Biomarkers for PD-1/L1 inhibitors: Regulatory Considerations

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Marc Theoret, M.D.

Lead Medical Officer

Division of Oncology Products 2

Office of Hematology and Oncology Products

Disclaimer

Views expressed here are those of the presenter and not necessarily those of the U.S. FDA

FDA Centers Active in Oncology

- **Center for Drugs Evaluation and Research**
  - Drugs – small molecules
  - Biologics – monoclonal antibodies, therapeutic proteins, cytokines
- **Center for Biologics Evaluation and Research**
  - Cellular and gene therapies, oncoloytic viruses, therapeutic vaccines
- **Center for Devices and Radiological Health**
  - Devices, including companion diagnostics, Radiologics

Summary of anti-PD-1/PD-L1 Approvals

Product	Date	Approval	Tumor Type / Prior Therapy	IVD
Pembro	9/4/14	Accel	Melanoma/Prior Ipi and, if indicated, BRAFi	N
Nivo	12/22/14	Accel	Melanoma/Prior Ipi and, if indicated, BRAFi	N
Nivo	3/4/15	Reg	NSCLC (Squamous)/Prior platinum	N
Nivo	9/30/15	Accel	Melanoma (BRAF WT), in combo with Ipi	N
Pembro	10/2/15	Accel	NSCLC (PD-L1^{+})/Prior platinum and, if EGFR or ALK genomic aberrations, approved therapy for these aberrations	Y
Nivo	10/9/15	Reg	NSCLC/Prior platinum and, if EGFR or ALK genomic aberrations, approved therapy for these aberrations	Y
Nivo	11/23/15	Reg	Melanoma (BRAF WT)	N
Nivo	11/23/15	Reg	RCC/Prior anti-angiogenic	N
Pembro	12/19/15	Reg	Melanoma	N
Nivo	1/23/16	Accel	Melanoma, in combo with Ipi Melanoma (BRAF V600 mut^{+})	Y

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Companion Diagnostics

Provides information that is <u>essential</u> for the safe and effective use of a corresponding drug or biological product, e.g.,

- Identify patients most likely to benefit
- Identify patients likely at increased risk of serious adverse reactions
- Monitor response to treatment to adjust treatment for improved safety or effectiveness
- Identify patients for whom therapeutic product has been found safe and effective—insufficient information about safety and effectiveness in any other population

Review and Approval of IVD Companion Diagnostics / Therapeutic Products

- IVD companion diagnostics - reviewed and approved or cleared under the device authorities of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and relevant medical device regulations
- Therapeutic product - reviewed and approved under section 505 of the FD&C Act (i.e., drug products) or section 351 of the Public Health Service Act (i.e., biological products) and relevant drug and biological product regulations.
- Contemporaneous regulatory approvals of the device and drug
- IVD companion diagnostic label – specifies the therapeutic
- Therapeutic product label – specifies FDA approved or cleared IVD companion diagnostic device

Example 1: Pembrolizumab - Companion Diagnostic

P001 Trial

- Evaluated in 280 patients with metastatic NSCLC progressed following platinum-containing chemotherapy, and if appropriate, targeted therapy for ALK or EGFR mutations and any evidence of PD-L1 expression by clinical trial IHC assay
- Prospectively defined subgroup retrospectively analyzed using an analytically validated test for PD-L1 expression tumor proportion score (≥50% tumor cells) as determined by PD-L1 IHC 22C3 pharmDx kit (n=61 patients)
- ORR was 25/61 [41% (95%CI: 29, 54)] with 21 (84%) patients with ongoing responses and 11 (44%) patients with ongoing responses ≥6 months

Pembrolizumab Label (USPI): NSCLC

Indications and Usage

- Keytruda is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) **whose tumors express PD-L1 as determined by an FDA-approved test** with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving Keytruda.

  This indication is **approved under accelerated approval** based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Pembrolizumab Label (USPI)

Dosage and Administration

2.1 Patient Selection

- **Select patients** for second line or greater treatment of metastatic NSCLC with Keytruda based on the presence of positive PD-L1 expression *[see Clinical Studies (14.2)]*. Information on FDA-approved tests for the detection of PD-L1 expression in NSCLC is available at: http://www.fda.gov/CompanionDiagnostics.

PD-L1 IHC 22C3 pharmDx Label

Intended use

For in vitro diagnostic use.

PD-L1 IHC 22C3 pharmDx is a qualitative immunohistochemical assay using Monoclonal Mouse Anti-PD-L1, Clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded (FFPE) non-small cell lung cancer (NSCLC) tissue using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression is determined by using Tumor Proportion Score (TPS), which is the percentage of viable tumor cells showing partial or complete membrane staining. The specimen should be considered PD-L1 positive if TPS ≥ 50% of the viable tumor cells exhibit membrane staining at any intensity.

