional state

**DNA and RNA (TCRseq and gene expression)**
Rapid mDC1 maturation induced by IMO-2125 in the tumor

Pre-dose

24 hours post i.t. IMO-2125 injection

Injected

Pre-dose

24 hours post i.t. IMO-2125 injection

Injected

mDC1
CD1c+
mDC2
CD141+
pDC
CD303+

Dose level 1 (4mg)

Dose level 2 (8mg)

Dose level 3 (16mg)

% HLA-DR+ of mDC1

0 20 40 60 80 100

0

Pt. 2

Pt. 3

Pt. 4

Pt. 6

Pt. 8

Pt. 10

Pt. 11

Pt. 12

* Biopsy delayed to 48hrs

SITC 2016

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
Combination therapy induces immune infiltration in distant lesions of responding patients

Prem-dose IMO-2125 (5) + Ipi (3)

Injected

Distant

Lesion resolved

Pre-dose

Week 8

Injected

Distant

% CD45+ live cells

0

10

20

30

40

50

60

70

80

90

100

Pt. 2
Pt. 6
Pt. 10
Pt. 3
Pt. 4
Pt. 8

NR

R

% CD45+ live cells

0

2

4

6

8

10

12

14

16

18

20

Pt. 2
Pt. 6
Pt. 10
Pt. 3
Pt. 4
Pt. 8

NR

R

Lesion resolved

0 0.15

IMO-2125 (5) + Ipi (3)

Advancing Cancer Immunotherapy Worldwide

SITC 2016
Combination therapy induces T cell expansion and activation

Pre-dose 24 hours post i.t. Week 8
IMO-2125 injection IMO-2125 (5) + Ipi (3)

Injected Injected Injected

NE = not evaluable
* Biopsy delayed to 48hrs

% Ki67+ of CD8+ T cells

% CD56+ of CD8+ T cells

NR

R

Pt. 2  Pt. 6  Pt. 10  Pt. 3  Pt. 4  Pt. 8

 IMO-2125 injection

 IMO-2125 (5) + Ipi (3)

Combination therapy induces T cell expansion and activation

NE = not evaluable
* Biopsy delayed to 48hrs
Expansion of top T cell clones in the distant lesion of responding patient

- **Pre-dose**
  - IMO-2125 (5) + Ipi (3)

**Week 8**

- Injected
- Distant

- **Non-responding patient**
  - Frequency of total T cell clones

- **Responding patient**
  - Frequency of total T cell clones
Late increase in IFNγ in patient plasma as a biomarker of response
Where do we go from here? 
Upregulation of PD-L1 early on therapy

Predose 24 hr post injection

20x magnification

* Malignant cells only
New Trial Design with addition of IMO-2125 + Pembro Arm

(NCT02644967)

i.t. IMO-2125 alone

i.t. IMO-2125 +ippi or pembro

* Pembro continues until time of progression

Intratumoral IMO-2125

Ipilimumab or Pembrolizumab

1 2 3 4 5 6 7 8 9 10 11 12 13

Week

Cycle 1 Cycle 2 Cycle 3 Cycle 4
Lessons and Take Home Messages

• Key points
  – IMO-2125 results in maturation of intratumoral mDC1 in injected lesion within 24h of drug administration
  – Increased immune infiltration measured in distant lesions of responding patients at week 8
  – Safety is acceptable through 3 dosing cohorts; MTD not yet reached
  – Preliminary clinical activity with IMO-2125 + ipilimumab in this refractory population is encouraging

• Potential impact on the field
  – Combining intra-tumoral DC activation to enhance T cell priming with checkpoint blockade may be key in IO refractory patient population
  – A local tumor can be used as a vaccine itself and injection of one lesion results in regression of distant lesions that may not be easily accessible

• Lessons learned
  – On-treatment biopsy timing is critical!!
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Poster #216