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CD8 PET imaging of tumor infiltrating T cells in advanced solid tumors: a phase I first-in-human study of ^{89}Zr-IAB22M2C, a radiolabeled anti-CD8 minibody

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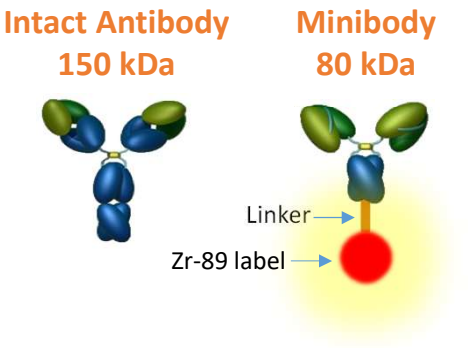
Disclosure

I have NO financial disclosure or conflicts of interest with the presented material in this presentation.

Background

- Tumor infiltration by CD8+ T cells is associated with favorable outcomes to cancer immunotherapy.
- Biopsies to assess T cell infiltration are invasive and prone to sampling error.
- CD8 PET imaging could provide a non-invasive method of visualizing T cell trafficking and tumor infiltration, to predict early response to immunotherapy.

Technology: ^{89}Zr-labeled anti-CD8 Minibody

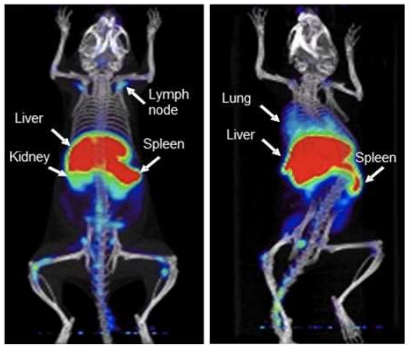


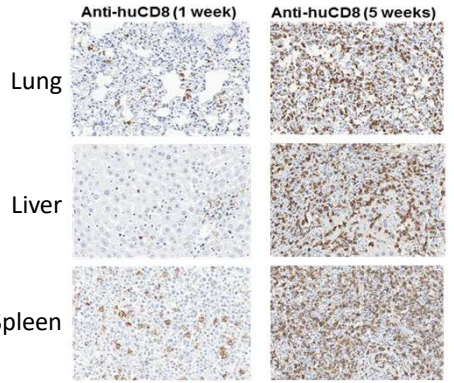
Minibody advantages:

- Smaller size – faster clearance from blood
- Lack of effector function – inert

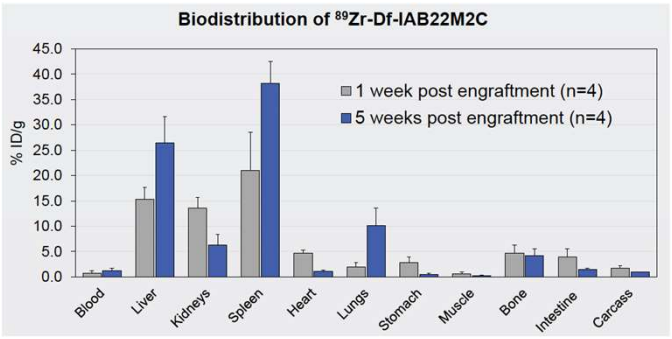
^{89}Zr advantages:

- Long half life of ^{89}Zr – repeat imaging
- Centralized manufacturing





- Validated pre-clinically as inert and specific



Olafsen T, Torgov M, Zhang GG, et al. PET imaging of cytotoxic human T cells using an 89Zr-labeled anti-CD8 minibody. *J Immunother Cancer*. 2015; 3 (Suppl 2):P388.

First-in-Human CD8 PET/CT Trial

Objectives:

- Determine safety, tolerability & whole body distribution (including tumor sites) of ^{89}Zr-IAB22M2C
- Determine optimal protein dose & scanning parameters for future studies

