Non-Invasive Quantification of Immune Checkpoint Blockade at the Tumor

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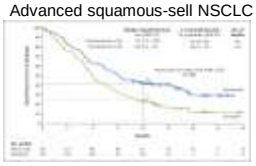
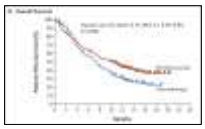
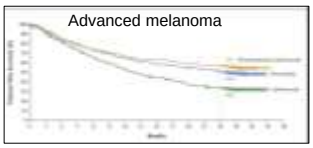
Advanced squamous-sell NSCLC



Advanced urothelial carcinoma



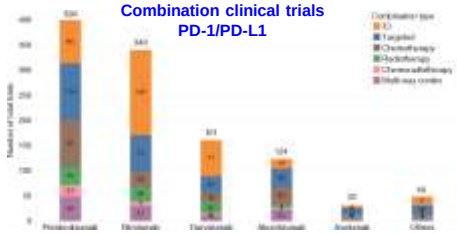
Advanced melanoma



N Engl J Med 2015; 373:1627-1639
N Engl J Med 2017; 376:1015-1026
N Engl J Med 2017; 377:1345-1356

Status of Immune Checkpoint Therapeutics

Combination clinical trials
PD-1/PD-L1



Number of approved biomarkers to guide therapy: 2

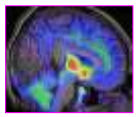
Ann Oncol. 2017;29(1):84-91. doi:10.1093/annonc/mdx755

Positron Emission Tomography (PET)

Radiotracer PET-CT image

Quantitative, highly sensitive, physiologic tracers
^{15}O, ^{13}N, ^{11}C, ^{18}F, ^{64}Cu ^{124}I, ^{89}Zr

Positron Emission Tomography (PET)



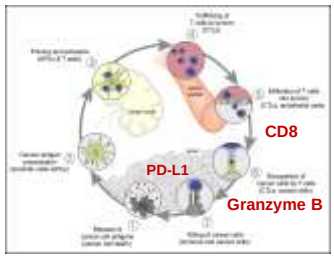
Tracer doses
[^{11}C]carfentanil (m opioid receptor ligand)
5.5 x 10^{-6} mg/kg mass dose

Dose for adult male elephants (1 Ton) ~ 10 mg

Molecularly targeted high affinity probe

- Target mapping (expression levels, enzyme activity)
- Probe disposition in the tumor and other tissues (PK)
- Changes in target expression (receptor density etc.,)
- Modulation of the biochemical pathway (effector pathways)
- Desired biological effect
- Clinical response

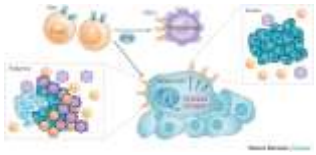
The Cancer Immunity Cycle & Imaging Targets



Chen and Mellman, Immunity, Volume 39, Issue 1, Pages 1-10

Programmed Cell Death Ligand 1 (PD-L1)

A target for imaging immune checkpoint blockade

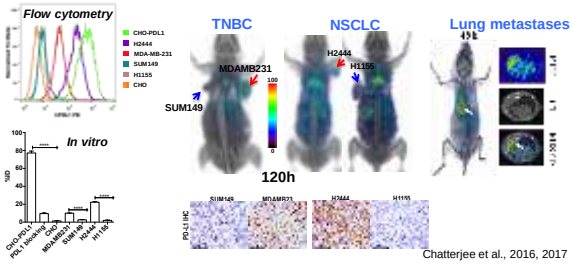


- Expressed in a variety of cancers
- Associated with aggressive disease
- Poor prognosis and poor survival.
- Three FDA approved antibody therapeutics
- PD-L1 IHC is a companion diagnostic
- Imperfect biomarker?
  - 50% of NSCLC are PD-L1 +ve
  - ~8% of PD-L1 –ve patients show response

Nature Reviews Cancer **16**, 275–287 (2016)

