Creating a Beneficial Tumor Microenvironment for Effective Cancer Immunotherapy

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Idera Pharmaceuticals

Oligonucleotide and Peptide Therapeutics Boston 2017
Immunotherapy of Cancer – Our Understanding has Evolved
Promise of Immunotherapy being realized

Anti-PD1, Anti-PDL1 and Anti-CLTA4 Agents have been approved

Anti-CTLA4
Ipilimumab

Anti-PD1  Pembrolizumab & Nivolumab
Anti-PDL1  Atezolizumab & Avelumab
Tumor microenvironment is key to the outcome of immunotherapy

1 Inducer of antitumour immunity

2 Anti-PD1

Strong endogenous antitumour immune response → PDL1 upregulation on tumour cells or TAMs → Response

Weak endogenous antitumour immune response → No PDL1 upregulation on tumour cells or TAMs → No response

Single-agent anti-PD1

Increased PDL1 expression on tumour cells or TAMs → Response

Increased endogenous antitumour immune response
Our approach is modulation of the tumor microenvironment
Creating a beneficial tumor microenvironment using innate immune pathways
Modulation of Tumor Microenvironment by Engaging Innate Immune Receptors

TLR9 is expressed on dendritic cells and B-cells
Understanding Structural Requirements for Design of TLR9 Agonists

11-mer forms intermolecular structure and avoids intramolecular interaction

Linked 3’-ends improve metabolic stability

Accessible 5’-ends is required for immune activation

TLR9 agonists with two 5’-ends show increased potency

IMO-2125: an optimized, novel, synthetic agonist of Toll-like receptor 9 (TLR9)

IMO-2125 at doses ranging from 0.04 to 0.48 mg/kg administered subcutaneously weekly in Hepatitis C infected subjects

- Treatment was well-tolerated
- Immune response parameters showed activation

IMO-2125 induces IFN-α and other cytokines in human trial

IMO-2125 induces Th-1 type cytokines through TLR9

Data presented at EASL 2010, AASLD Liver Meeting 2010

Modulation of the tumor microenvironment by intratumoral administration of IMO-2125

Intratumoral administration of IMO-2125

Draining Lymph node

Primed T-cells migrate to distant tumor sites

Primed T-cells

Metastases are targeted by primed T-cells

Increased TIL Infiltration

Dendritic Cells

TLR9

IFN-α

Tumor specific antigens

NK cells

CD8+ T-cells

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Intratumoral IMO-2125 is more potent than subcutaneously administered IMO-2125

A20 Lymphoma model

<table>
<thead>
<tr>
<th>Tumor implant</th>
<th>Treatment IMO-2125, 2.5 mg/kg, i.t. or s.c.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 x 10^6 cells</td>
<td></td>
</tr>
</tbody>
</table>

Day 0 8 10 12 14 21

BALB/c, female (n = 10)

Parameters evaluated

- Tumor volume
- Induction of tumor-infiltrating lymphocytes (TILs) in the tumor microenvironment
- Checkpoint gene expression in tumor nodules

Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Intratumoral IMO-2125 is more potent than subcutaneously administered IMO-2125

A20 Lymphoma model

CHANGES IN TUMOR VOLUME AND TIL INFILTRATION

Presented at CRI-CIMT-EATI-AA CR Cancer Immunotherapy Conference 2015
Intratumoral IMO-2125 is more potent than subcutaneously administered IMO-2125

A20 Lymphoma model

CHANGES IN CHECKPOINT GENE EXPRESSION

Fold increase over placebo

s.c  i.t.

