ImmunoPET for Whole Body Imaging of Immune Cell Subsets

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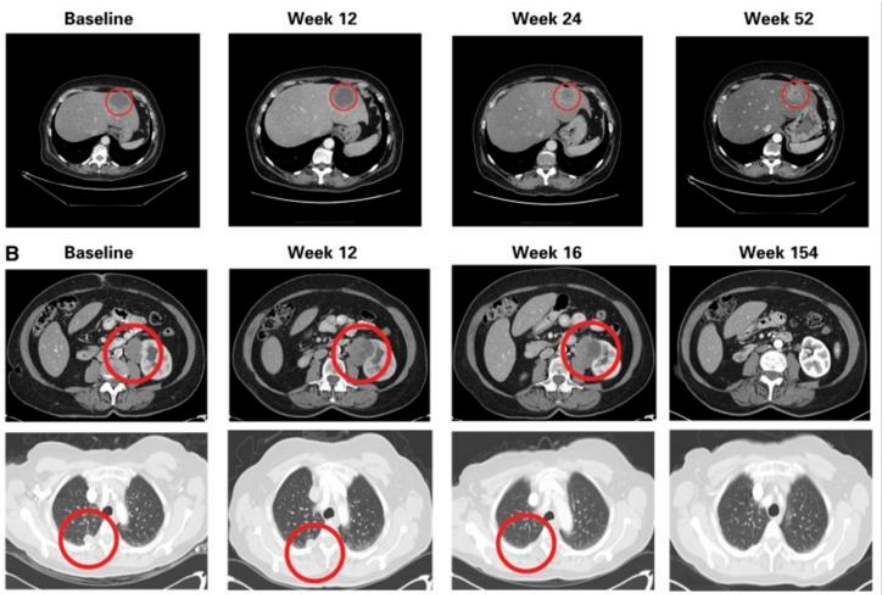
Disclosures

Anna M. Wu is a board member, and consultant to ImaginAb, Inc.

I will discuss investigational use of a non-FDA-approved agent.

Challenges in immuno-oncology

Pseudoprogression in advanced melanoma patients treated with pembrolizumab



Hodi, Ribas, Wolchok et al. J. Clin.Oncol. 2016

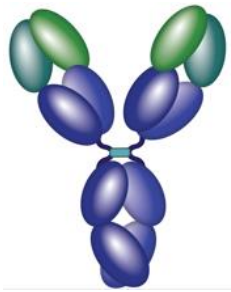
Diagnostic challenges: anatomic (CT, MRI) and metabolic imaging (FDG-PET)

- Identification of patients likely to respond to immunotherapy
- Heterogeneity of tumor biology and immune responses
- True responses vs. non-responses vs. pseudoprogression
- Similar metabolic shifts in active cancer *and* immune cells
- Biopsies can provide detailed and complex information
  - Sampling limitations
  - Invasive; not typically performed after initial diagnosis
- Blood sampling not necessarily representative
  - Only 2% of total T lymphocytes are in the circulation

Clinical challenges

- Real but modest response rates – patient selection
- Toxicities (pleuritis, colitis, cardiotoxicity, T1D, etc.)
- Rational development of combination therapies

immunoPET



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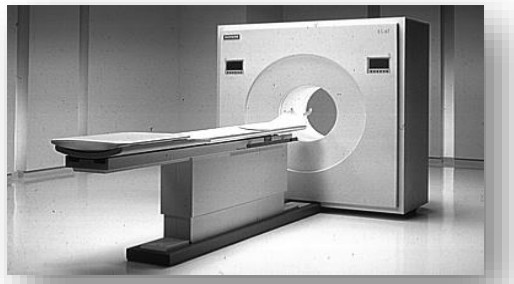


Antibodies: *Diversity and specificity*

PET: *Sensitivity, resolution, quantitation*

Therapeutics: over 80 antibodies approved by FDA

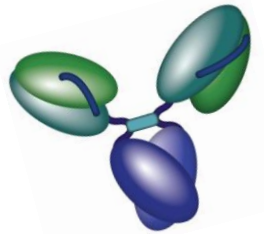
Imaging: Facilitated by long half-life PET radionuclides (^{64}Cu, ^{89}Zr, ^{124}I)

^{89}Zr-atezolizumab

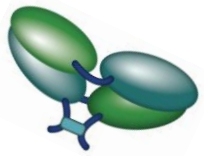
^{18}F-PD-L1 adnectin and ^{89}Zr-nivolumab

Beyond intact antibodies:

- Engineered antibody fragments: minibody and diabody
- Optimized pharmacokinetics for rapid imaging
- Biologically inert (no Fc)
- Site-specific conjugation/labeling



