TLR9 agonist harnesses innate immunity to drive tumor-infiltrating T-cell expansion in distant lesions in a phase 1/2 study of intratumoral IMO-2125+ipilimumab in anti-PD1 refractory melanoma patients

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Presenter Disclosure Information

Cara Haymaker

The following relationships exist related to this presentation:

No Relationships to Disclose
Modulation of the tumor microenvironment by intratumoral administration of the TLR9 agonist IMO-2125

1. TLR9 induction of IFNα and APC maturation
   - Activation of APCs to improve T-cell priming
   - Improved antigen presentation results in TIL activation and proliferation

2. TIL Activation and Proliferation
Trial Design (NCT02644967)

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

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

Intratumoral IMO-2125
Ipilimumab
Dose-finding phase: IMO-2125 + Ipilimumab

- 18 subjects treated with IMO-2125 doses from 4 – 32 mg (with standard ipilimumab)
  - Patient population was refractory to PD-1 inhibitors and had a high frequency of visceral metastases (M1c; 72%)
  - Patients were injected in a single focus of tumor; deep visceral injections were permitted

- Safety:
  - No DLT, treatment-related deaths or discontinuations from therapy
  - Immune-related AE were similar to ipilimumab monotherapy
  - RP2D selected as IMO-2125 8 mg with standard ipilimumab

- Efficacy (RP2D population):
  - 5/10 patients had either confirmed (4) or unconfirmed (1) RECIST response (BOR = 50%), including 1 durable CR (> 1 year)
  - Another 2 subjects had durable SD (>6 mos)
  - Clinical benefit rate = 67%
  - 1 additional durable PR (> 1 year) at the 4 mg IMO-2125 dose level

Diab, ESMO 2017
Early response data to IMO-2125 + Ipilimumab

Time on study ends at RECIST v1.1 PD (including death & start of new anti-cancer therapy) or study withdrawal for any reason. Subjects treated with IMO-2125 8mg + Ipilimumab with at least 1 post-baseline disease evaluation.

Data cut-off date: 03NOV2017

Produced on 06NOV2017

Data cut off: 3 Nov 2017
Image-guided intratumoral injection of deep lesions with IMO-2125
Tumor Imaging of Patient with a Partial Response: Ipilimumab + i.t. IMO-2125 (8mg)
Immune response monitoring to correlate with mechanism of action

Fresh flow cytometry

Formalin - IHC

DNA and RNA (TCRseq and gene expression)

Tumor Core Needle biopsy

Injected = Injected lesion
Distant = Un-injected Lesion

= collection of biopsy

= collection of PBMCs

Pre-dose

24 hours post i.t. IMO-2125 injection

Ipilimumab

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

C1W2
C2W5
C3W8
C4W11

Immunoresponse monitoring to correlate with mechanism of action

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
Induction of IFNα-response gene signature after i.t. IMO-2125
Rapid mDC1 maturation and macrophage influx induced by IMO-2125 in the tumor

Nanostring

Flow cytometry

p=0.07

n=15
n=12

CD84, CD163, CD64

% HLA-DR on mDC1 cells

Pre-dose 24hr

p=0.07

% HLA-DR on mDC1 cells

CD84, CD163, CD64
Combination therapy induces CD8+ TIL activation early on-treatment in responding patients

Activation at C3W8 by Nanostring

Pre-dose  C3W8

Injected  Distant

Injected (A)  Distant (B)

n=13

IFNG  PD-L1  TBX21  CXCL9  CD8  IL2  CD3  CD27  IL12  CD80

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
Combination therapy induces CD8⁺ TIL activation early on-treatment in responding patients

Activation at C3W8 by Nanostring

- Pre-dose
- C3W8
- Injected: (A)
- Distant: (B)

n=13

Expression of cytokines and immune checkpoint proteins:
- IFNG
- PD-L1
- TBX21
- CXCL9
- CD8
- IL2
- CD3
- CD27
- IL12
- CD68
- CD86
- IL2
- TBX21
- IFNG
- CD80