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Intratumoral IMO-2125 shows abscopal antitumor activity

Parameters evaluated:
- Tumor growth inhibition
- IHC: TILs
- Flow cytometry analysis of TILs
- CTLs against treated and distant tumors
- Roles of CD4+ and CD8+ T cells
- Durability of systemic immune response upon rechallenge

BALB/c mice (n=8 per group) were implanted s.c. with 2 x 10^6 CT26.WT cells on right flank (Tumor 1) and 2 x 10^6 CT26.CL25 cells on the left flank (Tumor 2). Treatment was initiated on Day 5 when tumor volume on right flank reached 50 to 150 mm^3. Test compound was administered by intratumoral (i.t.) injection (100 μl) on right side tumor nodules (Tumor 1) only at Days 5, 8, 11 and 14. Tumor nodules were collected at Day 28.
Intratumoral IMO-2125 treatment led to dose-dependent inhibition of tumor growth in both treated and distant tumors.
Antitumor activity was associated with increased tumor-infiltrating lymphocytes (TILs)

Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Intratumoral IMO-2125 treatment elicited specific cytotoxic T-cell responses to tumor antigens.
Role of CD8+ Cells in anti-tumor activity of intratumoral IMO-2125

- **Tumor Implantation**: Days 0
- **Treatment**: Days 6, 10, 13

**Anti-CD4 mAb treated**
- CD4+ T cell depletion

**Anti-CD8 mAb treated**
- CD8+ T cell depletion

Anti-CD4 or CD8+ mAb, 25 mg/kg (500 μg/mouse), i.p.

Tumor implantations:
- Tumor 1 (CT26.WT), right flank, s.c.
- Tumor 2 (CT26.CL25), left flank, s.c.

IMO-2125 2.5 mg/kg (50 μg/mouse), i.t.

CD4+ and CD8+ T cells were depleted by i.p. injections of 25 mg/kg (500 μg/mouse) anti-mouse CD4 mAb or anti-mouse CD8 mAb on Days 1, 6 and 13. Tumor-bearing mice were treated by i.t. injections with 2.5 mg/kg (50 μg/mouse) placebo or IMO-2125 at right tumor on Days 6, 10 and 13.

CD4 mAb (Clone GK1.5) and the CD8 mAb (YTS169.4) obtained from BioXcell

Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Antitumor activity of intratumoral IMO-2125 treatment is dependent on CD8+ T cells
Intratumoral IMO-2125 treatment led to durable and tumor-specific immune memory

Six tumor-bearing mice (6 of 9) whose tumors completely or partially regressed (<150 mm3) after IMO-2125 (5 mg/kg, i.t.) treatments and 8 naïve BALB/c mice (n = 8) were rechallenged on Day 33 with 1 x 10^6 CT26 cells by s.c. injection at abdominal right and left flank. Naïve BALB/c mice inoculated same way were used as tumor growth control. The mice that rejected CT26 tumor cell rechallenge (5 of 6) were then inoculated on Day 73 with 10^6 syngeneic, non-organ-related B cell lymphoma A20 cells by s.c. inoculation at the upper back area.
Intratumoral IMO-2125 treatment led to durable and tumor-specific immune memory

Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Combination treatment with intratumoral IMO-2125 and anti-CTLA-4 mAb showed potent anti-tumor activity

BALB/c mice (n=10 per group) were implanted s.c. with 2 x 10^7 CT26.WT cells on right flank (Tumor 1) and 3 x 10^6 CT26.WT cells by i.v injection to generate lung metastasis (Tumor 2). Treatment was initiated on Day 5 when tumor volume on right flank reached 200 to 300 mm^3. IMO-2125 (2.5 mg/kg) was administered by intratumoral (i.t.) injection (100 µl) on right side tumor nodules (Tumor 1) and anti-CTLA4 mAb (10 mg/kg in 100 µl PBS) was administered by i.p at Days 5, 6, 8 and 9. Tumor nodules and lungs were collected at Day 13.

Anti-CTLA-4 mAb (Clone 9H10) obtained from BioXcell

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Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Combination treatment with intratumoral IMO-2125 and anti-CTLA-4 mAb showed potent anti-tumor activity

Both treated and distant tumors showed growth inhibition

Lung Tumor Nodules

*Picture was taken on Day 13 after tumor implantation.