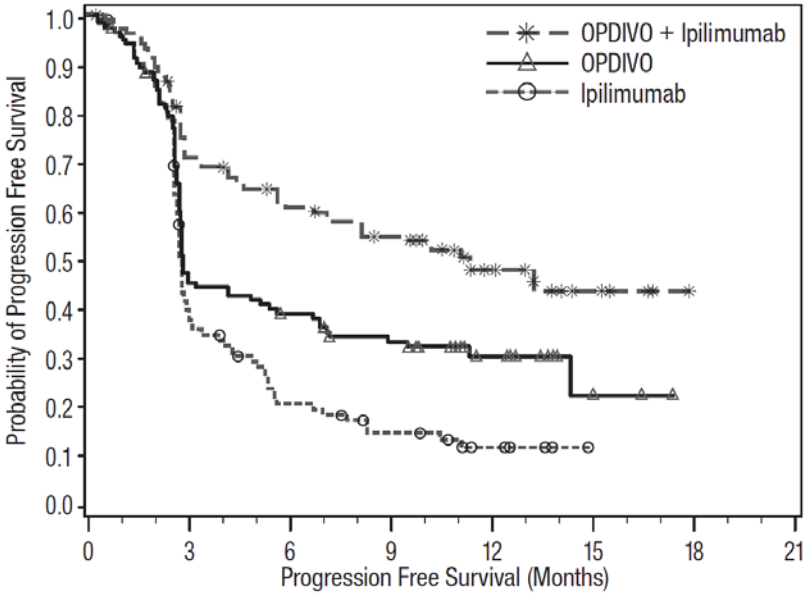
PD-L1 IHC 22C3 pharmDx is **indicated as an aid in identifying NSCLC patients for treatment with Keytruda (pembrolizumab).**

Example 2: Nivolumab (Melanoma)

- CA209067 - Multicenter, double-blind trial that randomized (1:1:1) 945 patients with previously untreated, unresectable or metastatic melanoma to nivomulab + ipilimumab (Nivo+Ipi), nivolumab (Nivo), or ipilimumab (Ipi)
- Randomization stratification factors included PD-L1 expression (≥5% vs. <5% tumor cell membrane expression) as determined by a clinical trial assay
- Met coprimary endpoint of PFS in nivo-containing arms vs. ipi
  - Nivo+Ipi vs. Ipi [HR 0.42 (95% CI: 0.34, 0.51; p <0.0001)]
  - Nivo vs. Ipi [HR 0.57 (95% CI: 0.47, 0.69; p <0.0001)]
- Exploratory efficacy subgroup analyses of PFS based on defined PD-L1 expression levels as determined in archival tumor specimens using the PD-L1 IHC 28-8 pharmDx (ascertained in 89% of study population)

Nivolumab Label: Clinical Studies

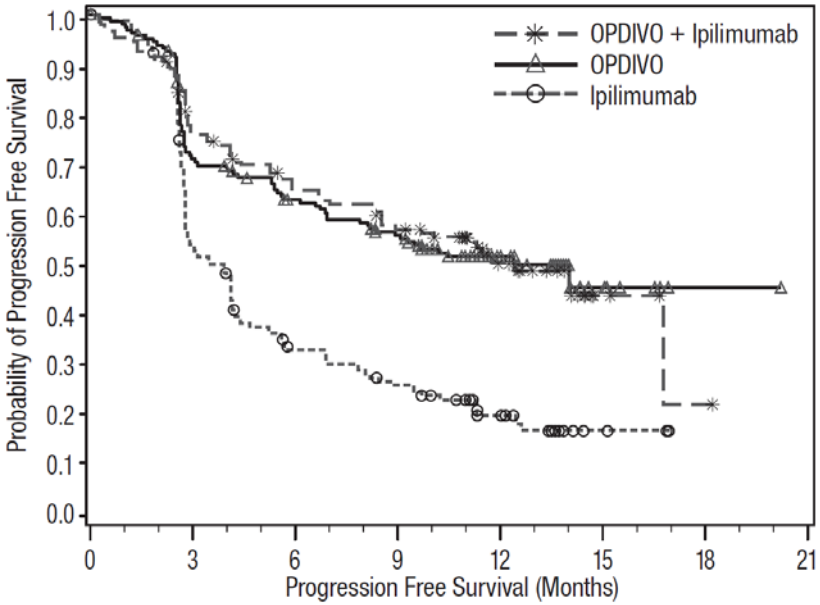
PFS – PD-L1 < 1%



Number of Subjects at Risk

OPDIVO + Ipilimumab	123	82	65	57	26	6	0	0
OPDIVO	117	50	42	34	13	2	0	0
Ipilimumab	113	39	19	12	5	0	0	0

PFS – PD-L1 ≥ 1%



Number of Subjects at Risk

OPDIVO + Ipilimumab	155	113	91	78	32	4	1	0
OPDIVO	171	115	97	83	34	7	1	0
Ipilimumab	164	83	47	36	16	3	0	0

- Description of IVD device and biomarker not included in Indications and Usage or in Patient Selection (Dosage and Administration) of label

PD-L1 IHC 28-8 pharmDx: Complementary Diagnostic

Intended use

For in vitro diagnostic use.