Tumor Site: B, A
Patient ID: 002, 003, 004, 006, 008, 010, 012, 015, 016, 023, 024, 025
Response: NR, R, SD

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
Combination therapy induces CD8⁺ TIL proliferation and CTL function

Proliferation by flow cytometry

Distant Lesion

\[ \frac{\% \text{ Ki67 on CD8}^+ \text{ T cells}}{\text{p} = 0.11} \]

\[ n = 12 \]
Combination therapy induces CD8+ TIL proliferation and CTL function

Proliferation by flow cytometry

Distant Lesion

% KI67 on CD8+ T cells

p=0.11

Function at C3W8 by Nanostring

n=13

HLA-C

HLA-A

HLA-B

GZMM

GZMH

GNLY

GZMK

GZMA

GZMB

PRF1

n=12
Combination therapy induces CD8^+ TIL proliferation and CTL function

Proliferation by flow cytometry

Distant Lesion

\[ p = 0.11 \]

\( n = 12 \)

Function at C3W8 by Nanostring

\( n = 13 \)

HLA-C
HLA-A
HLA-B
GZMM
GZMH
GNLY
GZMK
GZMA
GZMB
PRF1

\( \% \) Ki67 on CD8^+ T cells
Combination therapy induces CD8\(^+\) TIL proliferation and CTL function

Proliferation by flow cytometry

Distant Lesion

% Ki67 on CD8\(^+\) T cells

n=12

p=0.11
Combination therapy induces CD8\(^+\) TIL proliferation and CTL function at C3W8 by Nanostring.

**Proliferation by flow cytometry**

- **Distant Lesion**
  - \% KI67 on CD8\(^+\) T cells
  - \(p=0.11\)

- **n=12**

**Function at C3W8**

- PRF1
- GZMB
- GZMA
- GZMK
- GZMH
- GZMM
- GNLY
- HLA-C
- HLA-A
- HLA-B
- GZMM
- GZMH
- GNLY
- GZMK
- GZMA
- GZMB
- PRF1

**n=13**
Preferential CD8$^+$ T-cell proliferation at the distant lesion

\[ \text{Pre-dose} \quad \rightarrow \quad \text{C3W8} \]

**Time point: C3W8**

- PBMCs
- Distant Tumor

**Graph:**
- x-axis: % Ki67 on CD8$^+$ T cells
- y-axis: n=11
- p=0.04

**Legend:**
- PBMCs
- Tumor

ADVANCING CANCER IMMUNOTHERAPY WORLDWIDE
Selective increase in CD8$^+$ T-cell proliferation in the tumors of responding patients

**Responders**

- **tumor**
- **PBMCs**

**Non-Responders**

- **tumor**
- **PBMCs**

\[ p = 0.0071 \]

\[ p > 0.05 \]
Expansion of top 50 T-cell clones in the distant lesion of responding patients

Responders

- Pre-dose
- C3W8

Injected
Distant
Injected
Distant

CD8+TIL

Non-Responders
Expanding clones in the distant lesion are shared with the injected lesion

Top 50 clones in the distant lesion at C3W8 of responding patients

Number = clonal specific change in frequency (C3W8 – predose)
Circle size reflects the frequency of the clone relative to the other clones present

Pt 3
Pt 8
Pt 23
Pt 25

Clone shared between lesions

Yes
No
Lessons and Take Home Messages

• Key points
  – IMO-2125 induces a strong type 1 interferon gene signature, macrophage influx and robust DC maturation post injection independent of ipilimumab
  – Combination therapy induces CD8+ T cell proliferation and activation that is preferential to the tumor
  – Major T-cell clones expanding on therapy in responding patients are shared between local and distant lesions indicating that priming/reactivation is to a shared antigen

• 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 an in situ vaccine through activation of local APCs 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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