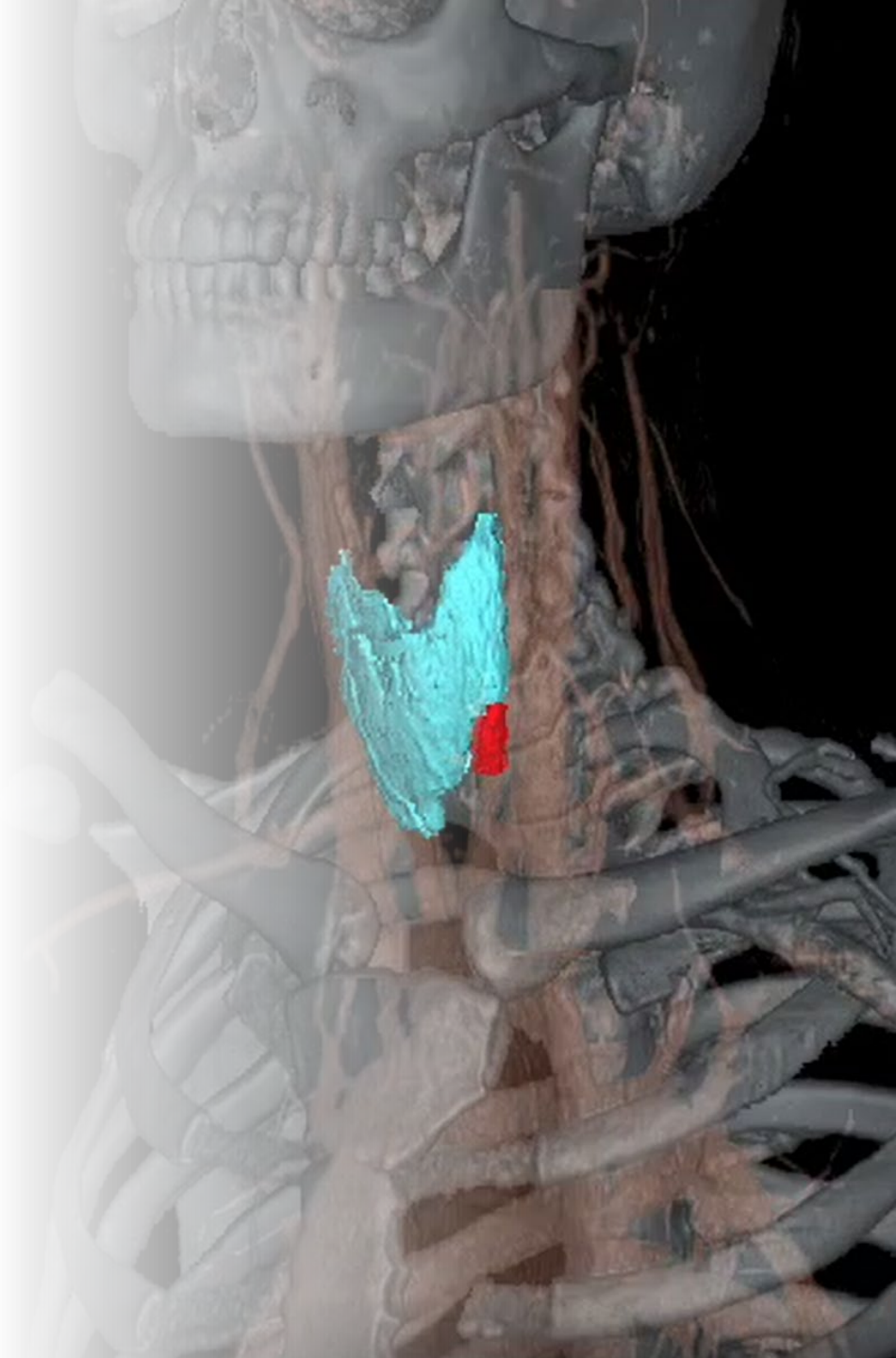
Update on Clinical Research Assessing PET Agent