Presented at CRI-CIMT-EATI-AACR Cancer Immunotherapy Conference 2015
Combination treatment with intratumoral IMO-2125 and anti-CTLA-4 mAb increased TILs in metastatic lung nodules

PBS group: a few T cells are present in the tumor tissues bordering normal tissue.
IMO-2125 group: increased T cells are infiltrating into tumor tissues.
Anti-CTLA-4 mAb group: increased T cells are infiltrating into tumor tissues.
Combination group: massive T cell infiltrate into tumor tissue.
Combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb showed potent anti-tumor activity

Presented at AACR-NCI-EORTC International Conference 2015

**Groups:**
1. PBS
2. IMO-2125: 2.5 mg/kg, i.t.
3. Anti-PD1 mAb, 10 mg/kg, i.p.
4. IMO-2125 + Anti-PD1 mAb

BALB/c mice (n=8 per group) were implanted s.c. with 1 x 10^7 murine colon carcinoma CT26 cells in right flank (Tumor 1) and left flank (Tumor 2). Treatment was initiated on Day 7 when tumor volume reached 200 to 300 mm^3. On Days 7, 8, 11 and 12, treatment with IMO-2125 a dose of 2.5 mg/kg (50 µg in 100 µl PBS) was administered intratumorally in right tumor nodules and treatment with anti-mouse PD1 mAb (10 mg/kg, 200 µg/mouse, Clone J43 from BioXcells) was administered by i.p. injection. Tumor nodules were collected at Day 14.

Anti-PD-1 mAb (Clone RMP1-14) obtained from BioXcell

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Combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb showed potent anti-tumor activity

**Treated tumors**

- **PBS**
- **IMO-2125**
- **Anti-PD-1 mAb**
- **Combination**

**Distant tumors**

- **Tumor volume, mm$^3$**
- **Days after tumor implantation**

Presented at AACR-NCI-EORTC International Conference 2015
Modulation of checkpoint gene expression with combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb

Presented at AACR-NCI-EORTC International Conference 2015
Combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb showed potent anti-tumor activity

C57BL/6 mice (n=10 per group) were implanted by s.c. inoculated with 1 x 10^7 B16.F10 melanoma cells in right flank (Tumor 1) and by i.v. injection with 2 x 10^6 B16.F10 melanoma cells to generate lung metastases (Tumor 2). Treatment was initiated on Day 5 when tumor volumes of s.c. implanted site reaches 100 -200 mm³. On Days 5, 6, 7, 8 and 9, treatment with IMO-2125 at the dose of 5 mg/kg (100 µg in 100 µl PBS) was administered intratumorally at right tumor nodules and treatment with anti-mouse PD-1 mAb (15 mg/kg, 300 µg/mouse) was administered by i.p. injection. Tumor nodules were collected at Day 15.
Combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb showed potent anti-tumor activity

Both treated and distant tumors showed growth inhibition.

Lung Tumor Nodules

Tumor Volume

Presented at AACR-NCI-EORTC International Conference 2015
Combination treatment with intratumoral IMO-2125 and anti-PD-1 mAb increased TILs in metastatic lung nodules.

Legend
Circle: Large tumor nodule
Inset figures: HE stained (x40)
Arrow: Small tumor nodule
Large figures: CD3 stained (x400)

Treatment with intratumoral IMO-2125 and anti-PD1 mAb combination led to:
- Decreased lung tumor metastasis (inset and large figures)
- Increased TILs (large figure)
Intratumoral IMO-2125 anti-tumor activity is potentiated by co-treatment with an IDO-1 inhibitor