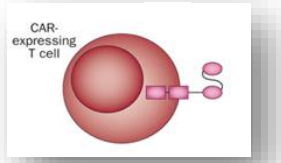
Minibody
80 kDa



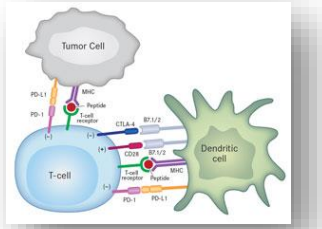
Diabody
55 kDa

ImmunoPET imaging of cell surface markers in immunology

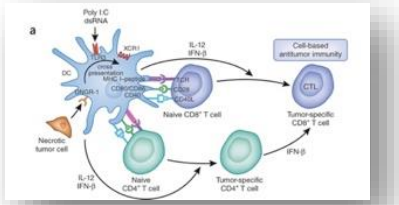
- FDG-PET non-specific
- CD antigens as markers of lineage, differentiation, activation
- Applications:
  - Immune responses and inflammation
  - Cancer immunotherapy



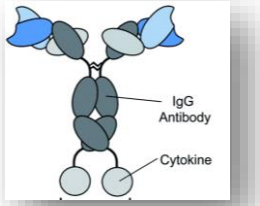
Cell-based therapies



Checkpoint inhibitors

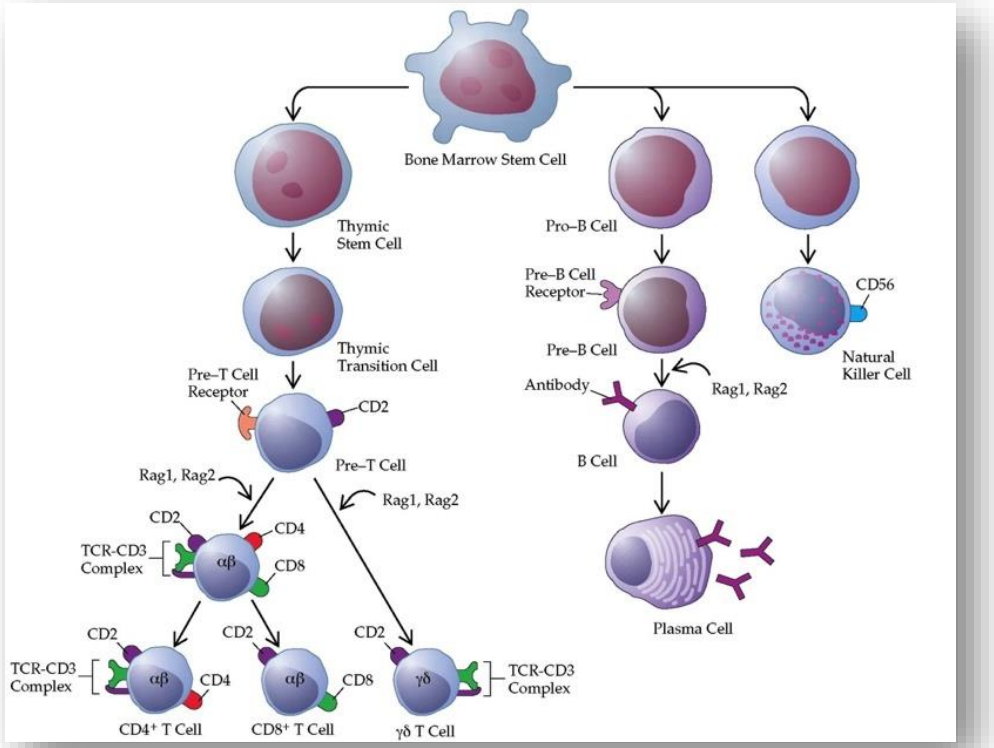


Vaccines



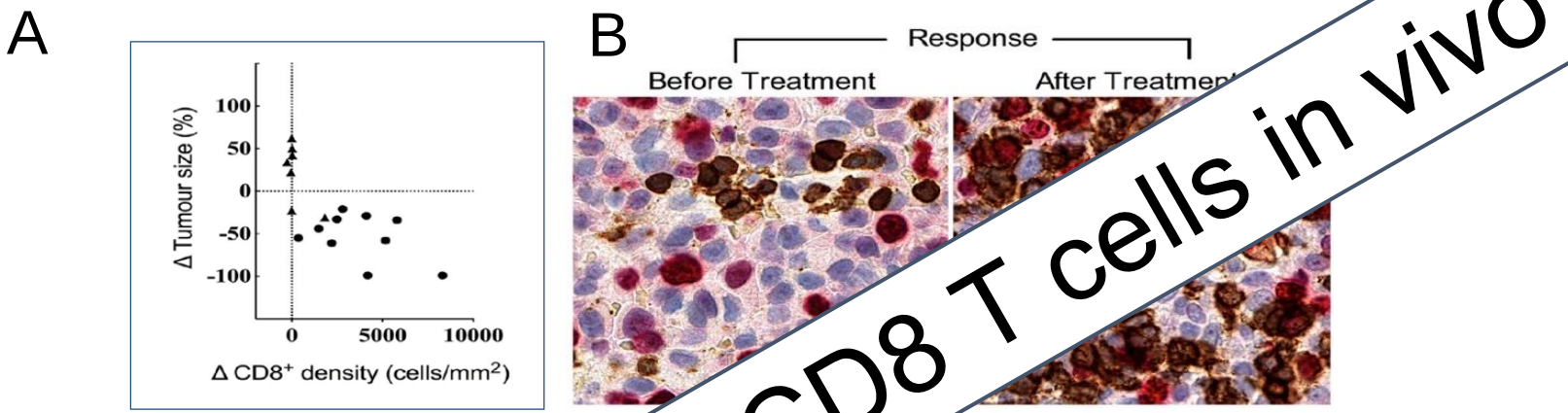