6 April 2021

David Leung, MD, PhD
Senior Director, Imaging

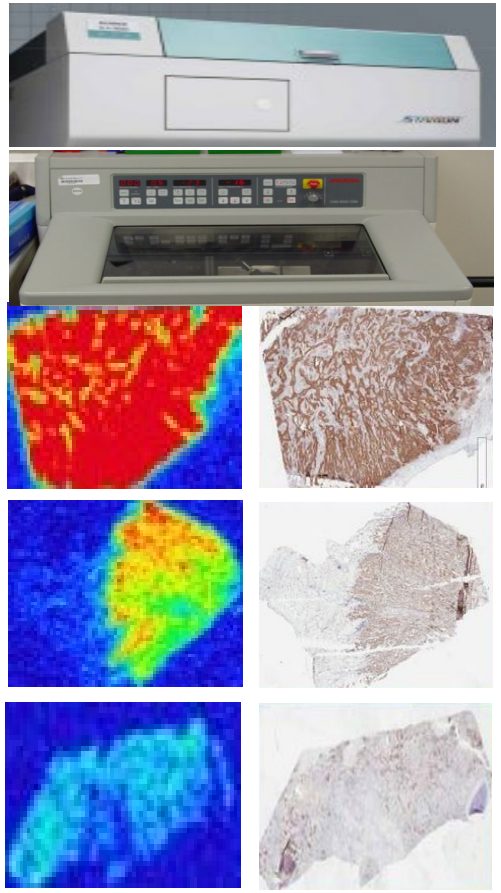
Bristol Myers Squibb™

End-to-End Imaging Enhances Understanding of Disease Biology

Discovery

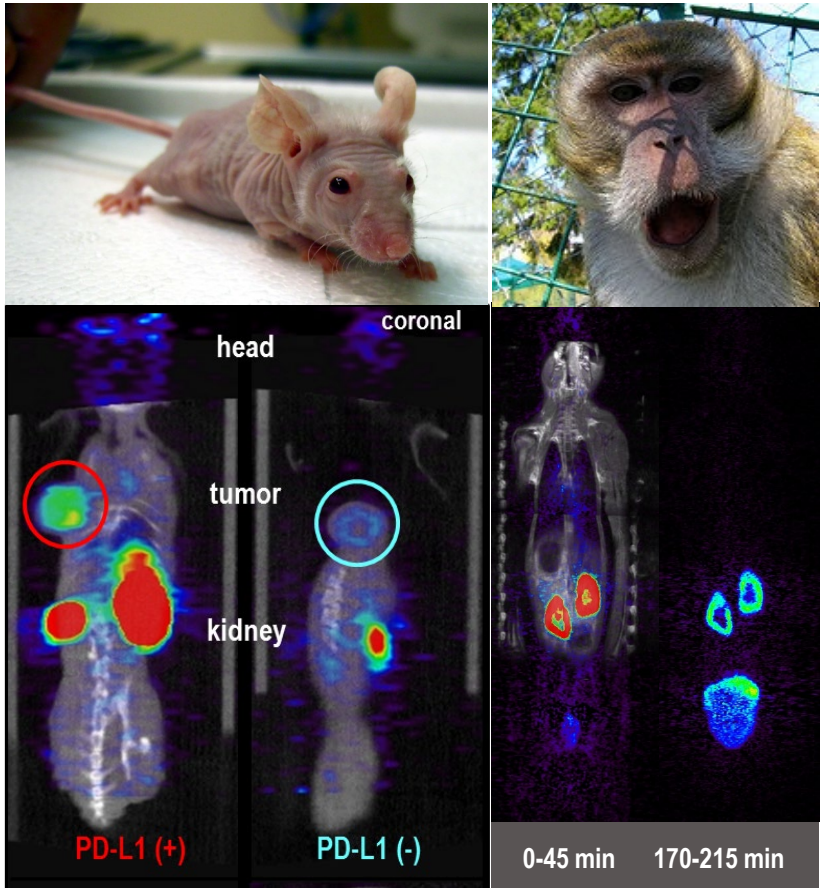
Maximize Molecular Options

In vitro imaging



Confirm Target Specificity

Preclinical in vivo imaging



Proof of Concept

Increase Translational Confidence

Clinical imaging

Inform Clinical Development

Adding Value Across the Portfolio

Discovery/Development Questions Addressable by Molecular Imaging

In-vivo biodistribution of a drug

In-vivo target expression

Target engagement

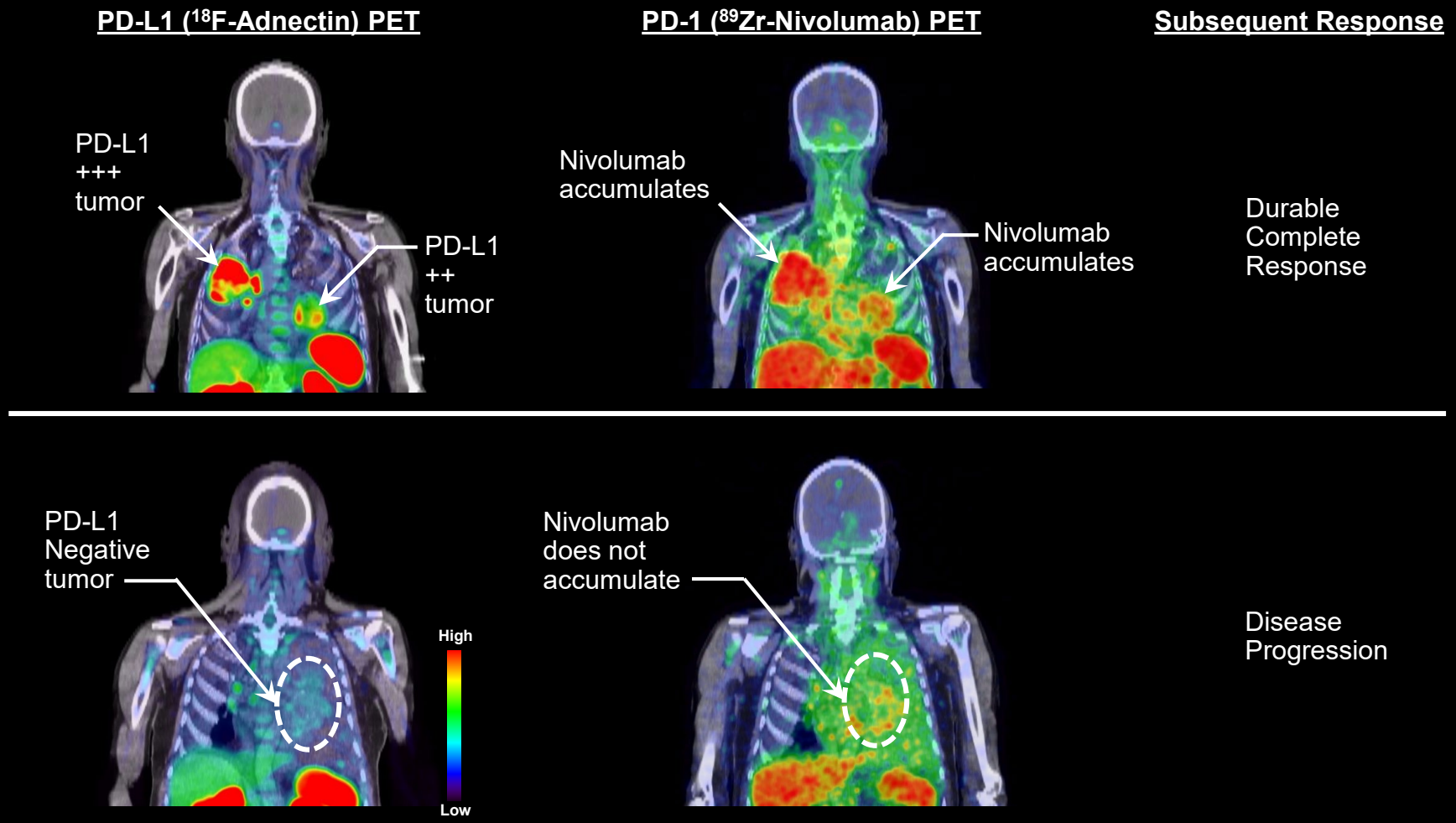
Pharmacodynamics

Target occupancy and dose projection

Safety/Toxicity

in vivo Visualization of Tumor Biology and Asset MoA