PD-L1 IHC 28-8 pharmDx is a qualitative immunohistochemical assay using Monoclonal Rabbit Anti-PD-L1, Clone 28-8 intended for use in the detection of PD-L1 protein in formalin-fixed paraffin-embedded (FFPE) non-squamous non small cell lung cancer (NSCLC) and melanoma tissue using EnVision FLEX visualization system on Autostainer Link 48. PD-L1 protein expression is defined as the percentage of tumor cells exhibiting positive membrane staining at any intensity.

PD-L1 expression as detected by PD-L1 IHC 28-8 pharmDx in non-squamous NSCLC **may be associated with enhanced survival** from Opdivo® (nivolumab).

Positive PD-L1 status as determined by PD-L1 IHC 28-8 pharmDx in melanoma **is correlated with the magnitude of the treatment effect on progression-free survival** from Opdivo.

Melanoma Interpretation Manual. From company website

In vitro Diagnostics for PD-L1 Biomarker - Challenges

- **Multiple anti-PD-1/anti-PD-L1 Products and Multiple IVD Diagnostic Devices Being Developed in Parallel Based on Different Assays and Clinical Decision points**
- **Performance of Each IHC Antibody Optimized for a Particular Protocol and Platform**
- **Multiple Tests of the PD-L1 Biomarker for Each Patient not Feasible From Multiple Stakeholder Perspectives**
- **High Potential for Mismatched Approved Drug/Device Combination in the Clinical Setting. Patient Treatment may not be Based on Testing With the Matched IVD Diagnostic Device**

Summary

- In Vitro Companion Diagnostic Devices Provide Information That is Essential for The Safe and Effective Use of a Corresponding Drug or Biological Product
- Contemporaneous Development and Approval of Therapeutic Product and IVD Companion Diagnostic Device
- Complementary Diagnostics (draft definition)
  - Tests that identify a biomarker-defined subset of patients that respond particularly well to a drug and aid risk/benefit assessments for individual patients, but that are not pre-requisites for receiving the drug
- 3 of 10 Approvals for Original / Supplemental Indications with anti-PD-1 Monoclonal Antibodies had Concurrent IVD Diagnostic
  - Pembrolizumab (NSCLC, P001 Trial) - patient selection for use of therapeutic product based on PD-L1 IHC biomarker (22C3 pharmDx)
  - Nivolumab (Melanoma, CA209067 Trial; Non-sq NSCLC; CA209057 Trial) -- provide additional information on treatment effects based on PD-L1 IHC biomarker (28-8 pharmDx)