BALB/c mice (n=10 per group) were implanted by s.c. inoculation with 1 x 10^7 murine CT26 colon carcinoma cells (CT26) in right flank (Tumor 1) and by i.v. injection with 3 x 10^6 CT26 cells to generate lung metastases (Tumor 2). Treatment was initiated on Day 4 when tumor volumes of s.c. implanted sites reach 100 to 200 mm^3. Treatment with IMO-2125 at the dose of 2.5 mg/kg IMO-2125 (50 μg in 100 μl PBS) was administered i.t. q.d. at right tumor nodules and treatment with IDO-1 inhibitor (100 mg/kg) was administered by intragastric administrations b.i.d. on Days 4, 5, 7 and 8. Tumor nodules and lungs were collected at Day 12 for various immunoassays.
Intratumoral IMO-2125 anti-tumor activity is potentiated by co-treatment with an IDO-1 inhibitor

Both treated and distant tumors showed growth inhibition

Presented at the AACR Annual Meeting 2016
Intratumoral IMO-2125: a Phase 1/2 trial in PD-1 refractory melanoma patients in combination with ipilimumab or pembrolizumab

Data as presented at ASCO-SITC, Feb 24, 2017
Dosing Schedule Overview

- **Study population:** Adults with unresectable or metastatic melanoma that progressed ≥12 wks PD-1-directed therapy (alone or in combination); no prior immune-related dose-limiting toxicities; accessible tumor for biopsy and injection (2 lesions)

- **Endpoints:**
  - **Primary:** Investigator assessed overall response using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)
  - **Secondary:** Overall response by RECIST, duration of response (DoR), durable response rate (DRR), progression-free survival (PFS), overall survival (OS), and pharmacokinetics
  - **Exploratory:** Immunophenotyping with flow cytometry, assessment of TCR Vβ CDR3 clonal diversity using ImmunoSeq™, and NanoString gene expression analyses

- **Trial #** NCT02644967
Dosing Arms

Dose-finding:
IMO-2125 + ipilimumab
SAFETY ASSESSMENT COMPLETED

Dose-finding:
IMO-2125 + pembrolizumab
ONGOING

“Backfill” cohort(s):
IMO-2125 + ipilimumab
ONGOING

Phase 2
IMO-2125 + ipilimumab and
IMO-2125 + pembrolizumab
PLANNED

Dosing:
IMO-2125 4, 8, 16, or 32 mg single i.t. injection week 1, 2, 3, 5, 8, 11
Ipilimumab and pembrolizumab are administered per label beginning week 2

*Recommended Phase 2 dose
## Patient and Disease Characteristics

IMO-2125 + ipilimumab safety population (N=13)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>58 (39,78)</td>
</tr>
<tr>
<td>Male</td>
<td>8 (62)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>1 (8)</td>
</tr>
<tr>
<td>IV</td>
<td>12 (92)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>11 (85)</td>
</tr>
<tr>
<td>Mucosal</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Visceral metastases</td>
<td>10 (77)</td>
</tr>
<tr>
<td>Elevated LDH</td>
<td>3 (23)</td>
</tr>
<tr>
<td>BRAF mutation</td>
<td>9 (69)</td>
</tr>
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## Prior Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N (%)</th>
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</thead>
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<tr>
<td>PD-(L)1 inhibitor</td>
<td>12 (92)</td>
</tr>
<tr>
<td>CTLA-4 inhibitor</td>
<td>7 (54)</td>
</tr>
<tr>
<td>BRAF inhibitor</td>
<td>5 (39)</td>
</tr>
<tr>
<td>MEK inhibitor</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Interferon</td>
<td>5 (39)</td>
</tr>
<tr>
<td>IL-2</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Other systemic therapy</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Radiation</td>
<td>5 (39)</td>
</tr>
</tbody>
</table>
Exposure to treatment