- *in vivo* proof of MoA of Nivolumab
- PD-L1 negative tumors grow by immune suppression via other mechanism(s, not PD-1/PD-L1)
- Claim of response in PD-L1 negative patients may be related to tumor heterogeneity, sampling error, and/or dynamic changes in PD-L1 expression



EudraCT Number: 2015-004760-11

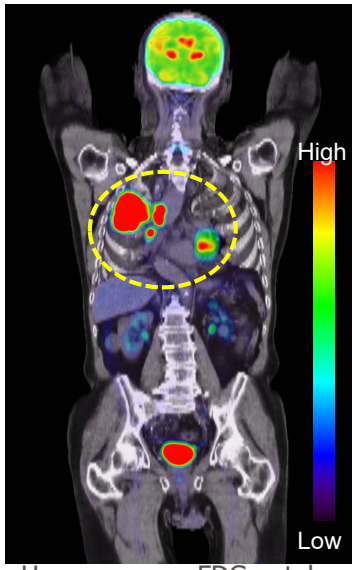
Niemeijer et al. (2018) Nature Communications

in vivo Imaging of Tumor Heterogeneity of PD-L1 Expression

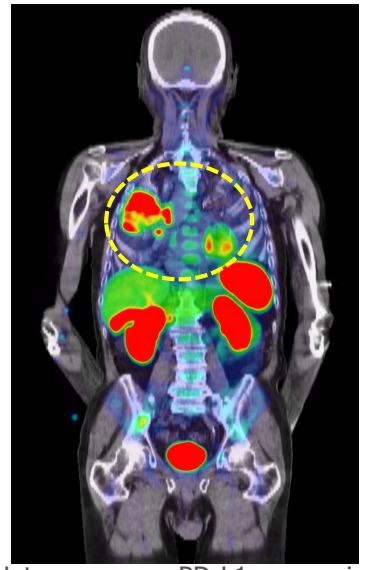
- POC PD-L1 expression is spatially heterogeneous
  - Intra-lesion and inter-lesion

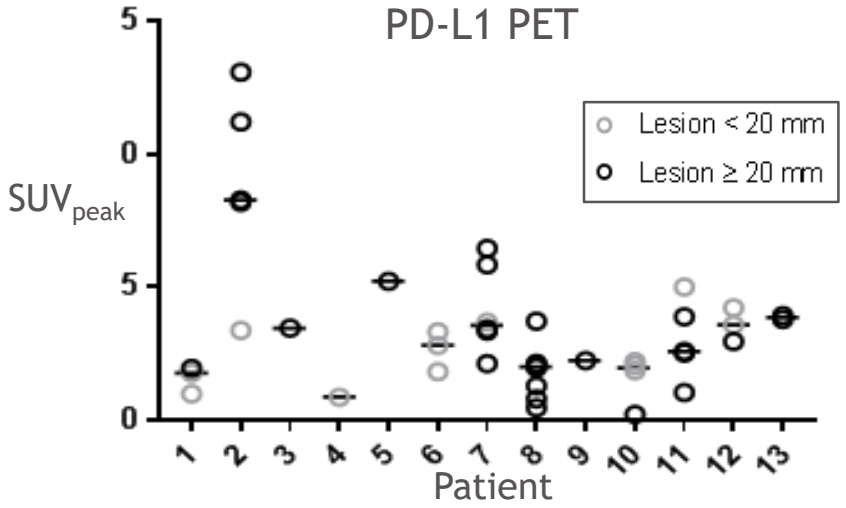
- *in vivo* visualization of PD-L1 expression of all lesions
  - Non-invasive procedure
  - Entire tumor burden including heterogeneity
  - Minimize sampling error