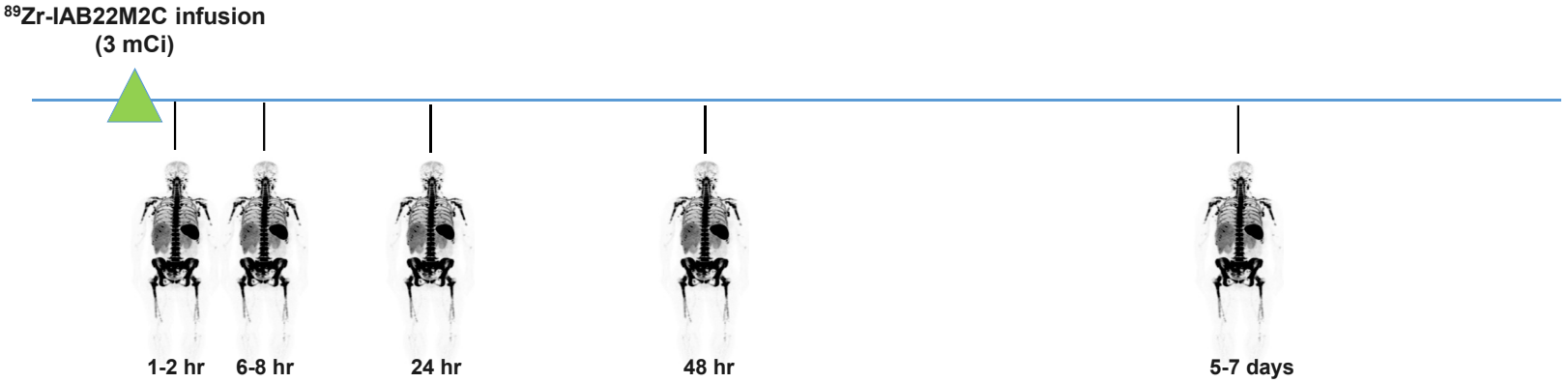
Design:

- Open-label, non-randomized, 2 stage (dose escalation and dose expansion)
- Solid malignancies with at least 1 RECIST measurable lesion on CT/MRI
- 3 clinical sites (MSKCC, Honor Health, UPenn)

First-in-Human CD8 PET/CT Trial

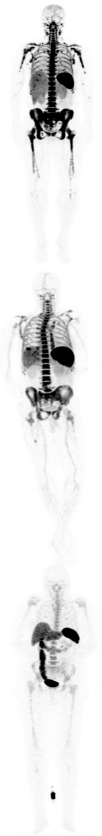
Stage 1: Dose escalation (n=6) – 1 subject each at 0.2 mg through 10 mg

Stage 2: Dose expansion (n=9) – 4 subjects at 0.5 mg and 5 subjects at 1.5 mg



Pandit-Taskar N, Postow MA, Hellmann MD, et al. First-in-Humans Imaging with ^{89}Zr-Df-IAB22M2C Anti-CD8 Minibody in Patients with Solid Malignancies: Preliminary Pharmacokinetics, Biodistribution, and Lesion Targeting. *J Nucl Med.* 2020; 61:512.