Immunocytokines

Bispecifics

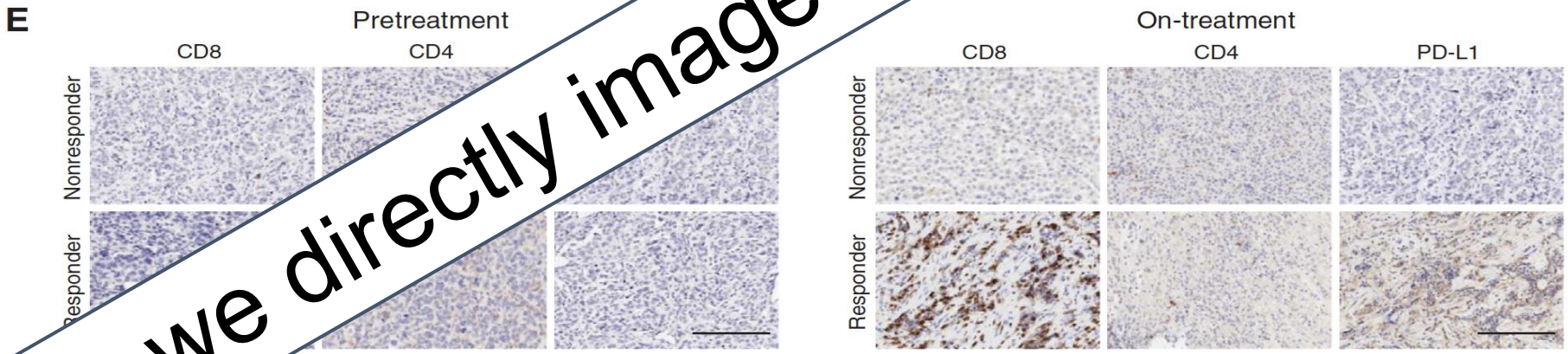


"The cytotoxic T cell is the drug."
-Toni Ribas

CD8 T cell infiltration in early on-treatment biopsies can predict ultimate response



PD-1 blockade; Tumeh ... ure 2014



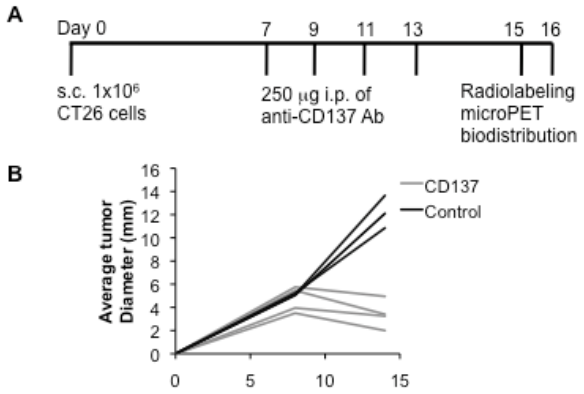
... blockade; Chen, Sharma, Allison, Wargo, et al. Cancer Discovery 2016

Can we directly image CD8 T cells in vivo?

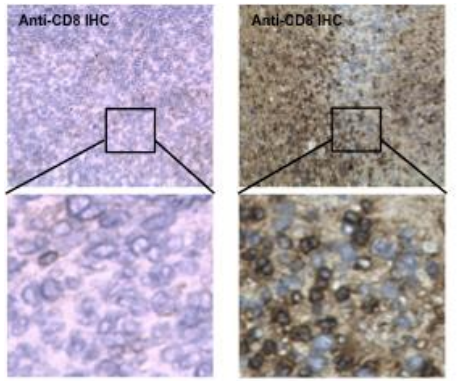
Imaging **CD8** T cell infiltration in tumor immunotherapy

CT26 syngeneic tumor treated with anti-CD137 (4-1BB)