- PD-L1 analysis at both lesion level and patient level
  - IHC result may not be representative to all tumors
  - Imaging can predict which lesions will respond versus progress



Homogeneous FDG uptake

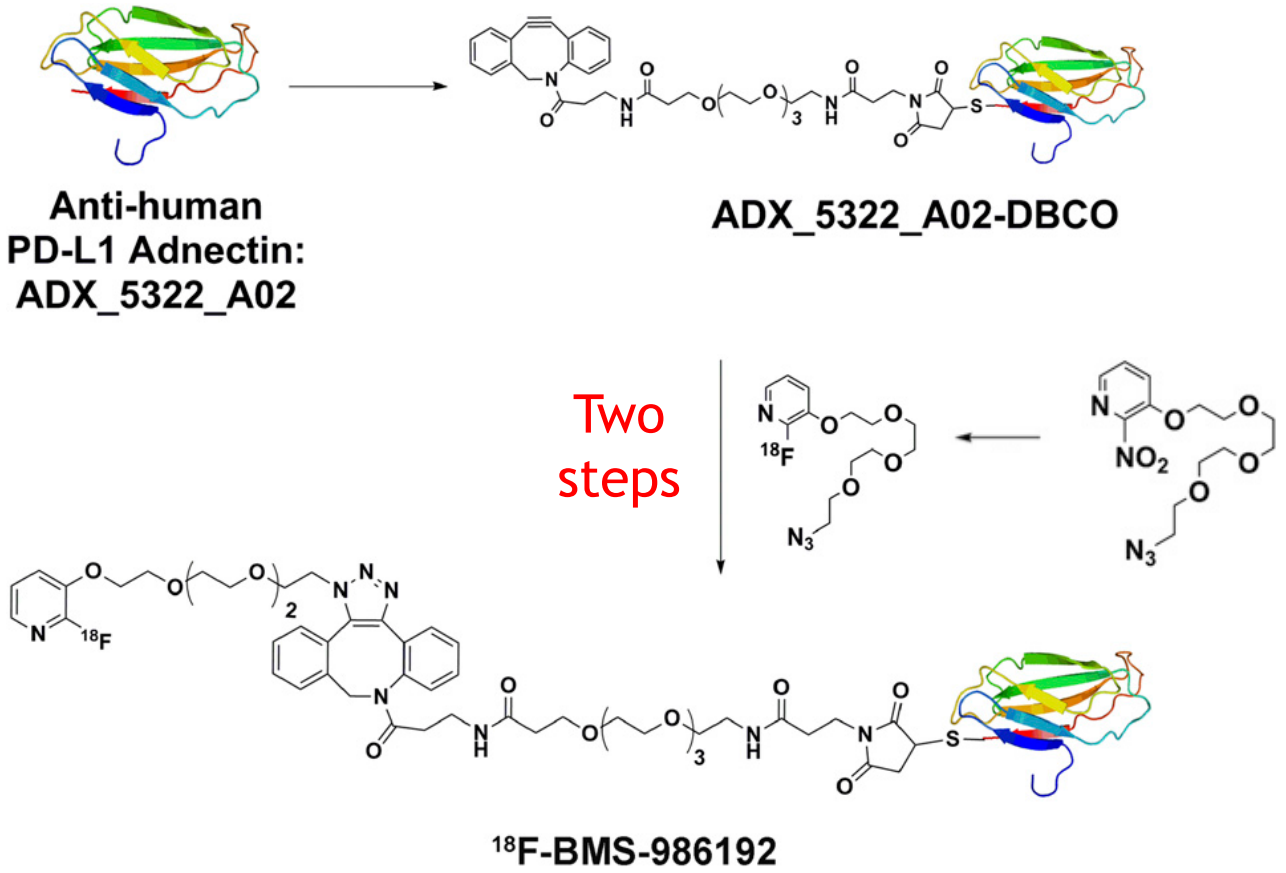

Heterogeneous PD-L1 expression



EudraCT Number: 2015-004760-11

Niemeijer et al. (2018) Nature Communications

Novel Small Molecule Prosthetic Group in ^{18}F Protein labeling



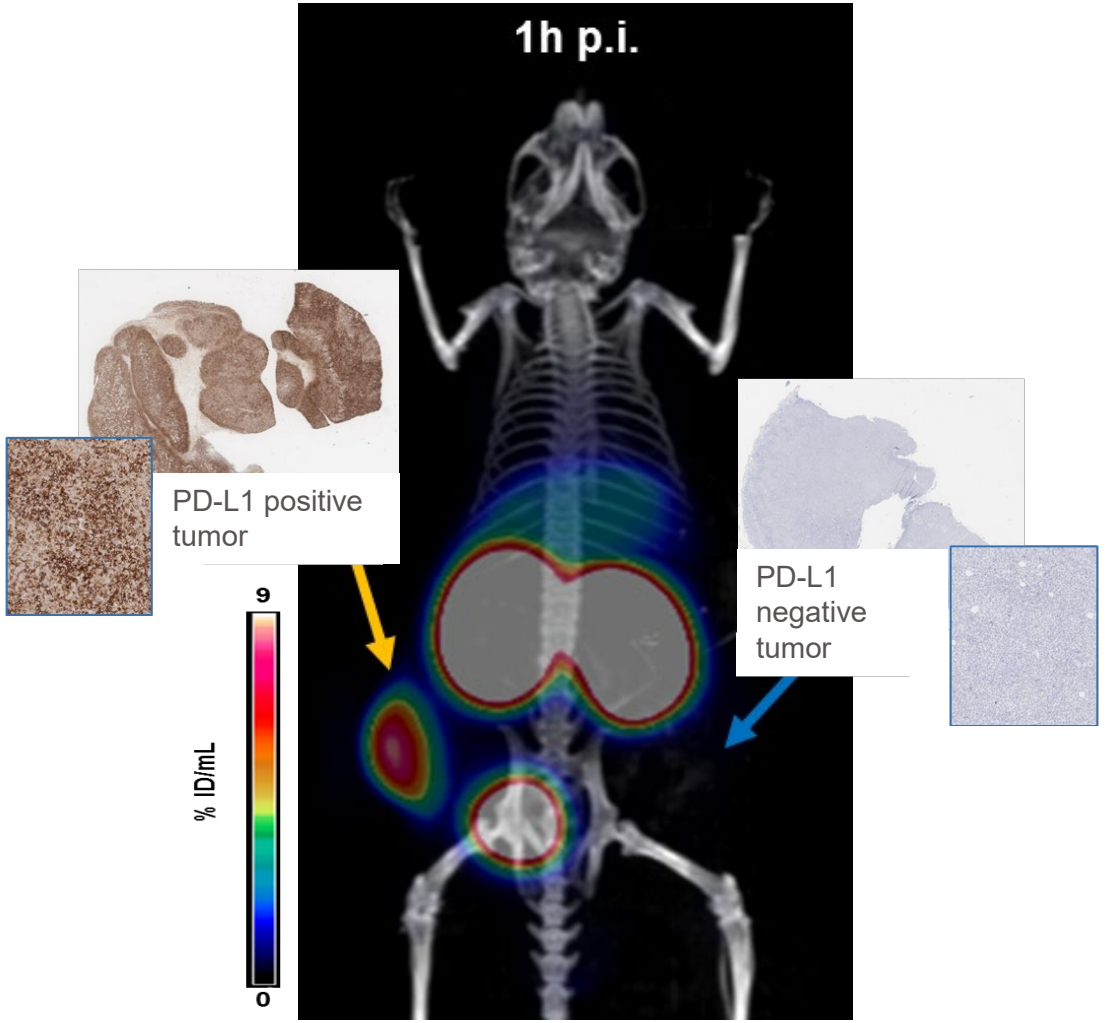
Donnelly et al. (2017) J Nucl Med

^{68}Ga Labeled PD-L1 Adnectin

- Collaboration with Technical University of Munich

- Same PD-L1 Adnectin scaffold
  - High affinity and specificity
  - Same biodistribution in mice
  - Same day imaging at 60 min post injection (p.i.)

- Simplified synthesis using DOTA conjugation
  - One step with high labeling efficiency (15 min)
  - High radiochemical yield >97% and purity >98%
  - Good metabolic stability (95% after 4 hours)



Robu et al. (2021) J Nucl Med

Examples of Other Targets: This is the Beginning

PD-L1 imaging

- ^{89}Zr-Atezolizumab – Nature Medicine 2018
- ^{99m}Tc-PD-L1 Single domain Ab – JNM 2019