Thank you

Backup Slides

Nivolumab Label (USPI): Melanoma

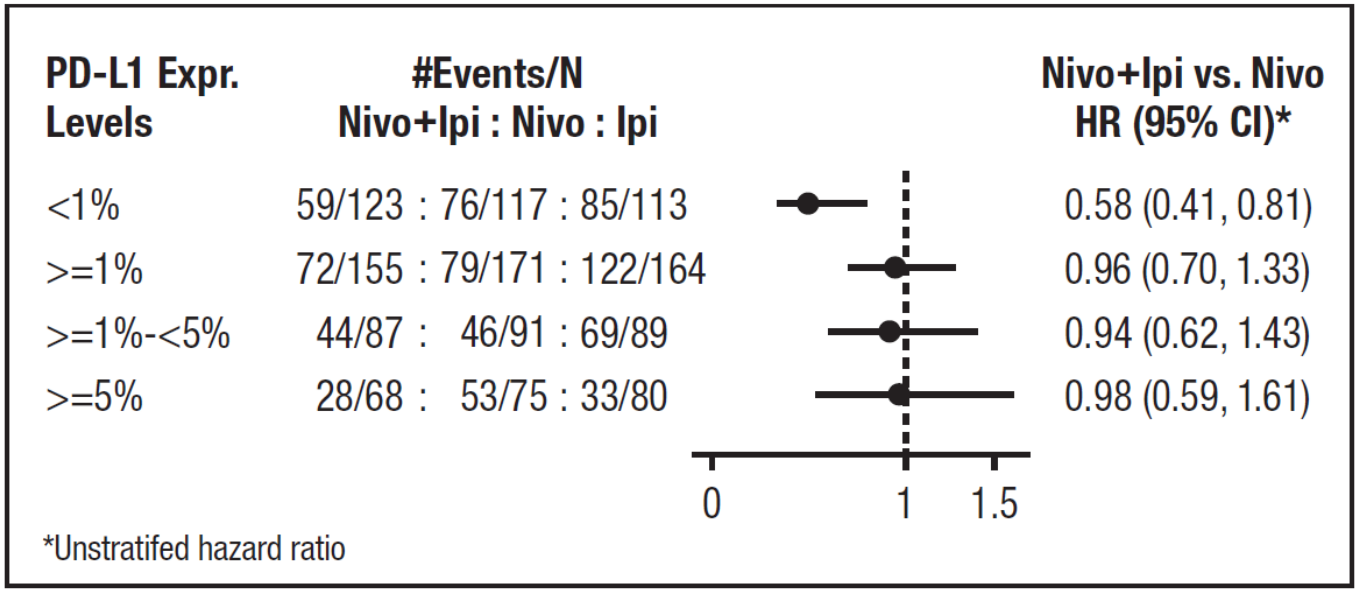
Indications and Usage

- OPDIVO (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma
- Opdivo (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma*
- Opdivo (nivolumab), in combination with ipilimumab, is indicated for the treatment of patients with unresectable or metastatic melanoma*

*Indications approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

Nivolumab Label: Clinical Studies (067 Trial)

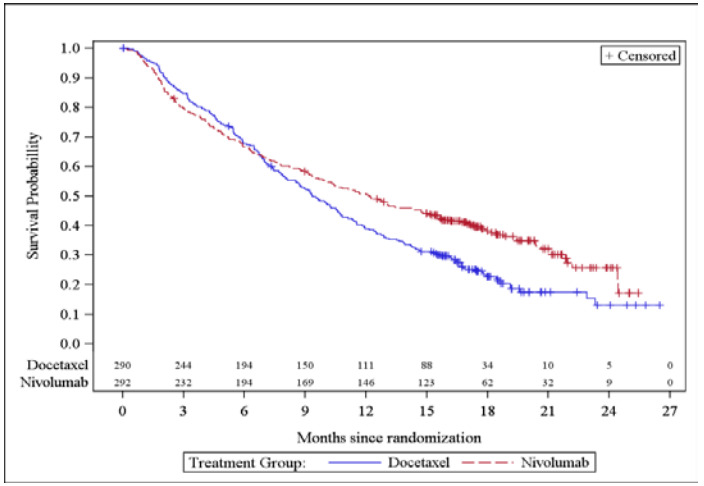
Forest Plot: PFS Based on PD-L1 Expression Comparing Nivolumab-Containing Arms

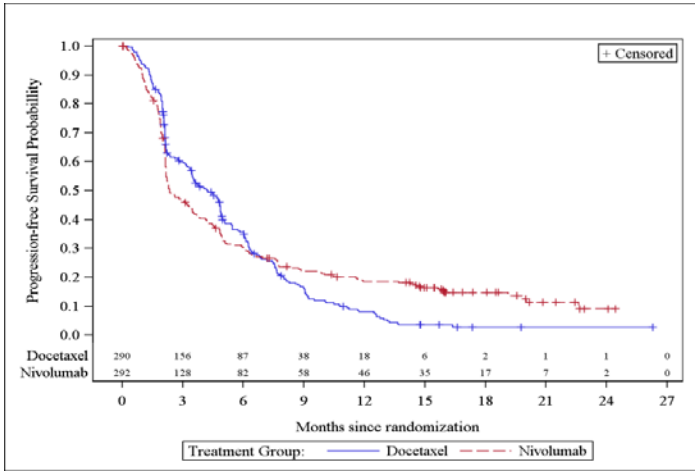


- Description of IVD device and biomarker not included in Indications and Usage or in Patient Selection (Dosage and Administration) of label

Basis for approval of nivolumab 2nd line non squamous (NSQ) mNSCLC

- Approved October 2015: 057 trial
- OS advantage versus docetaxel: HR=0.73, median difference 2.8 months
- PDL-1 1, 5, 10% appeared to be predictive
- Complementary diagnostic approval (Dako 28-8 PharmDx kit)





Basis for approval of nivolumab 2nd line NSQ mNSCLC

- Archival tumor specimens evaluated for PD-L1 expression
- 22% (127/582) had non-quantifiable results
- Of remaining 455:
  - 46%(209/455) PDL1 <1%
  - 54% (246/455) PDL ≥1%
- Of 246 PDL1 positive:
  - 26% (65/246) between ≥1% and 5%
  - 7% (16/246) between ≥5% and 10%
  - 67% (165/246) ≥10%

Subgroup analysis of PFS and OS by PDL-1 expression levels: 057 trial

Forest Plot: OS Based on PD-L1 Expression - Trial 3