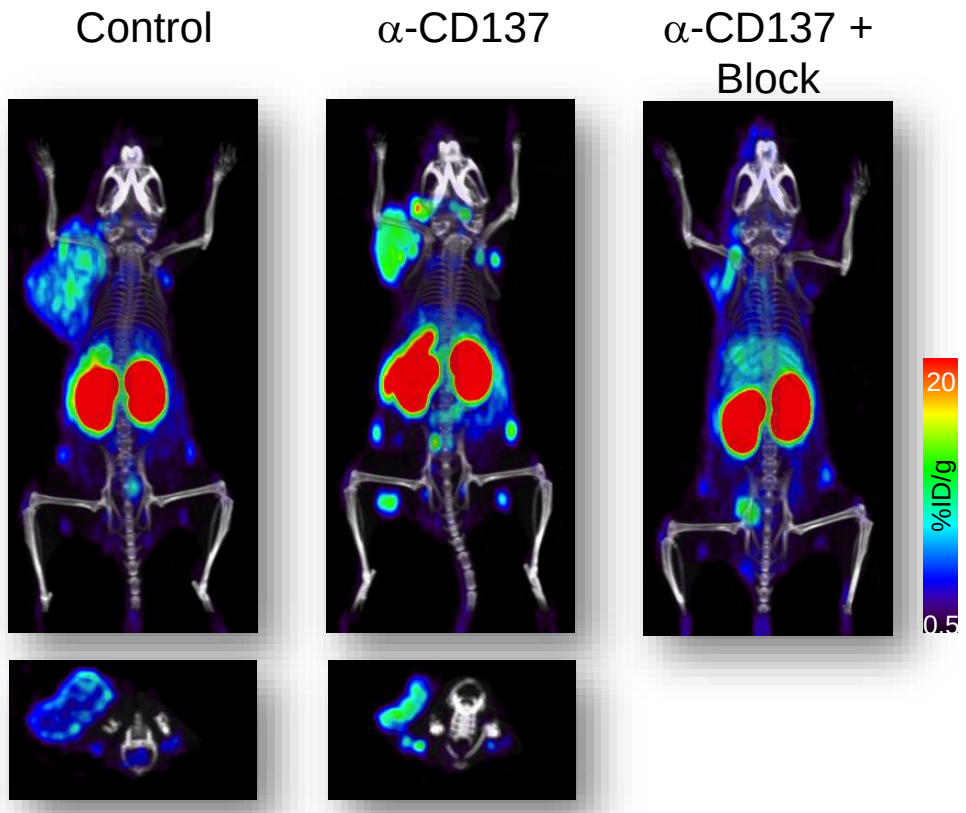
Zr-89-DFO-169
Rat anti-mouse
CD8 cys-Db



CD8 IHC



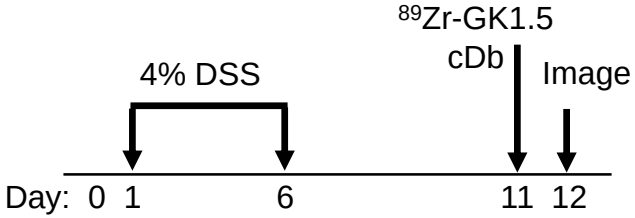
Tavaré, R. et al., Canc. Res. 2016

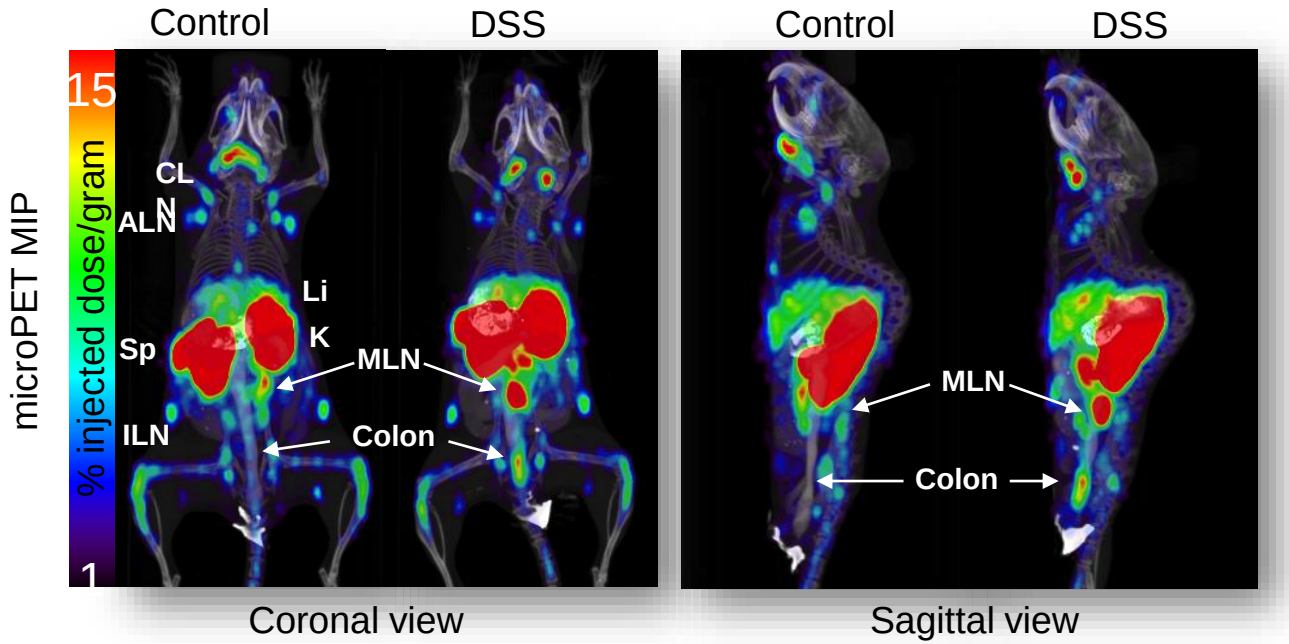


MicroPET imaging using ^{89}Zr anti-CD8 169 cys-diabody

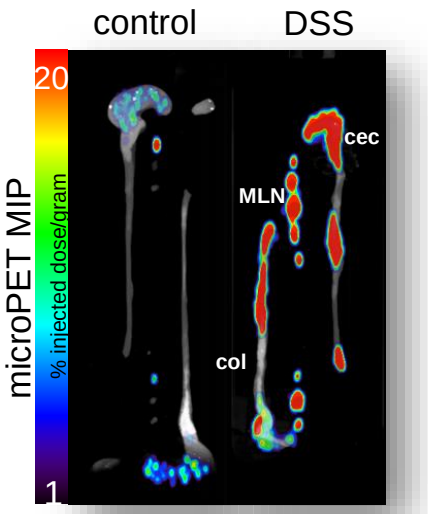
Imaging **CD4 T** cells in colitis

- Dextran sulfate sodium (DSS) induced colitis with infiltration of $CD4^+$ T cells into colon
- Oral and intrarectal CT contrast
- ^{89}Zr-mal-DFO-GK1.5 cDb (2 µg; 8 µCi)

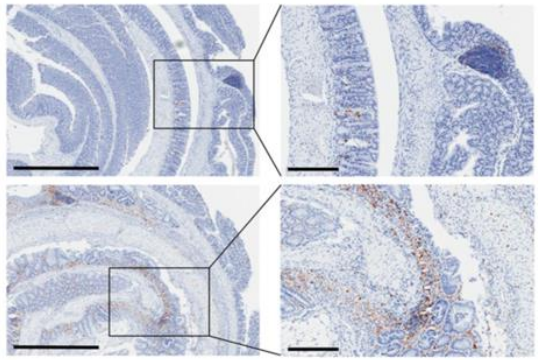




Ex vivo imaging



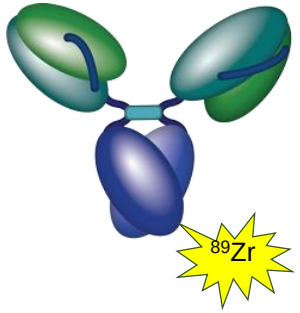
CD4 IHC