CD8 imaging

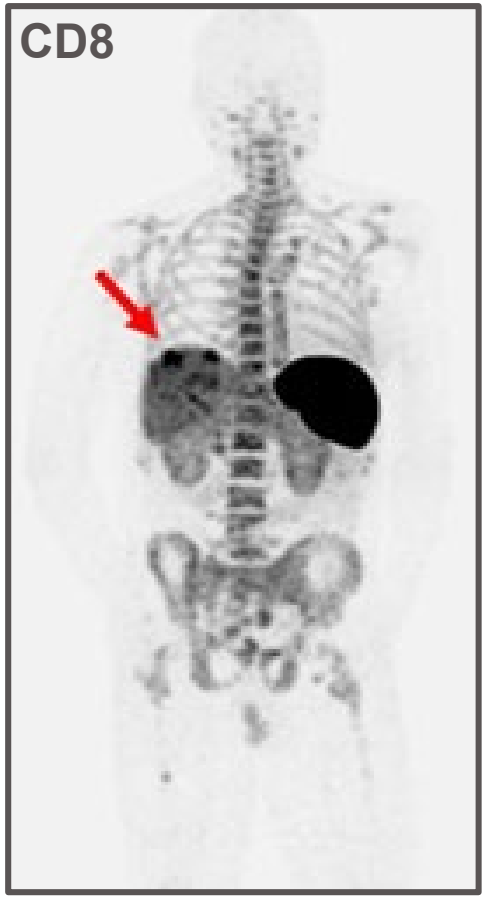
- ^{89}Zr-IAB22M2C – ImaginAb

T-cell activation

- ^{18}F-AraG – Cellsight

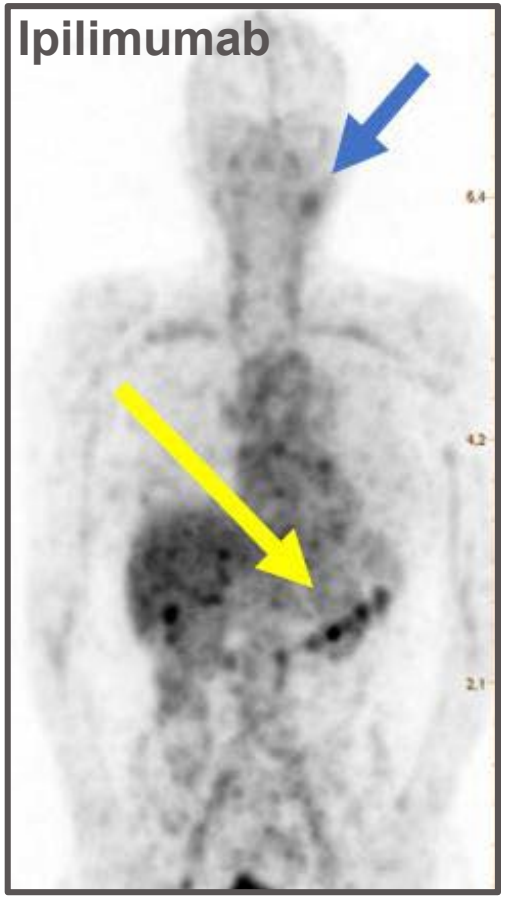
CTLA-4

- ^{89}Zr-Ipilimumab – VUMC AACR 2019



Pandit-Taskar N, et al. JNM 2018

Gordon MS, et al. SITC Annual Meeting 2018



Miedema et al. AACR 2019

Adding Value Across the Portfolio

Discovery/Development Questions Addressable by Molecular Imaging

In-vivo biodistribution of a drug

In-vivo target expression

Target engagement

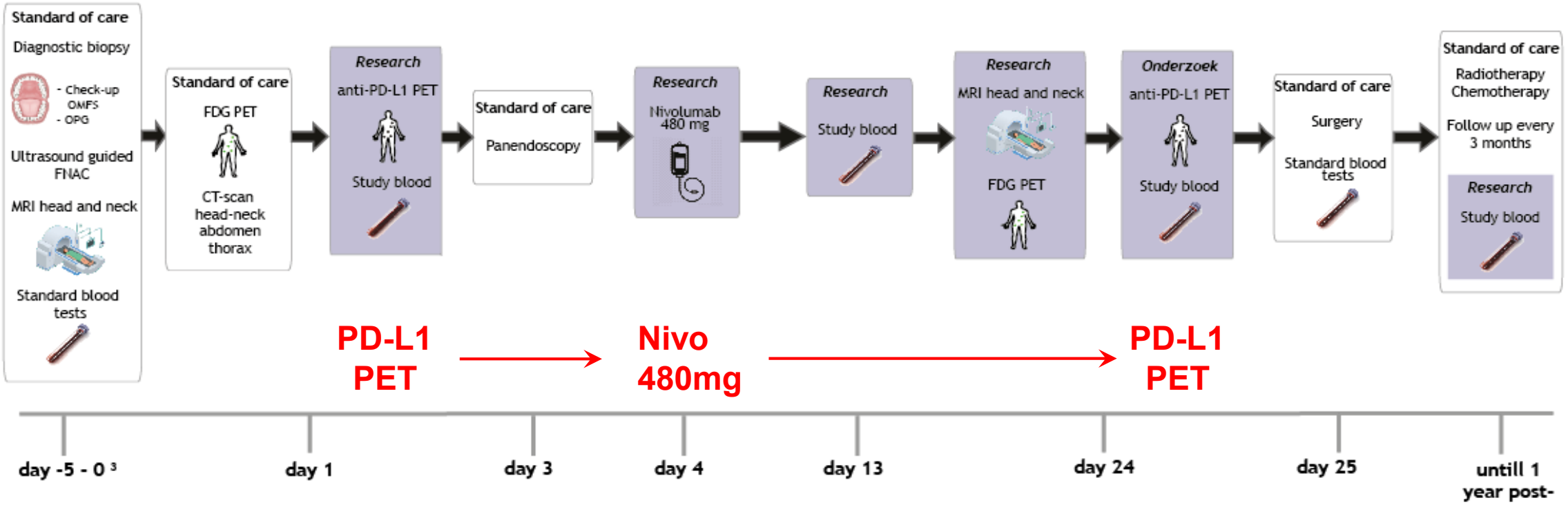
Pharmacodynamics

Target occupancy and dose projection

Safety/Toxicity

Neoadjuvant Head and Neck Cancer

- Collaboration with AmsterdamUMC
- Surgery followed by adjuvant (chemo)radiotherapy only yields 50% cure rate
- Nivolumab shows promise in patients with recurrent/metastatic HNSCC
- Neoadjuvant treatment with Nivolumab may improve the outcome