CD8 PET/CT Trial: Results

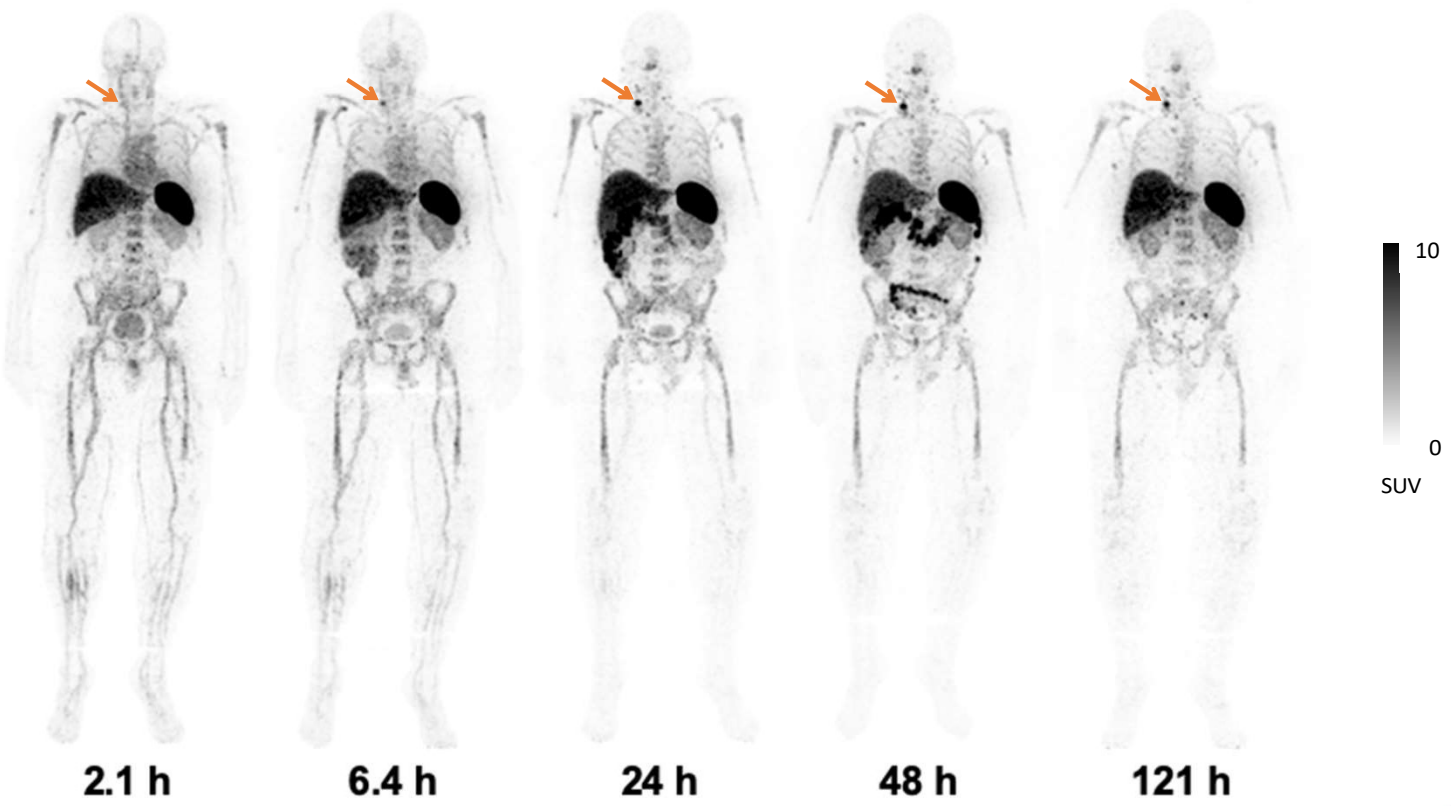


Demographics and safety:

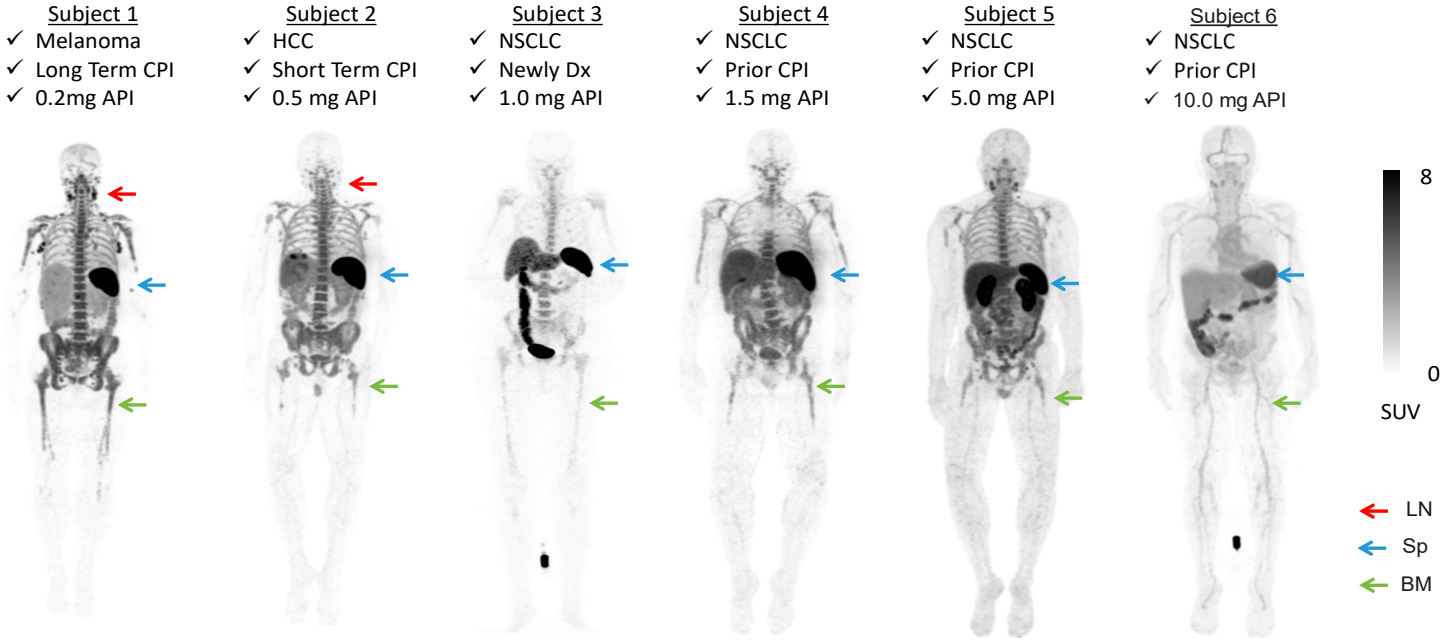
- 15 subjects with metastatic cancer (30-81 years; M/F=9/6)
- Melanoma (n=8), NSCLC (n=6), and HCC (n=1)
- Subjects were on immunotherapy (n=8), on targeted therapy (n=2) or were treatment naïve / discontinued treatment (n=5)

- No drug-related AEs, cytokine release or blood test abnormalities
- Transient ADA in 1/15 subjects
- Mean estimated radiation dose 0.65 mSv/MBq