<table>
<thead>
<tr>
<th>IMO-2125 dose mg (N)</th>
<th># IMO-2125 injections Median (range)</th>
<th># ipilimumab infusions Median (range)</th>
<th># Discontinuations (Reasons)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (3)</td>
<td>6 (3,6)</td>
<td>3 (1,4)</td>
<td>2 (insurance, death)</td>
</tr>
<tr>
<td>8 (4)</td>
<td>6 (5,6)</td>
<td>4 (3,4)</td>
<td>1 (w/ withdrawal)</td>
</tr>
<tr>
<td>16 (3)</td>
<td>5 (3,6)</td>
<td>2 (1,4)</td>
<td>1 (w/ withdrawal)</td>
</tr>
<tr>
<td>32 (3)</td>
<td>5 (4,5)</td>
<td>3 (2,3)</td>
<td>0</td>
</tr>
</tbody>
</table>

Ipilimumab dose = 3 mg/kg Q3wks x 4
## Safety Summary

<table>
<thead>
<tr>
<th>IMO-2125 dose</th>
<th>4 mg (N=3)</th>
<th>8 mg (N=4)</th>
<th>16 mg (N=3)</th>
<th>32 mg (N=3)</th>
<th>Total (N=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 TEAE¹</td>
<td>3 (100)</td>
<td>4 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>13 (100)</td>
</tr>
<tr>
<td>Related TEAE¹</td>
<td>2 (67)</td>
<td>4 (100)</td>
<td>3 (100)</td>
<td>3 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>≥ 1 SAE²</td>
<td>2 (67)</td>
<td>2 (50)</td>
<td>2 (67)</td>
<td>1 (33)</td>
<td>7 (54)</td>
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<tr>
<td>Discontinued for AE³</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Death from AE³</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>DLT⁴</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>irAE⁵</td>
<td>1 (33)</td>
<td>1 (25)</td>
<td>2 (67)</td>
<td>0</td>
<td>4 (31)</td>
</tr>
</tbody>
</table>

¹treatment-emergent adverse event  
²serious adverse event  
³adverse event  
⁴dose-limiting toxicity  
⁵immune-related adverse event: hypophysitis (2), adrenal insufficiency (1), autoimmune hepatitis (1)
## Most Frequent TEAE

<table>
<thead>
<tr>
<th>AE Preferred Term</th>
<th>All grade, N (%)</th>
<th>Grade 3, N (%)</th>
<th>Grade 4, N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>13 (100)</td>
<td>6 (46)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Anemia</td>
<td>6 (46)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (46)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (46)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (46)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Decreased WBC</td>
<td>4 (31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>4 (31)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
<tr>
<td>Increased TG</td>
<td>4 (31)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (31)</td>
<td>2 (15)</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (23)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (23)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3 (23)</td>
<td>-</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (23)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urinary Tract Infection</td>
<td>3 (23)</td>
<td>1 (8)</td>
<td>-</td>
</tr>
</tbody>
</table>
Patient Time on Study and RECIST v1.1 Responses by Dose Cohort

- **Ipi + IMO-2125 4mg**
- **Ipi + IMO-2125 8mg**
- **Ipi + IMO-2125 16mg**
- **Ipi + IMO-2125 32mg**

**Legend:**
- Confirmed Response Start
- Unconfirmed Response Start
- Ongoing

**Weeks:**
- 0
- 2
- 4
- 6
- 8
- 10
- 12
- 14
- 16
- 18
- 20
- 22
- 24
- 26
- 28
- 30
- 32
- 34
- 36
- 38
- 40
- 42
- 44
- 46
- 48
- 50
- 52
- 54
- 56

**Data cut-off date:** 13 Feb 2017

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Presented at ASCO-SITC 2017
Immune Response Monitoring for elucidating MoA

24 hours post intratumoral IMO-2125 injection

Week 8
5 doses of IMO-2125 and 3 doses of ipilimumab

Week 13

Pre-dose

Injected lesion

Un-injected lesion

Injected lesion

Injected lesion

Un-injected lesion

Injected lesion

Un-injected lesion

Injected lesion

Un-injected lesion

= collection of biopsy

Tumor biopsy

Formalin - IHC

Fresh flow cytometry
mDC1 vs mDC2 vs pDC
CD8 T cell : Treg ratio
T cell proliferation via Ki67 of both Tregs and CD8+ T cells
Immune subsets ratio (T cell vs B cell vs NK cells)