Imaging PD-L1 using Antibodies

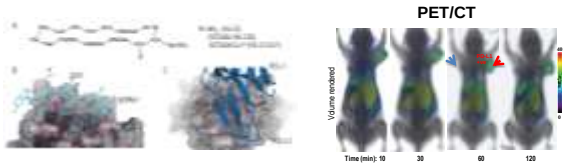
SPECT and PET Imaging with Atezolizumab



Chatterjee et al., 2016, 2017

PD-L1 Detection with a Peptide

[^{64}Cu]WL12

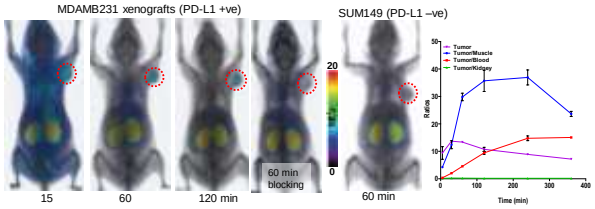


PD-L1 specific images within 60 min

Chatterjee et al., 2017

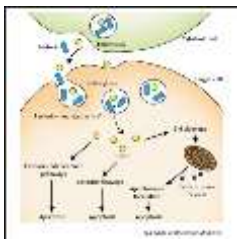
PD-L1 Imaging Agents with Improved Image Contrast for Clinical Translation, [^{18}F]DK222

TNBC models

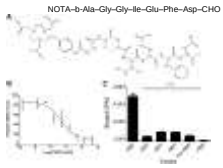


High contrast PD-L1 specific images within 60 min

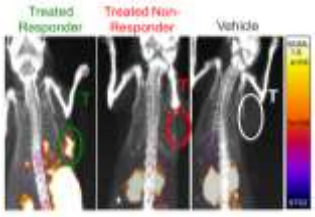
Imaging Functional Activity of T-cells using Granzyme B

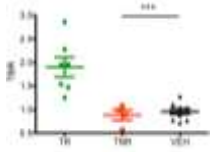


- Lymphocyte granule protease
- Essential for cytolytic activity of T-cells
- Increased GrB activity at the disease site



^{68}Ga-GZP PET Imaging Quantitatively Detects Response to I-O Therapy





CENTER FOR PRECISION IMAGING

Larimer et al. *Cancer Research*. 2017

Success of Anti-cancer Therapies

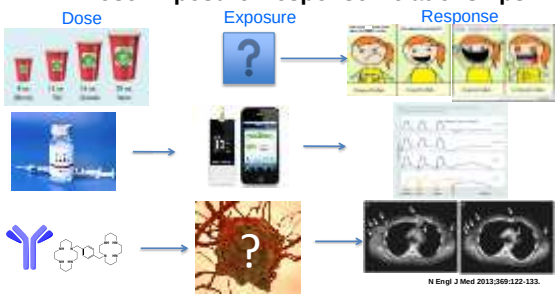
- Cancer and immune cell heterogeneity (Target expression, mutational burden, gene rearrangements, TCR clonality etc.,)
- Drug activity (affinity, selectivity, ADME, drug access, target engagement, biological activity)

Success of Anti-cancer Therapies

Cancer and immune cell heterogeneity
- Programmed death-ligand 1 (PD-L1)
- MSI-high
- Tumor mutation burden
- CD8+ cells
- Neoantigen burden
- T-cell clonal diversity
- Multiplex IHC
- Microbiome

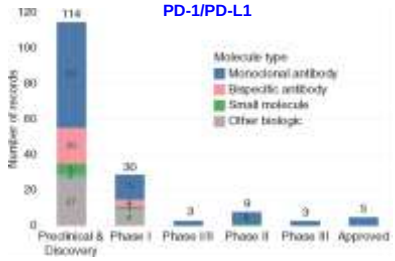
Drug activity at the tumor

Dose-Exposure-Response Relationships



Status of Immune Checkpoint Therapeutics

Agents in development
PD-1/PD-L1



Ann Oncol. 2017;29(1):84-91. doi:10.1093/annonc/mdx755

Antibody Therapeutics

FDA approved antibodies ~79
Oncology focused ~ 35

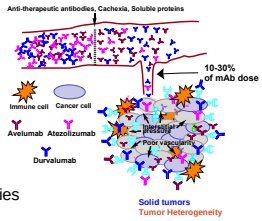
mAbs, ADCs, bi-specific antibodies, fusion proteins