Whole Body Biodistribution vs. Time

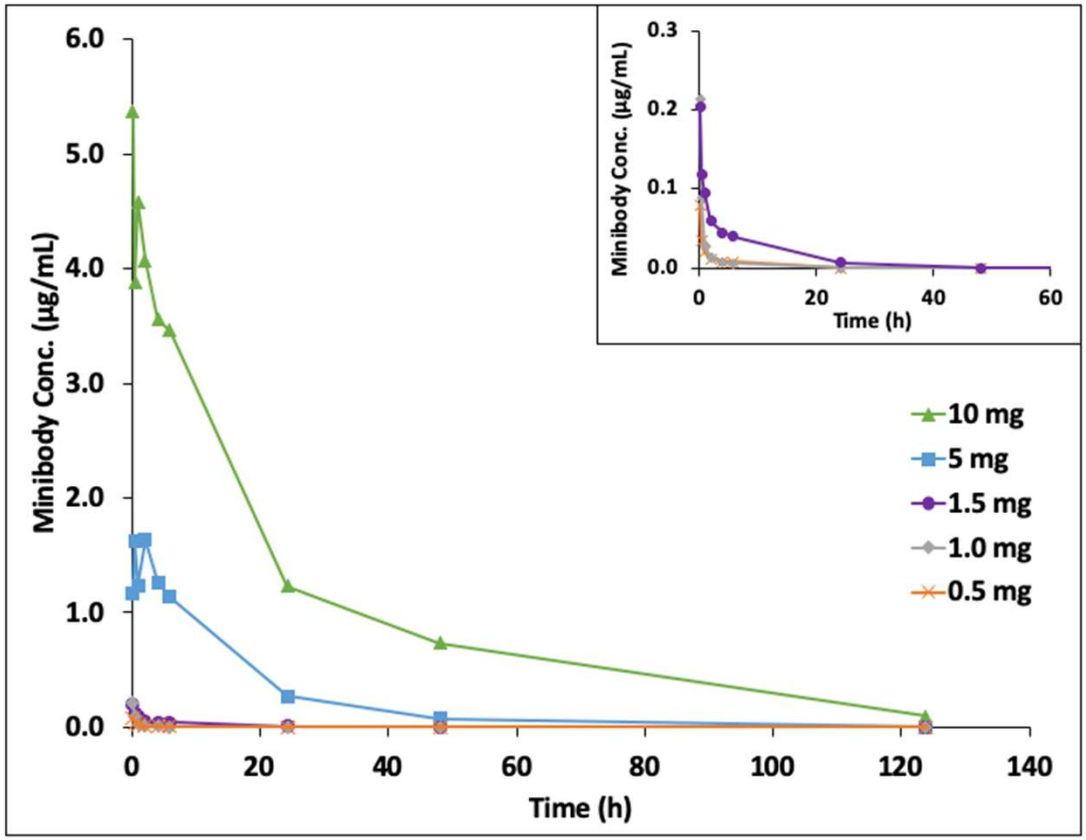


Whole Body Biodistribution vs. Dose



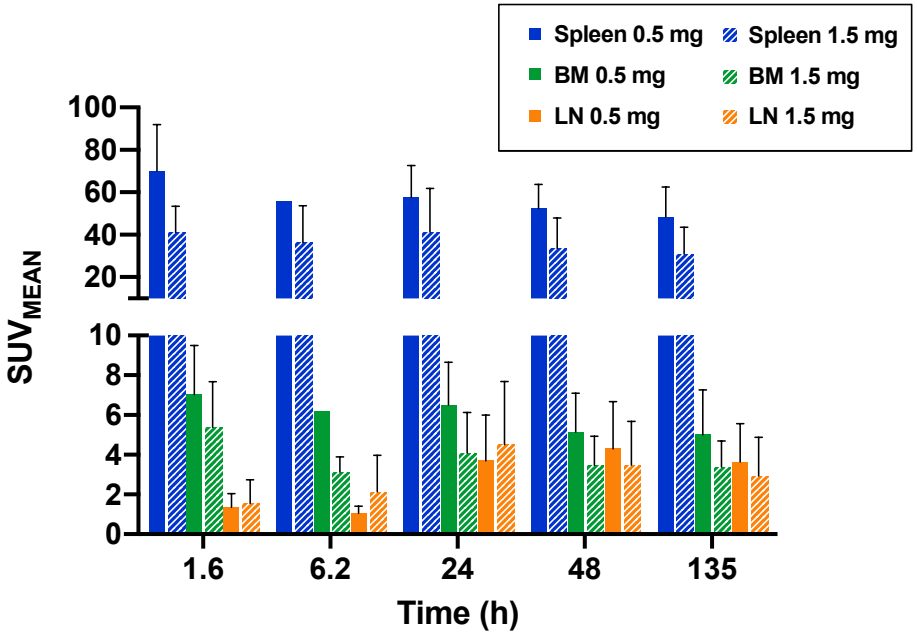
- All dose levels safe
- Increase in IAB22 protein dose changes biodistribution of agent
- See saturation of T-cell rich tissue with increased dose (i.e. Spleen & BM)