RNA (TCRseq and Nanostring)

Presented at ASCO-SITC 2017
Demonstration of Clinical and Translational Responder

Patient 003 – 4mg IMO-2125 Cohort

• 58 y/o WM with BRAF wild-type melanoma originating base of penis
  – Metastases to inguinal lymph nodes and liver

• Rapid progression on nivolumab (4 cycles) prior to enrollment

• Received 6 doses IMO and 3 doses ipi (last one held for hypophysitis)
  – Well-known AE deemed related to ipi
DC Maturation in the Injected Tumor

Patient 003 – 4mg IMO-2125 Cohort

IMO-2125 → pDCs → B-cells → IFN-α and Th1-type immune response → mDCs

Migration and expansion of T-cells

Pre-dose

24 hours post i.t. IMO-2125 injection

Graphical representation

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T-cell Activation Occurring in the Injected and Distant Tumor

Patient 003 – 4mg IMO-2125 Cohort

Graphical representation
Expansion of top T-cell clones in the distant lesions, induction of IFN-γ

Patient 003 – 4mg IMO-2125 Cohort

Patient 003 Remains PR at 6 Mos. Visit
Additional Clinical Responder Case Study

Patient 004 – 8mg IMO-2125 Cohort

• 68 y/o male with BRAF wt melanoma, metastatic to lung (bulky), pleura, LN, widespread soft tissue
• Marked progression on Nivo + Urelumab (anti-4-1BB)
  – Marked progression w/ severe dyspnea
  – Referred to hospice
• Pleural effusion drained, then begun on study treatment
• Received 6 doses IMO + 4 doses ipi
• Dramatic response after 6 wks of therapy
• Investigator-assessed CR at 5 months
Tumor Imaging: Patient 004 Remains a CR at 6 Months Visit

Ipilimumab 3mg plus i.t. IMO-2125 8 mg
Long-term Expansion Opportunity Significant

INTRODUCE

Unresectable metastatic melanoma

- Maturing I/O market primed for combo
- High unmet need in anti-PD1-refractory patients

Est. U.S. addressable patient population at 2025:
- 13,000
- 20,000
- 0

EXPAND

Emerging I/O addressable tumors

- Moderate response to cornerstone anti-PD1
- PD-L1 expression guided treatment is restrictive

Est. U.S. addressable patient population at 2025:
- 70,000
- 160,000

TRANSFORM

“Cold” tumors unaddressable with current I/O

- Significant opportunity in tumors with:
  - Low mutation load
  - Low dendritic cell infiltration
- Bioinformatics research ongoing to identify attractive tumor targets

1 Proprietary Idera Commercial Research
2 NSCLC, head and neck, RCC and bladder only

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Two upcoming presentations at AACR 2017

- 5652 / 6 - Translational evidence of reactivated innate and adaptive immunity with intratumoral IMO-2125 in combination with systemic checkpoint inhibitors from a Phase I/II study in patients with anti-PD-1 refractory metastatic melanoma

- 5659 / 13 - Local treatment with novel TLR9 agonist IMO-2125 demonstrates antitumor activity in preclinical models of pancreatic cancer
<table>
<thead>
<tr>
<th>PROGRAM</th>
<th>MECHANISM</th>
<th>INDICATION</th>
<th>COMMERCIAL RIGHTS</th>
<th>DISCOVERY</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PIVOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMMUNO-ONCOLOGY</td>
<td>TLR9 Agonist</td>
<td>IMO-2125 Refractory PD-1 Metastatic Melanoma / CPI Comb.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>IMO-2125 Monotherapy Additional Tumor Types</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>IMO-2125 Combo Additional Tumor Types + CPI Comb.</td>
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