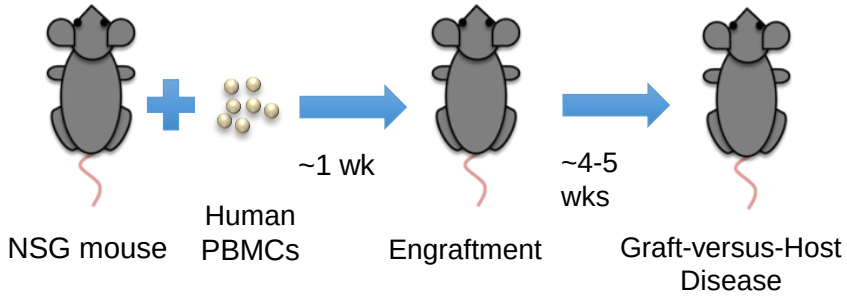
Anti-CD4 immunohistochemistry on sections of colon tissue validates infiltration of CD4+ T cells in colitic mice

A. Freise et al. J. Nucl. Med. 2018

Translation: ImmunoPET of **human CD8 T** cells in humanized mice



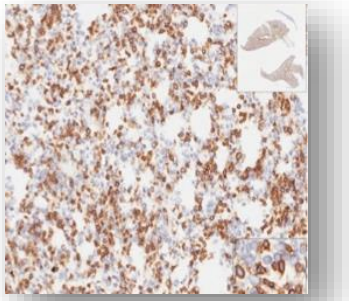
- Fully humanized anti-human CD8 minibody
- 0.4 nM affinity
- Conjugated with DFO and labeled with ^{89}Zr



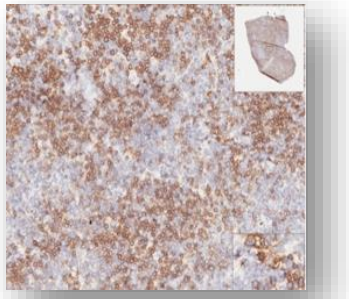
1 week Engraftment

4 weeks GVHD

huCD8 IHC



Lung



Spleen

T. Olafsen et al. abstract AACR 2016

Clinical imaging of CD8 T lymphocytes using ^{89}Zr-IAB22M2C

Objectives: Phase I study looking at:

- Safety, tolerability & whole body distribution (including tumor sites)
- Determine recommended protein dose & scanning parameters for future studies

Design

- Open-label, non-randomized, 2 stage:
  - dose escalation (6 patients)
  - dose expansion (9 patients)
- Solid malignancies with at least 1 RECIST measurable lesion on CT/MRI

Demographics

- 15 subjects with metastatic cancer (31-82 yrs; M/F=9/6)
- Melanoma (n=8), NSCLC (n=6), and HCC (n=1)
- Treatment naïve (2), prior CPI (3), on CPI for 2 wks to >2 yrs (10)

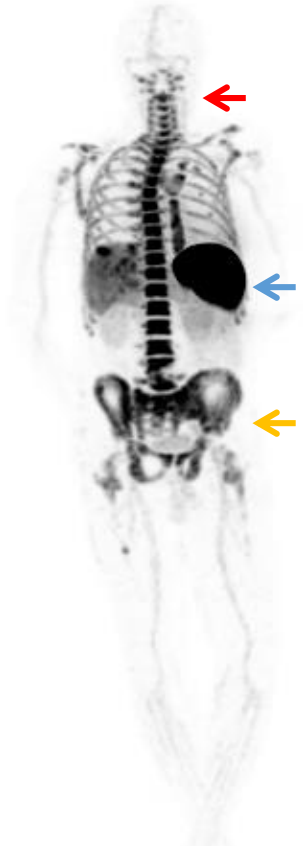
Safety

- No drug-related AEs, cytokine release or blood test abnormalities
- Transient ADA in 1/15 subjects

M. Gordon et al. SITC 2018
N. Pandit-Taskar et al. J. Nucl. Med. 2019

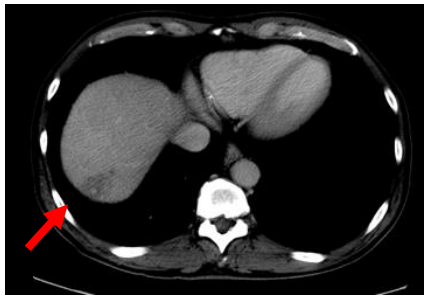
MSKCC, UPenn, HonorHealth and ImaginAb, Inc.

^{89}Zr CD8 immunoPET - CD8 in lymphoid tissues and tumor



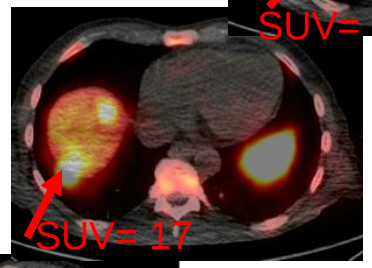
Day 1: 6 h

Contrast CT

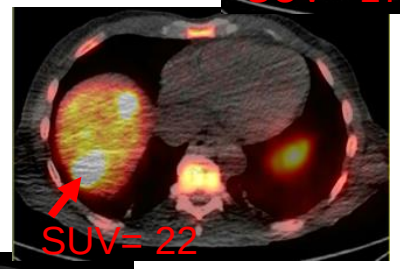


6d

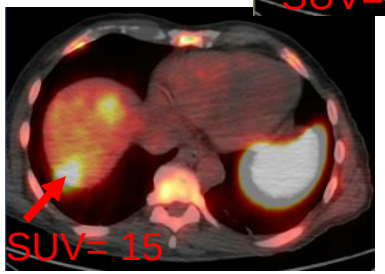
2d



1d

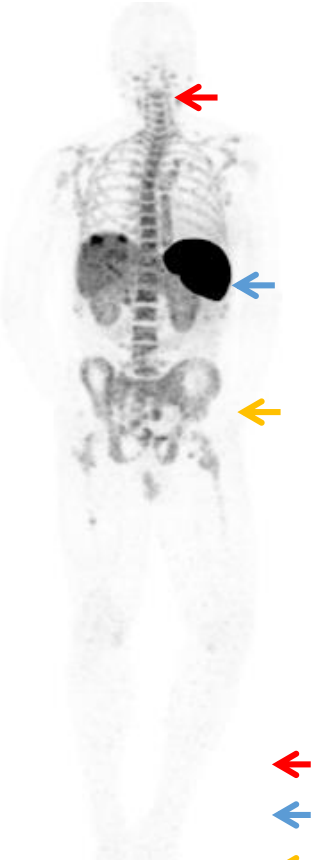


~1h



64 year old male with HCC
Nivolumab initiated 2 wks prior to CD8 immunoPET

- ✓ Localization in known tumor additional lesion detected
- ✓ Same day imaging possible