Dose escalation: Rapid Clearance from Serum



Dose expansion: Organ Uptake

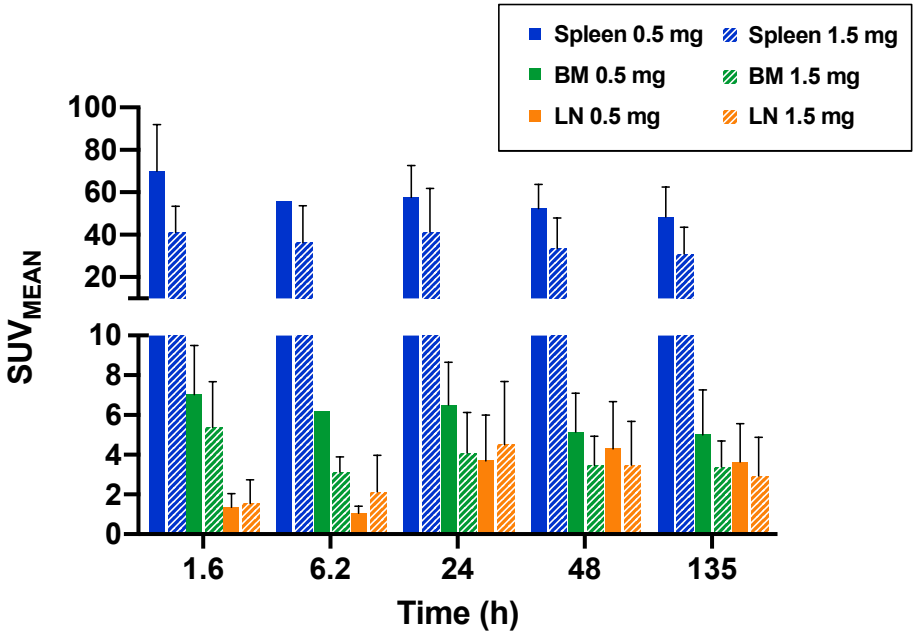
CD8-high tissues



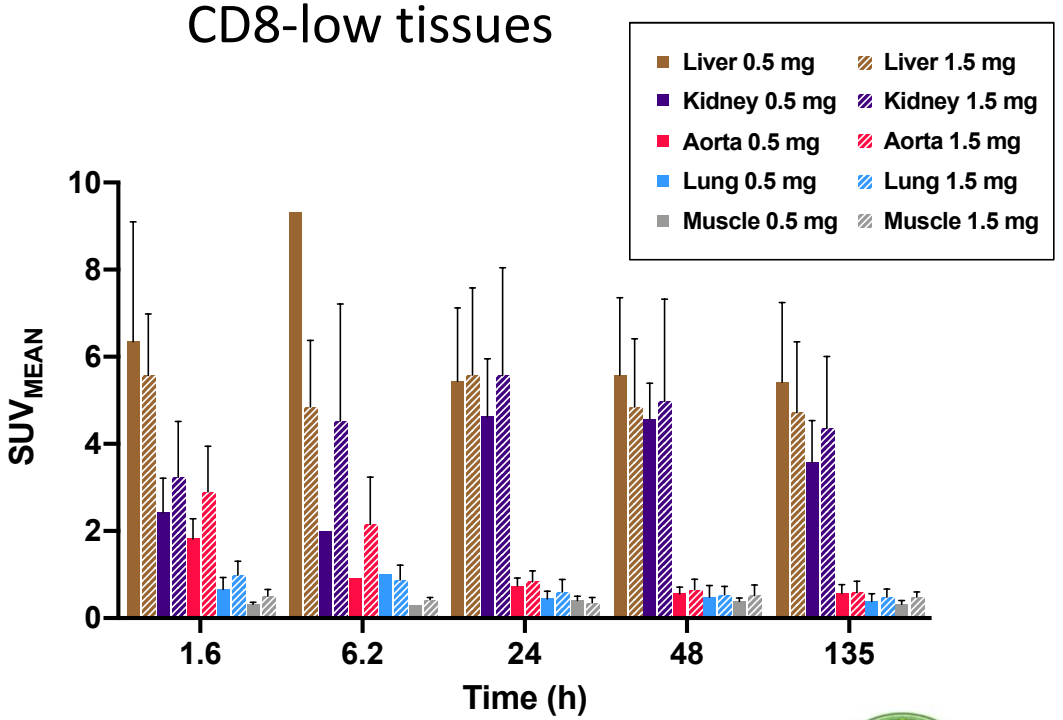
Higher protein dose => reduced uptake in spleen and bone marrow but similar uptake in lymph nodes.

