Update on clinical research assessing CD8 immunoPET

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DISCLOSURE: Anna M. Wu is a Founder, Board Member, and consultant to ImaginAb, Inc.
Humanized anti-human CD8 minibody; $K_D = 0.4$ nM
- Conjugated with DFO, labeled with Zr-89
- In vitro characterization showed no impact on proliferation, depletion, or cytokine release on normal human donor T cells
- In vivo studies in humanized mice showed no impact on T cell populations or cytokine release
- In vivo imaging in humanized mouse model
CD8-targeted PET Imaging of Tumor Infiltrating T cells in Patients with Cancer: A Phase I First-in-Human Study of $^{89}$Zr-Df-IAB22M2C, a Radiolabeled anti-CD8 Minibody


UPENN, MSKCC, Honor Health Imaging Endpoints, ImaginAb
Study Design: Clinical imaging of CD8 T leukocytes using $^{89}$Zr-IAB22M2C

- Solid malignancies with at least 1 RECIST measurable lesion on CT/MRI
- Eligible for/on checkpoint inhibitor therapy
- Open-label, non-randomized, 2 stage:
  - Protein dose escalation (6 patients: 3 mCi $^{89}$Zr; 0.2, 0.5, 1, 1.5, 5, 10 mg protein)
  - Protein dose expansion (9 patients: 3 mCi $^{89}$Zr; 0.5 or 1.5 mg protein)
- Serial imaging at 1-2 h; 6-8 h; 24 h; 48 h; 96-144 h
- Serial blood draws for pharmacokinetics
- Also assayed cytokines (baseline, 4h, 24 h) and ADA (anti-drug antibody) (baseline, 3-4 wk, 8-12 wk)

One patient had transient ADA (3-4 wk) which became undetectable by 8-12 wks

Stage 2 (all 15 patients): M. Farwell et al., submitted
Clinical imaging of CD8 T leukocytes using $^{89}$Zr-IAB22M2C

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median years (range)</td>
<td>64 (30–81)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Female</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Tumor type, n (%)</td>
<td></td>
</tr>
<tr>
<td>Melanoma</td>
<td>8 (53)</td>
</tr>
<tr>
<td>Non-small cell lung carcinoma</td>
<td>6 (40)</td>
</tr>
<tr>
<td>Hepatocellular carcinoma</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Treatment profile at the time of imaging, n (%)</td>
<td></td>
</tr>
<tr>
<td>On immunotherapy (&lt;2 months)</td>
<td>3 (20)</td>
</tr>
<tr>
<td>On immunotherapy (&gt;2 months)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>On targeted therapy (1–6 months)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Discontinued prior treatment (&gt;5 months)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Treatment naïve</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>
Results: Pharmacokinetics

- Rapid, biexponential serum clearance
- Rapid localization to spleen, BM, LN
- Tumor uptake increases through 24 h

<table>
<thead>
<tr>
<th>Dose</th>
<th>$t_{1/2\alpha}$</th>
<th>$A_\alpha$</th>
<th>$t_{1/2\beta}$</th>
<th>$A_\beta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg (n=4)</td>
<td>0.33 ± 0.10 h</td>
<td>61.5%</td>
<td>14 ± 7.0 h</td>
<td>38.5%</td>
</tr>
<tr>
<td>1.5 mg (n=5)</td>
<td>0.38 ± 0.29 h</td>
<td>75.5%</td>
<td>6.4 ± 3.4 h</td>
<td>24.5%</td>
</tr>
</tbody>
</table>
Results: Examples of negative lesions

Figure S1. (A) CT and fused CD8 PET/CT images of a patient with metastatic melanoma on targeted therapy demonstrate a large nodal metastasis in the left pelvis (arrow) with tracer uptake at background. (B) CT and fused CD8 PET/CT images of a patient with non-small cell lung cancer prior to initiation of therapy demonstrate a large tumor lesion in the left lung (arrow) with tracer uptake at background.
Results: Example of positive CD8 immunoPET

Figure 4. 71-year-old man with locally advanced stage III melanoma treated with pembrolizumab. Baseline CT and fused FDG PET/CT images (left) demonstrate two FDG avid metastases in the left axilla ($\text{SUV}_{\text{MAX}} = 10.0$, medial node; $\text{SUV}_{\text{MAX}} = 7.6$, lateral node). CT and fused CD8 PET/CT images (middle) performed 28 days after starting immunotherapy demonstrate increased tracer activity in both metastases ($\text{SUV}_{\text{MAX}} = 11.7$, medial node; $\text{SUV}_{\text{MAX}} = 12.3$, lateral node), suggestive of tumor infiltration by CD8+ T cells. Follow-up imaging with contrast-enhanced CT (right) demonstrated a complete response to therapy.

Follow-up: Complete response, 2.3+ years
Phase I Summary

Imaging conclusions:

- Rapid clearance; excretion primarily hepatobiliary
- Uptake in T-cell rich tissues (spleen, BM, LN)
- No/low uptake in normal organs (muscle, heart, brain, lungs)
- Tumor uptake variable ($SUV_{MAX}$ up to $>20$) and seen in 10/15 (67%) patients
- Protein dose range with favorable biodistribution: 0.5-1.5 mg
- Most favorable imaging time: 24 hrs, although tumors seen as early as 1-2 hrs

Gordon et al. SITC 2018; Farwell et al. submitted.
Phase II Pre-treatment/On-treatment study
(NCT03802123)

- Patients with metastatic solid tumors, initiating checkpoint inhibitor therapy
  - Pre-treatment (baseline) CD8 PET scan and biopsy (3 mCi* /1.5 mg; 24 h)
  - Initiate immunotherapy (ipi/nivo/pembro standard of care)
  - On-treatment CD8 PET scan and biopsy (4-5 weeks after therapy initiation)
- Goals
  - Safety of repeat dosing and imaging
  - Correlation of CD8 PET with CD8 IHC
  - Correlation with RECIST and outcome
- Multi-center trial, ongoing with ~ 10 sites active; ~ 30 patients enrolled

*Amended to reduce activity to 1 mCi/1.5 mg
RECIST 1.1. Response

Early (1 mo) CD8 immunoPET correlated with response (4 mo)

Lack of change of CD8 signal from baseline to 1 mo post-treatment

Courtesy ImaginAb, Inc.
CD8 immunoPET Logistics

- PET scanner validation (SNMMI/Nuclear Medicine Clinical Trial Group) includes calibration of dose calibrator and shipment of calibrated Zr-89-filled phantom. Multiple manufacturers/scanners supported. NMCTG will send specific acquisition and reconstruction parameters back to the site.
- 16 sites validated in US; 9 sites in Canada/UK/EU/Australia
- Manufacturing and dose supply from 2 sites in US: MSKCC (NY) and Optimal Tracers (CA)
- Cloud-based product ordering platform, doses available M-F
- Doses shipped in lead shielding, thermally controlled and tracked
Point of Contact

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