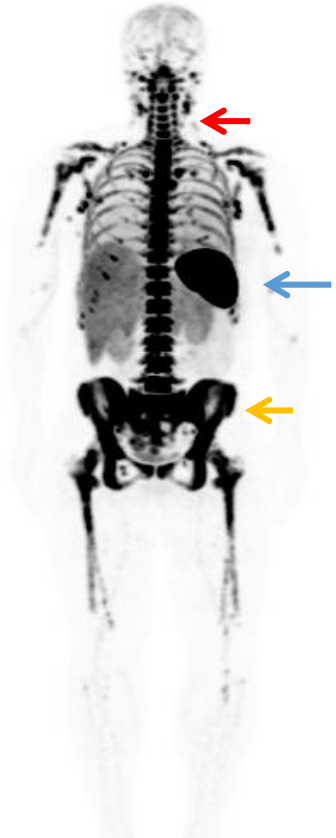


Day 6

LN
Sp
BM

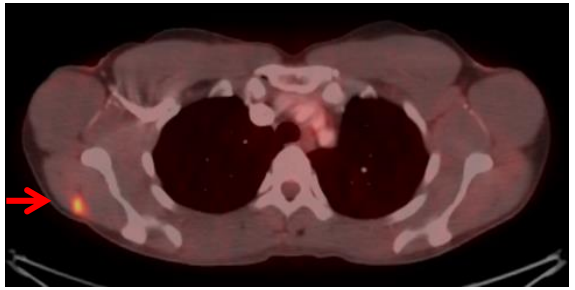
M. Gordon et al. SITC 2018
N .Pandit-Taskar et al. J. Nucl. Med.2019

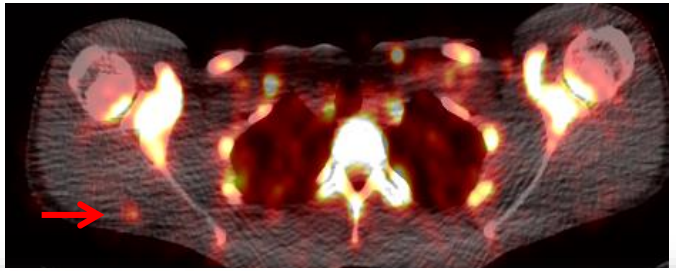
^{89}Zr CD8 immunoPET - CD8 in lymphoid tissues and tumor