Dose expansion: Organ Uptake

CD8-high tissues



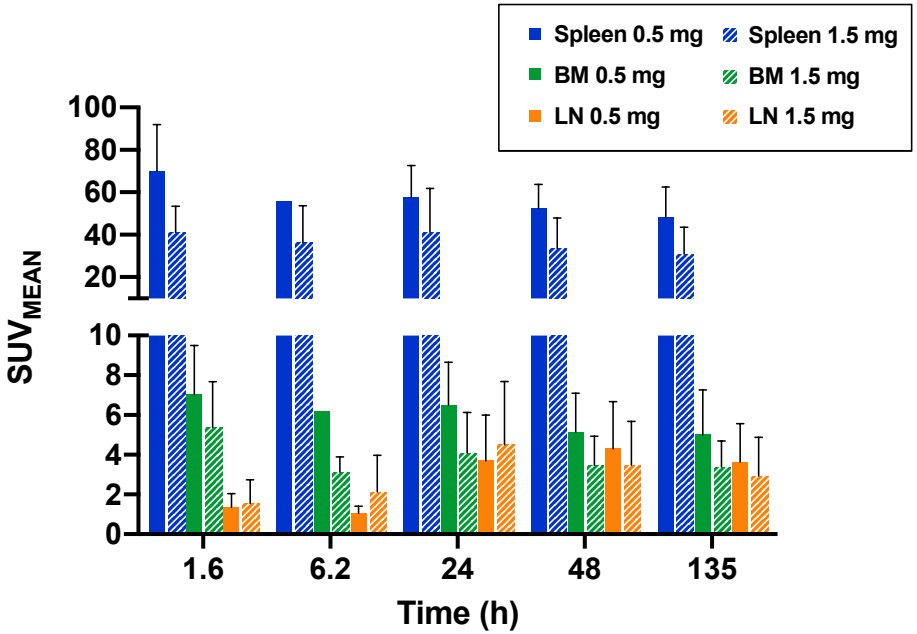
CD8-low tissues



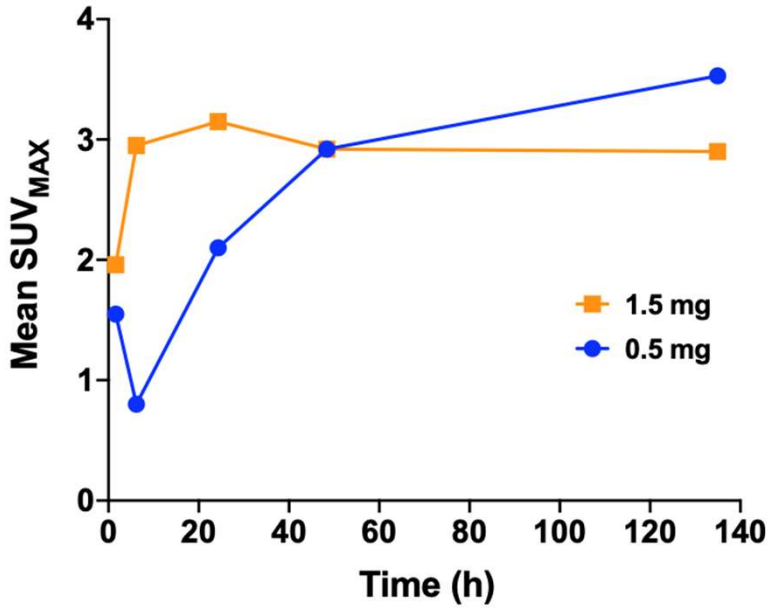
Higher protein dose => no change in uptake in CD8-low tissues.

Dose expansion: Organ Uptake and Tumor Uptake

CD8-high tissues



Tumor Uptake



Higher protein dose => similar to slightly higher tumor uptake.

Dose expansion: Dosimetry

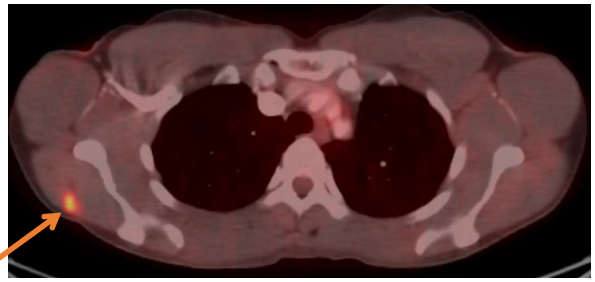
	Mean Organ Dose (mGy/MBq)	
Target Organ	**0.5 mg**	**1.5 mg**
Bone Marrow	0.81	0.68
Spleen	15	11
Effective Dose (mSv/MBq)	0.67	0.64

Higher protein dose => reduced radiation dose to bone marrow, spleen, and whole body.

