Development and Potentials for ImmunoPET Imaging

David Leung, MD, PhD

Head of Oncology Imaging
Bristol-Myers Squibb

13 September 2019
Agenda

• A translational imaging roadmap

• First-in-human results of PD-L1 and PD-1 PET Imaging

• Moving forward
End-to-End Bidirectional Translational Imaging

- **In vitro rad-path correlations**
- **Animal imaging**
- **Clinical imaging**

**Confirm Target Specificity**

**In vivo Proof of Concept**

**Increase Translational Confidence**

**Inform Clinical Development**

- 0-45 min
- 170-215 min
FIH PD-L1 and PD-1 Imaging of (NSCLC) Patients

Rationale:

- PD-L1 has prognostic implications and predicts response to PD-1 checkpoint inhibitor therapy
- Biopsy cannot reflect expression heterogeneity within and among tumors

Key Eligibility Criteria

- **EGFR** WT and **ALK**-negative
- Stage IV NSCLC
- 2nd line or beyond
- ECOG PS 0 or 1
- Asymptomatic CNS mets allowed
- PD-L1 status from recent biopsy

**Days 0–20**

- **18F-PD-L1 PET**
- **89Zr-Nivolumab (PD-1) PET**
- Up to 2 additional biopsies allowed based on imaging

**Nivolumab** 3mg/kg Q2W

**Until PD or unacceptable toxicity**

EudraCT Number: 2015-004760-11
FIH PD-L1 and PD-1 Imaging of (NSCLC) Patients

Rationale:
- PD-L1 has prognostic implications and predicts response to PD-1 checkpoint inhibitor therapy
- Biopsy cannot reflect expression heterogeneity within and among tumors

Key Eligibility Criteria
- **EGFR** WT and **ALK**-negative
- Stage IV NSCLC
- 2nd line or beyond
- ECOG PS 0 or 1
- Asymptomatic CNS mets allowed
- PD-L1 status from recent biopsy

**Days 0–20**
- **18F-PD-L1 PET**
- **89Zr-Nivolumab (PD-1) PET**
- Up to 2 additional biopsies allowed based on imaging

**Nivolumab 3mg/kg Q2W**

**Until PD or unacceptable toxicity**

EudraCT Number: 2015-004760-11
PD-L1 Adnectin\(^1\) PET Biodistribution

- Preclinical dosimetry\(^2\) estimated a human dose of 228 MBq
- Human dosimetry from patients with NSCLC or melanoma\(^3\) estimated maximal injected activity 1450 MBq (typical injection \~200 MBq each)
- No adverse reaction to date
- PD-L1 Adnectin (~10kDa) has renal excretion > biliary excretion
- High physiologic uptake in spleen – Internal control
- Low tracer uptake in normal lung and brain
- Low-to-moderate uptake in bone marrow and liver

1. Lipovšek, D. Protein Eng Des Sel (2011); 2. Donnelly et al. J Nucl Med (2017); 3. From CA209-511 trial; data beyond dosimetry from this study will be reported separately
PD-L1 PET Correlates with IHC and Response

Patient 1

PD-L1 PET

PD-L1 IHC

Baseline CT

Follow-up CT

Patient 2

PD-L1 PET

PD-L1 IHC

Baseline CT

Follow-up CT

Patient 1:
- PD-L1 PET: Arrow pointing to tumor with PD-L1 expression.
- PD-L1 IHC: Arrow pointing to tumor with PD-L1 expression.
- Baseline CT: Arrow pointing to tumor.
- Follow-up CT: Arrow pointing to tumor.

Patient 2:
- PD-L1 PET: Arrow pointing to tumor with PD-L1 expression.
- PD-L1 IHC: Arrow pointing to tumor with PD-L1 expression.
- Baseline CT: Arrow pointing to tumor.
- Follow-up CT: Arrow pointing to tumor.

Statistical analysis:
- SUV_{peak}^{18F-BMS-986627} for PD-L1 < 50% vs. PD-L1 > 50%:
  - P-value: 0.018

- SUV_{peak}^{18F-BMS-986627} for Non-responding vs. Responding:
  - P-value: 0.03
in vivo Whole Body PD-L1 Expression

Coronal PET-CT fusion images from two NSCLC patients, 1 hour post tracer injection

Real-Time Visualization of PD-1 ↔ PD-L1 Pathway

PD-L1 Positive tumor
Nivolumab accumulates
Durable Complete response

PD-L1 Negative tumor
Nivolumab does not accumulate

Patient progressed
Examples of Other Targets: This is Just the Beginning

Other PD-L1 imaging
- 89Zr-Atezolizumab – Nature Medicine 2018
- 99mTc-PD-L1 Single domain Ab – JNM 2019

CD8 imaging
- 89Zr-IAB22M2C – ImaginAb

T-cell activation
- 18F-AraG – Cellsight

CTLA-4
- 89Zr-Ipilimumab – AACR 2019

Pandit-Taskar N, et al. JNM 2018
Gordon MS, et al. SITC Annual Meeting 2018
Miedema et al. AACR 2019
Information Adds Value

In vivo bio-distribution
  • Where does a drug distribute within the body?

Target engagement
  • Does the drug engage the target in vivo?

In vivo target expression
  • Where is a specific target of interest located within the body?
  • How do targets/pathways interact?
  • Does tissue/tumor express a specific target (and when)?

Target occupancy and dose projection
  • Does the drug occupy a sufficient number of targets to achieve the desired efficacy?

Safety/Toxicity
  • Does the drug accumulate in areas of concern for negative effects?
Thank You!
Whole body PD-1 and PD-L1 positron emission tomography in patients with non-small-cell lung cancer


Reference:
https://www.nature.com/articles/s41467-018-07131-y#Sec18

Supplementary information:
https://static-content.springer.com/esm/art%3A10.1038%2Fs41467-018-07131-y/MediaObjects/41467_2018_7131_MOESM1_ESM.pdf

ASCO-SITC 2018 presentation:
http://ascopubs.org/doi/abs/10.1200/JCO.2018.36.5_suppl.139

BMS discovery and preclinical imaging:
FDG, PD-L1, PD-1 PET Images of a NSCLC Patient
Specific $^{18}$F-PD-L1 uptake in Brain Metastases
CA209-511 (Melanoma) Rationale and Study Design

Rationale:
• Responses with Nivolumab are seen across PD-L1 expression levels
• Single biopsy cannot reflect expression heterogeneity within and among tumors

Objectives:
• Safety of BMS-986192 (\(^{18}\)F-labeled anti-PD-L1 Adnectin) in human
• BMS-986192 accumulation in tumors and normal tissue at baseline, during IO therapy, and at disease progression
• Correlation of tumor PD-L1 tracer uptake with IHC (baseline and progression) and treatment outcome
• Intra- and inter-patient tracer uptake differences in tumors

Key Eligibility Criteria
• Previously untreated/unresectable stage III, or metastatic melanoma
• No prior systemic therapy
• ECOG PS 0 or 1
• PD-L1 status from recent biopsy

• \(^{18}\)F-PD-L1 PET
  • Baseline
  • Prior to C3D1
  • RECIST PD
  • Up to 5 subjects undergoing dosimetry studies
  • Up to 2 additional biopsies allowed

Nivolumab 3mg/kg + Ipilimumab 1 mg/kg
Q3W x 4
Or
Nivolumab 1mg/kg + Ipilimumab 3 mg/kg
Q3W x 4

Nivolumab 480 mg
Q4W
Until PD or unacceptable toxicity