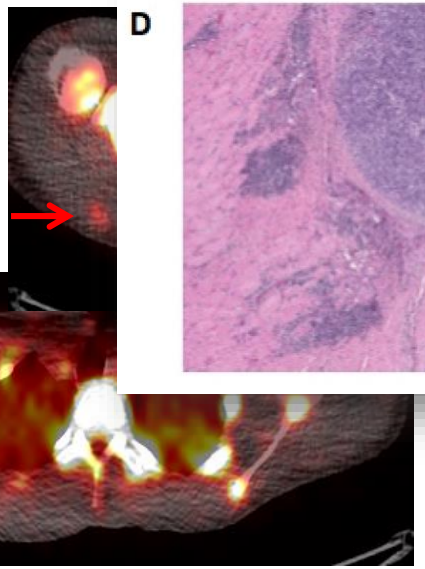
Day 1: 6 h

FDG PET/CT





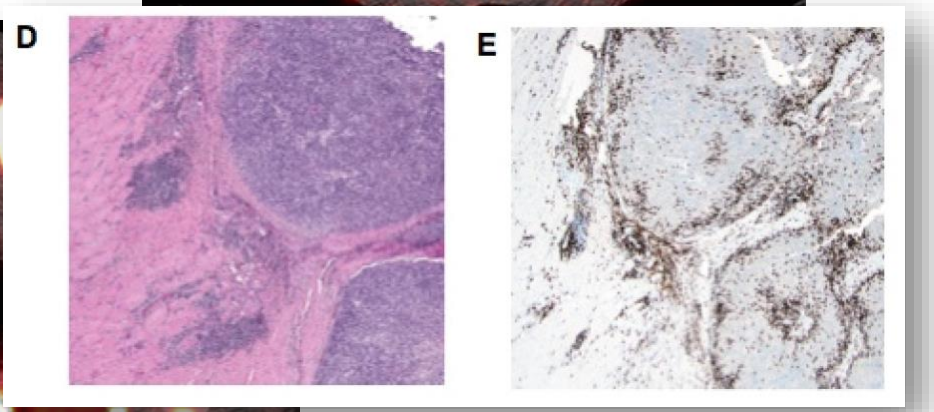
1.4



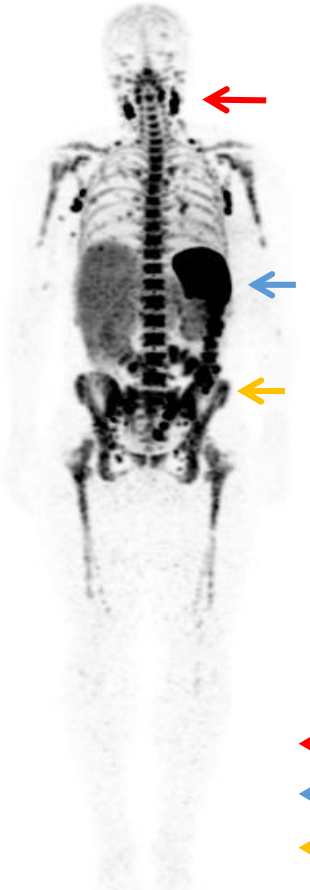
0.8

SUV
0.7

6h



- 37 year old female with metastatic melanoma
- Ipi/Nivo (w yr); Pembro



Day 6

LN
Sp
BM

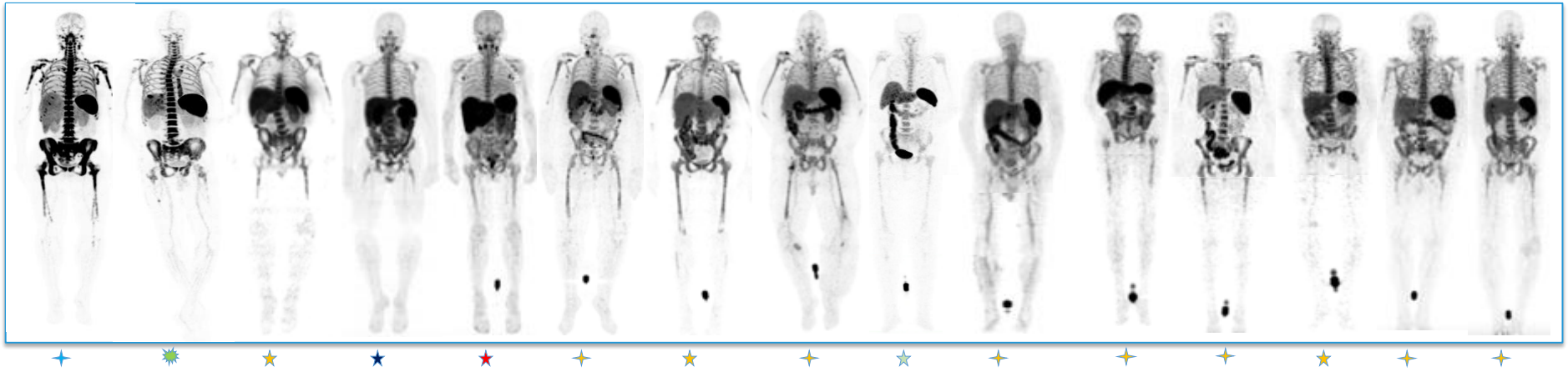
M. Gordon et al. SITC 2018
N .Pandit-Taskar et al. J. Nucl. Med.2019

Summary: Phase I CD8 imaging

Imaging conclusions:

- Rapid clearance; excretion primarily hepatobiliary
- Uptake in T-cell rich tissues (spleen, LN, BM)
- Low activity in background (muscle, heart, brain, lungs)
- Tumor uptake exhibits a range
- Established protein dose (1.5 mg) and imaging time (24 h) for Phase II

Multi-center Phase II in progress: Pre-treatment and early on-treatment CD8 immunoPET and biopsy (NCT03802123)



M. Gordon et al. SITC 2018

Summary and future: Non-invasive whole-body imaging in immuno-oncology

- ImmunoPET for whole-body imaging of lymphoid tissues and tumor
- Immune cell subsets, expansion, trafficking, activation; microenvironment
- Heterogeneity
- Potential role in cancer immunotherapy
  - Patient selection
  - Early on-treatment response, ongoing response
  - Optimization of combination therapy
  - Identification/management of toxicities
- Potential role in other immune-mediated conditions and diseases
- Limitations:
  - Radioactivity
  - Multiplexing challenges
  - Resolution and scale

Clinical immunoPET of CD8 cytotoxic T cells

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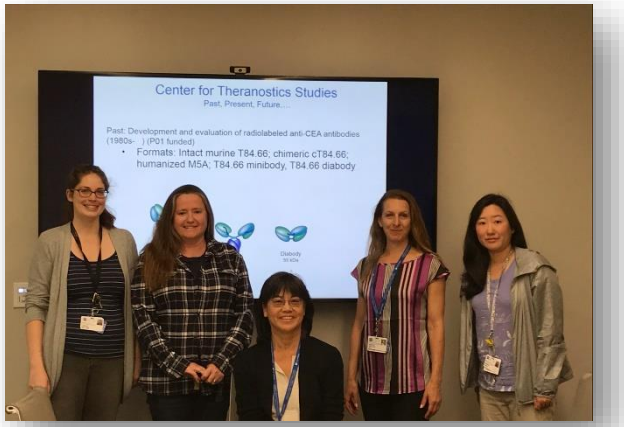

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and our patients