EudraCT Number: 2018-002643-28

Adding Value Across the Portfolio

Discovery/Development Questions Addressable by Molecular Imaging

In-vivo biodistribution of a drug

In-vivo target expression

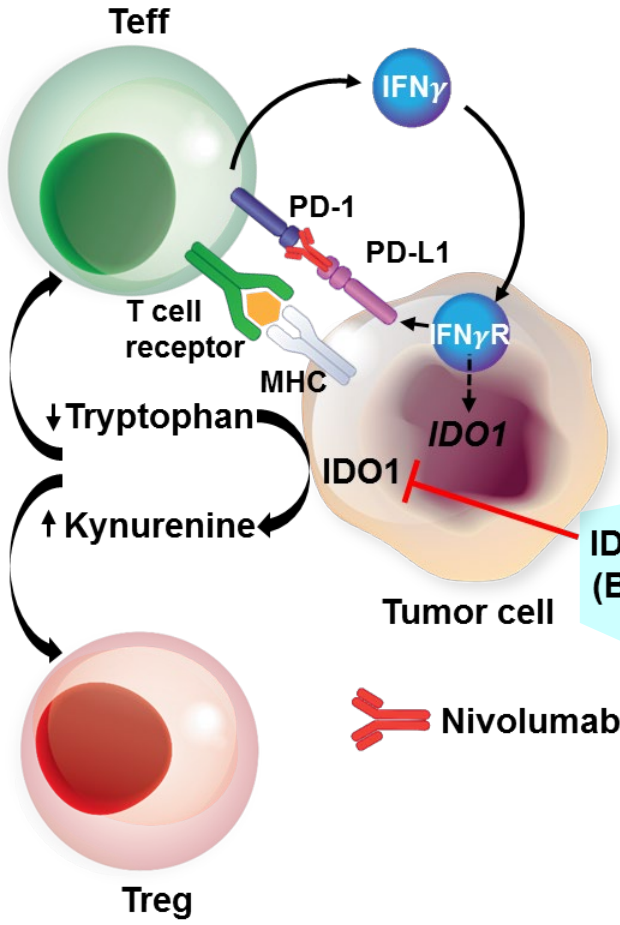
Target engagement

Pharmacodynamics

Target occupancy and dose projection

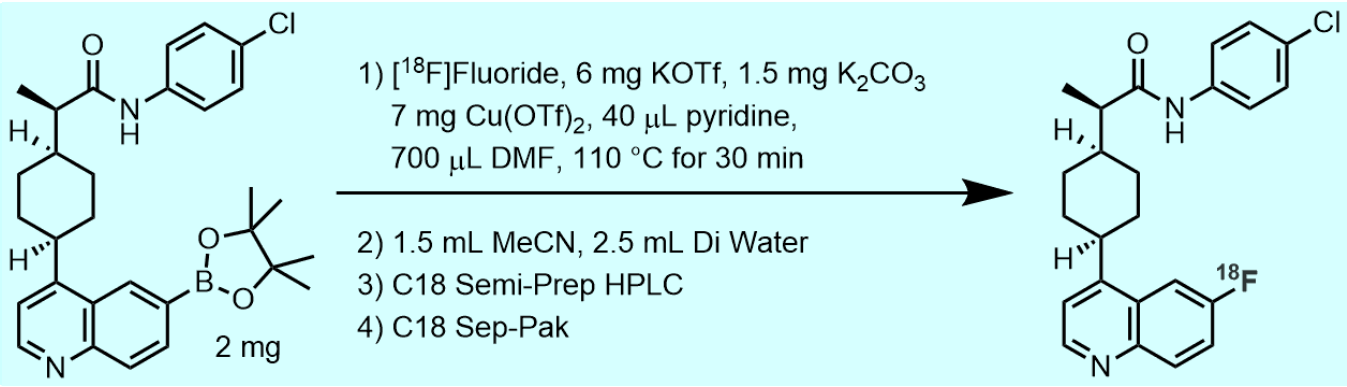
Safety/Toxicity

^{18}F Labeling of IDO1 Inhibitor BMS-986205



BMS designed ^{18}F-labeled BMS-986205 PET tracer which is chemically identical to the IDO inhibitor asset

IDO1 Inhibitor (BMS-986205)



Radiosynthesis presented by E. Cole at SNMMI 2018

Adding Value Across the Portfolio

Discovery/Development Questions Addressable by Molecular Imaging

In-vivo biodistribution of drugs	– Oncology and other therapeutic areas
In-vivo target expression	– Patient enrichment
Target engagement	– Confirm mechanism of action
Pharmacodynamics	– Biology is never static
Target occupancy and dose projection	– Challenges increase with heterogenous diseases
Safety/Toxicity	– Always consider patient safety