Advantages

- Long half-lives
- High therapeutic index

Disadvantages

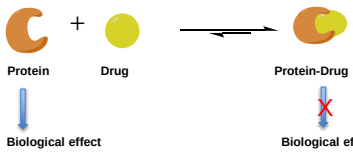
- Large size
- Development of anti-therapeutic antibodies
- Poor tissue penetration-solid tumors
- Expensive treatments



Peripheral T cell vs. Tumor Target Occupancy

Because peripheral-blood T cells express PD-L1, it is possible to assess in vivo receptor occupancy by anti–PD-L1 antibody as a pharmacodynamic measure. Median receptor occupancy was more than 65% for the doses tested. Although these studies provide a direct assessment and evidence of target engagement in patients receiving anti–PD-L1 antibody, relationships between receptor occupancy in peripheral blood and the tumor microenvironment remain poorly understood.

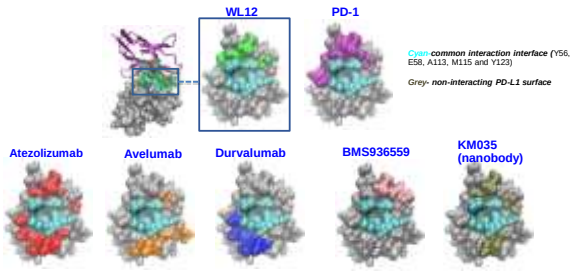
Drug-Target Engagement



Measurements in Cells and Tissues
The Cellular Thermal Shift Assay
Mass Spectrometry
Fluorescence Anisotropy Imaging

No real-time information, multiple measurements across multiple lesions are difficult

Structural analysis indicates an overlap between mAb and peptide interaction surfaces on PD-L1



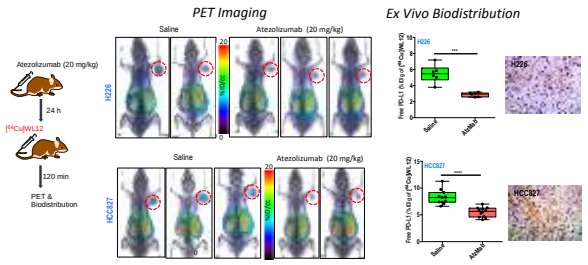
Target Engagement by Antibodies

Antibody *vs.* peptide
<1 nM vs. ~ 20 nM
Slow vs. Fast **PK**

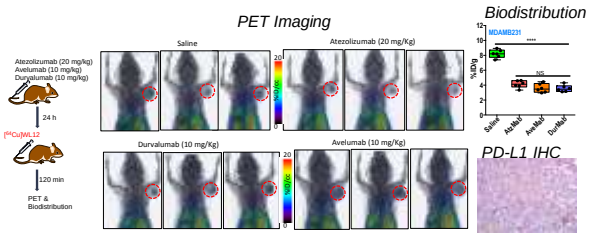
Courtesy: Sports illustrated

- Free fraction PD-L1 levels
- Effect of combination therapy on PD-L1 levels
- Dose optimization
- Target potency of different antibodies
- Dose-Exposure-Response relationships
- Drug development and evaluation- Biosimilars

Free Fraction PD-L1 Levels Quantified using [^{64}Cu]WL12 after Atezolizumab Treatment



[^{64}Cu]WL12-PET: A common denominator to Quantify PD-L1 Therapeutic Activity at the Tumor



Summary and future directions..

- High affinity and high contrast imaging agents for quantitation of target expression and dynamics
- A PD-L1 specific imaging agent to determine mAb kinetics at the tumor
- Dose selection, optimization and intensification
- Quantitative relationships between dose→ tumor and tissue exposure→ response and toxicity
- Drug development and evaluation

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