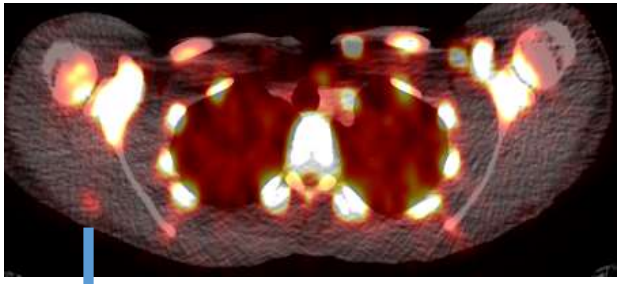
CD8 PET concordant with FDG PET

- 37 y/o, female with metastatic melanoma, on pembrolizumab for ~2 years.

FDG PET/CT

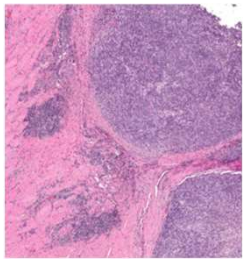


^{89}Zr-IAB22M2C PET/CT

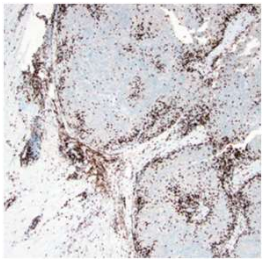


Biopsy

H&E

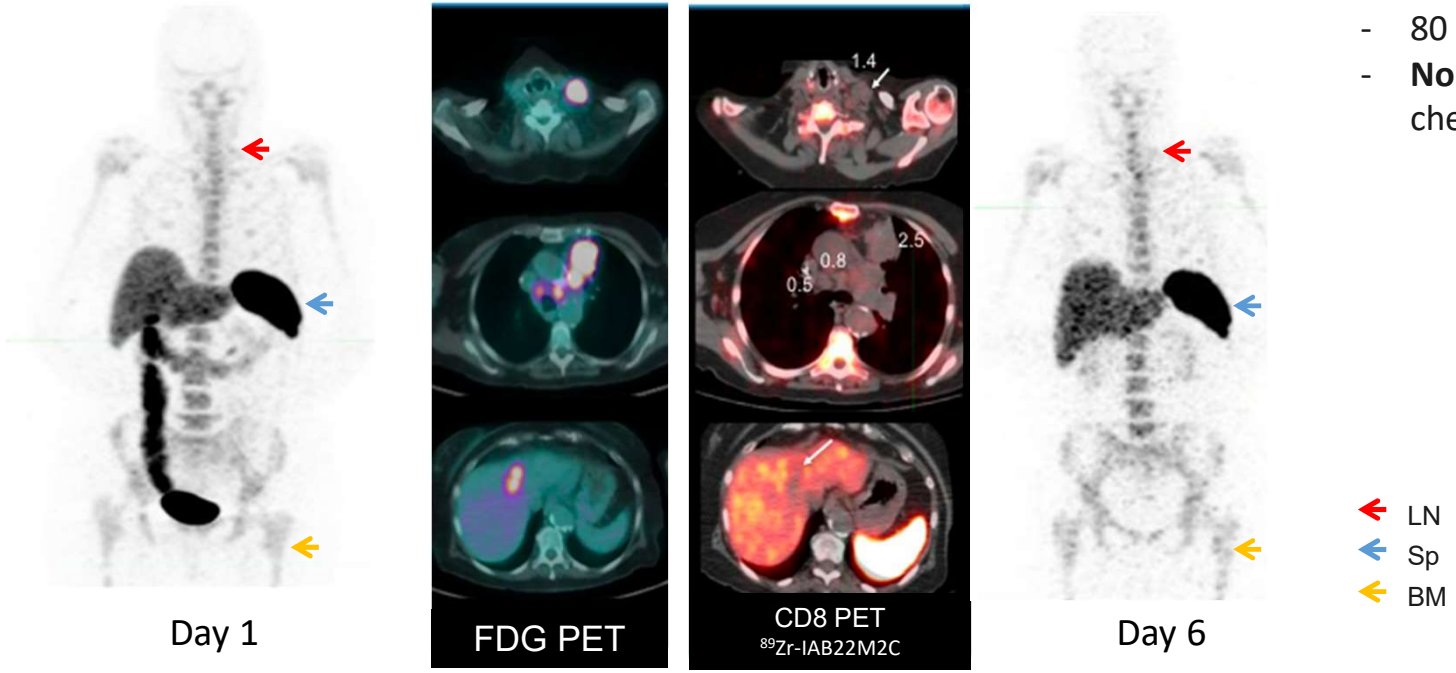


CD8 IHC



- Co-Localization of ^{89}Zr-IAB22M2C in tumor with high uptake
- Co-Localization with CD8+ T cell infiltration