Thank you

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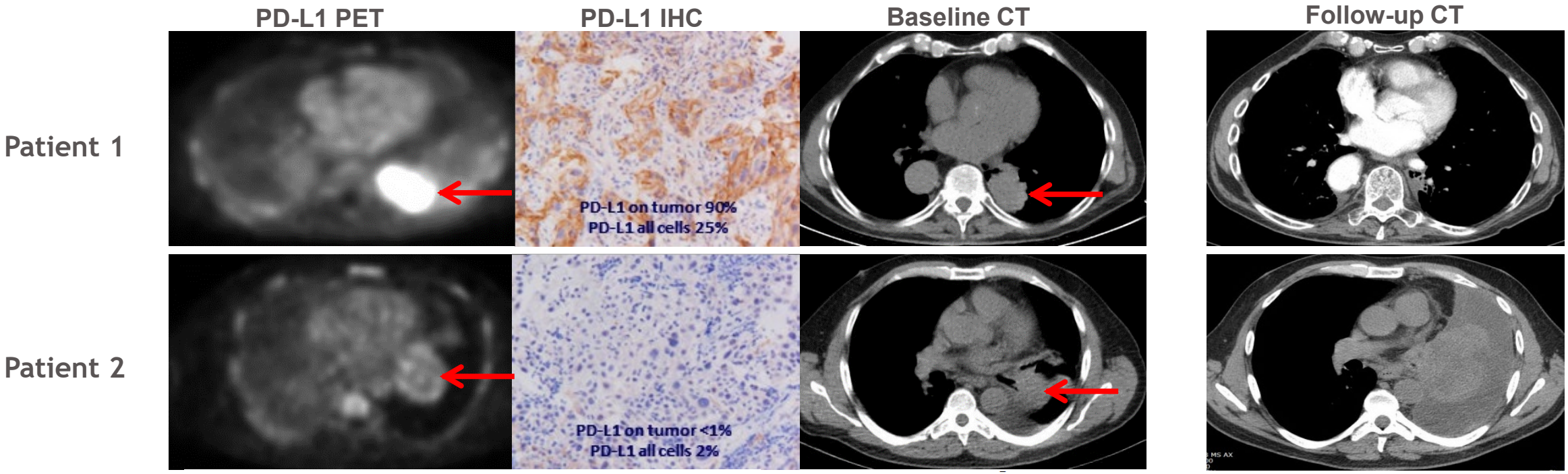
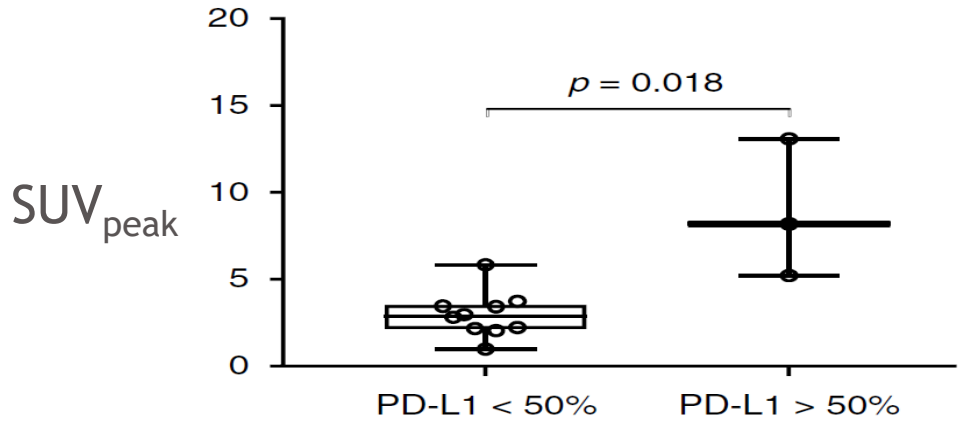
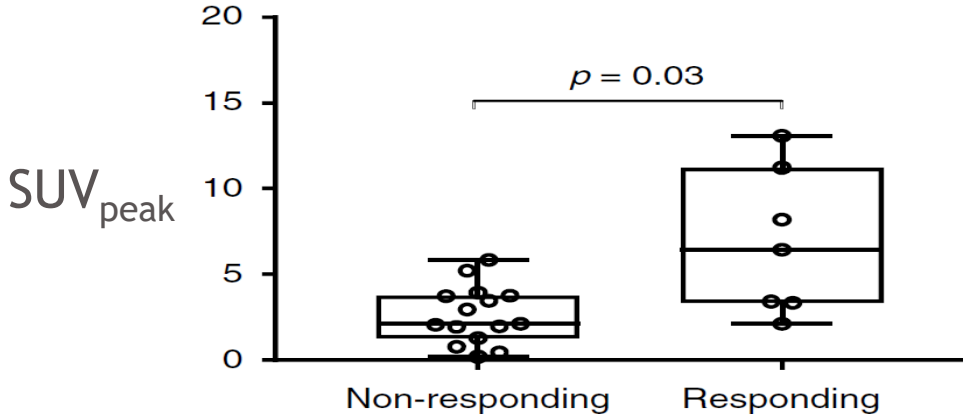
PD-L1 PET Correlates with IHC and Response







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Niemeijer et al. (2018) Nature Communications