CD8 PET discordant with FDG PET

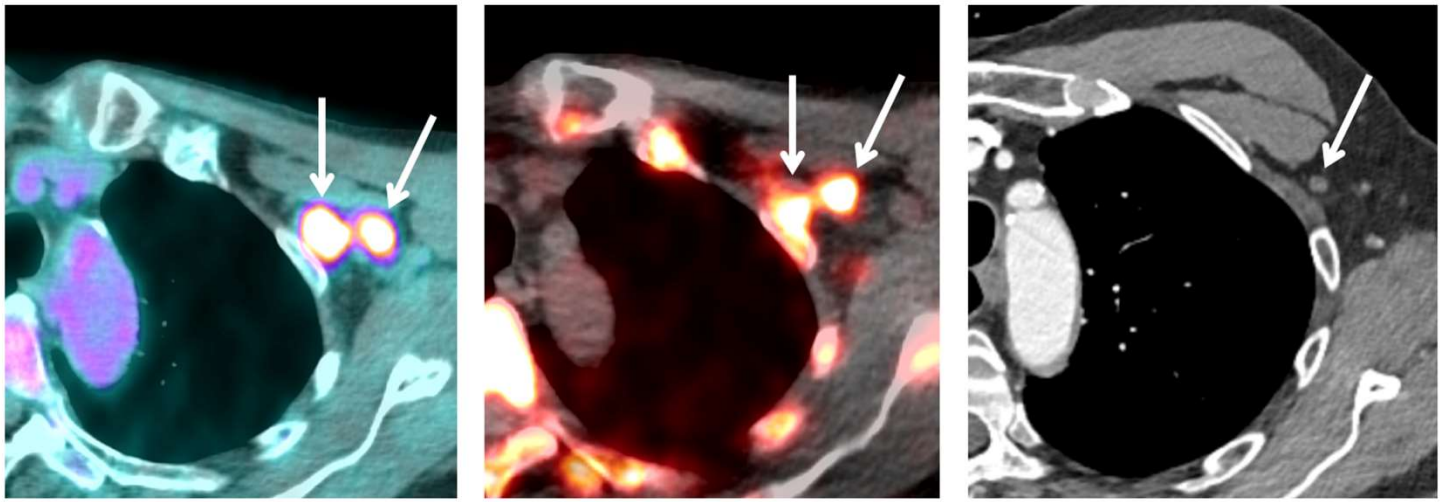


- 80 y/o, female with NSCLC
- **No prior treatment** (began chemotherapy post scan)

- Specific uptake: not an effect of vascularity/permeability or non-specific retention

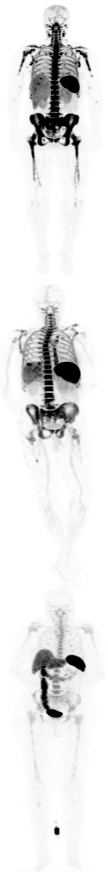
^{89}Zr-IAB22M2C uptake correlates with response

- 71 y/o, male with metastatic melanoma treated with pembrolizumab.



Baseline (FDG PET/CT) | **28 days post Tx (CD8 PET/CT)** | **21 months post Tx (CT)**

Summary of First-in-Human CD8 PET/CT



- *^{89}Zr-IAB22M2C is safe and well tolerated*
- *Rapid clearance of tracer; excretion primarily hepatobiliary*
- *Uptake in T-cell rich tissues*
- *No uptake in background tissues (muscle, heart, brain, lungs)*
- *Tumor uptake variable and seen in 10/15 patients*

- *1.5 mg API provides favorable biodistribution and dosimetry*
- *Imaging time: 24 hrs post injection is optimal*

CD8 PET/CT imaging has the potential to *address fundamental questions* regarding CD8 T cell trafficking, and may predict early response to cancer immunotherapy

Next Steps

Phase II study is ongoing:

- Correlate CD8 PET/CT imaging with synchronous biopsy data
- Correlate pre- and post treatment CD8 PET/CT scans with response to cancer immunotherapy

Acknowledgements

ImaginAb

- Ian Wilson, PhD (CEO)
- Alessandro Mascioni, PhD
- William Le
- Avital Weiss, PhD
- Ronald Korn, MD PhD

City of Hope

- Anna M. Wu, PhD (ImaginAb Founder and Chief Scientific Advisor)

MSKCC

- Neeta Pandit-Taskar, MD
- Mike Postow, MD

Honor Health

- Michael S. Gordon, MD

UPenn

- Raymond F. Gamache, PhD