Biomarkers for Cancer Immunotherapy Debate

- Moderator: Maria Karasarides, PhD – AstraZeneca
- Pro: Daniel S. Chen, MD, PhD – Genentech
- Con: Steve Averbuch, MD – Bristol-Myers Squibb

Biomarkers to Select Patients for Cancer Immunotherapy: Con

Steven D. Averbuch, MD
Vice President
Development, Oncology & Pharmacodiagnostics

Disclosure

- Full time employee of Bristol-Myers Squibb Company

Oasis or Mirage: Should Biomarkers Be Used to Select Patients for Cancer Immunotherapy?

Not yet . . .

- Randomized phase III trials in all comers demonstrate overall survival benefit:
  - Both PD-L1 expressing and non-expressing tumors
  - In metastatic NSCLC*, melanoma, and RCC
- Excluding patients based on PD-L1 expression may inappropriately deny access to treatment from which they may benefit
- PD-L1 as a biomarker:

* OS for both nivolumab and docetaxel treated patients similar in PD-L1 non-expressing tumors in Nivolumab CA209057

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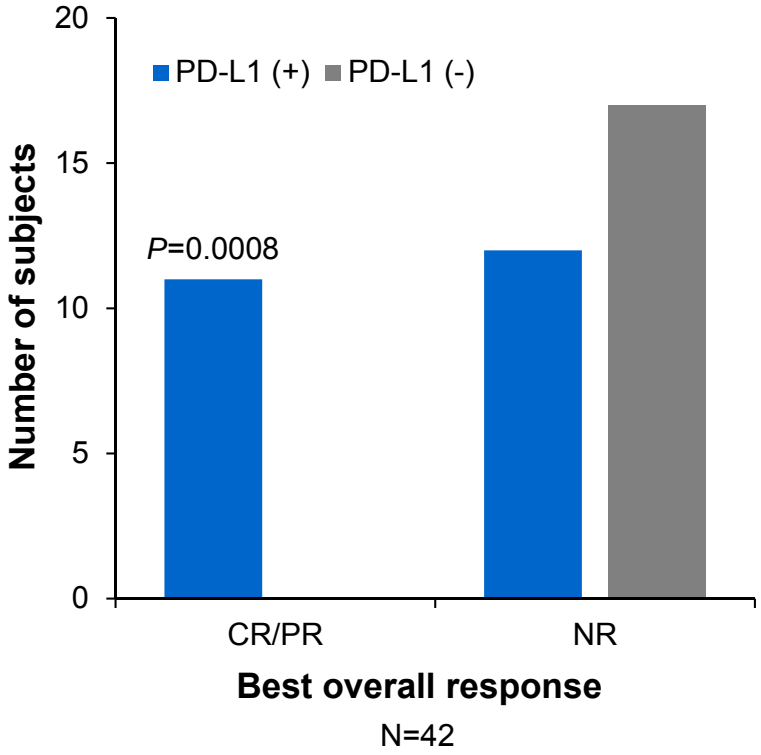
- PD-L1 as a biomarker:

"There is still a lot to learn about the PD-1/PD-L1 pathway and its effects in lung cancer, as well as other tumor types"

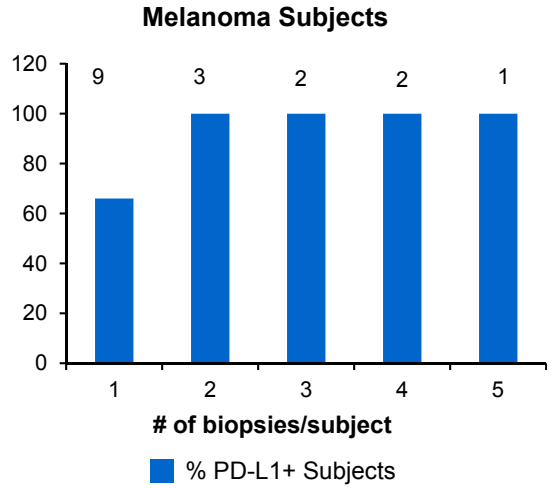
—Richard Pazdur, Director of the Office of Hematology and Oncology Products, FDA

* OS for both nivolumab and docetaxel treated patients similar in PD-L1 non-expressing tumors in Nivolumab CA209057

PD-L1 Subset From Nivolumab CA209003 Showed a Correlation With Objective Response: Generating the Hypothesis



- Multiple biopsies used to define PD-L1 status



PD-L1 status defined as: >5% PD-L1 expression on tumor membrane

Adapted from Topalian et al, ASCO 2012.

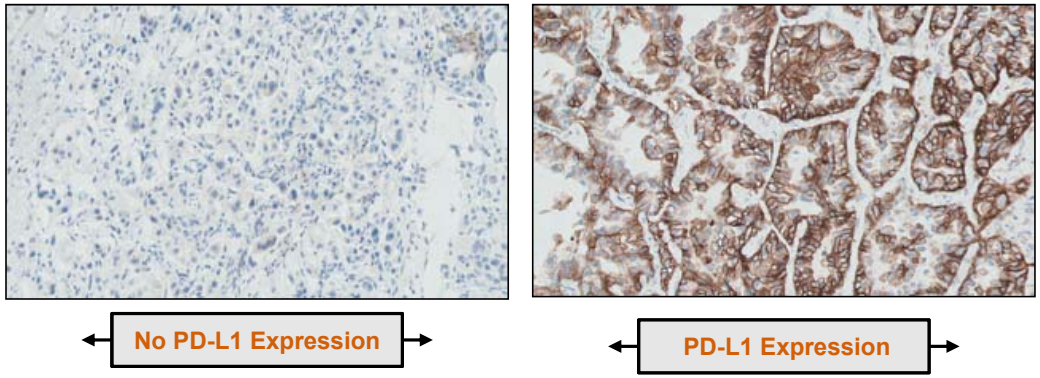
BMS Nivolumab Example: Clinical Development Designed to Address the PD-L1 Hypothesis

- Primary objective: Establish efficacy and safety compared to SOC
  - Melanoma, NSCLC, and RCC
  - Large, randomized, phase III trials
  - PD-L1 unselected populations

- Secondary objective: Evaluation of tumor tissue by analytically validated Dako PD-L1 assay
  - Predefined, retrospective analysis of efficacy by PD-L1 expression
    - Across dynamic range of 1%, 5%, 10%
    - Predefined significance level ($p < 0.2$)
  - If a statistically robust treatment-marker interaction exists:
    - Potential role for a companion diagnostic

PD-L1 Expression Was Determined by a Validated Dako 28-8 PD-L1 IHC pharmDx[1,2]

PD-L1 Staining



PD-L1 Staining Score

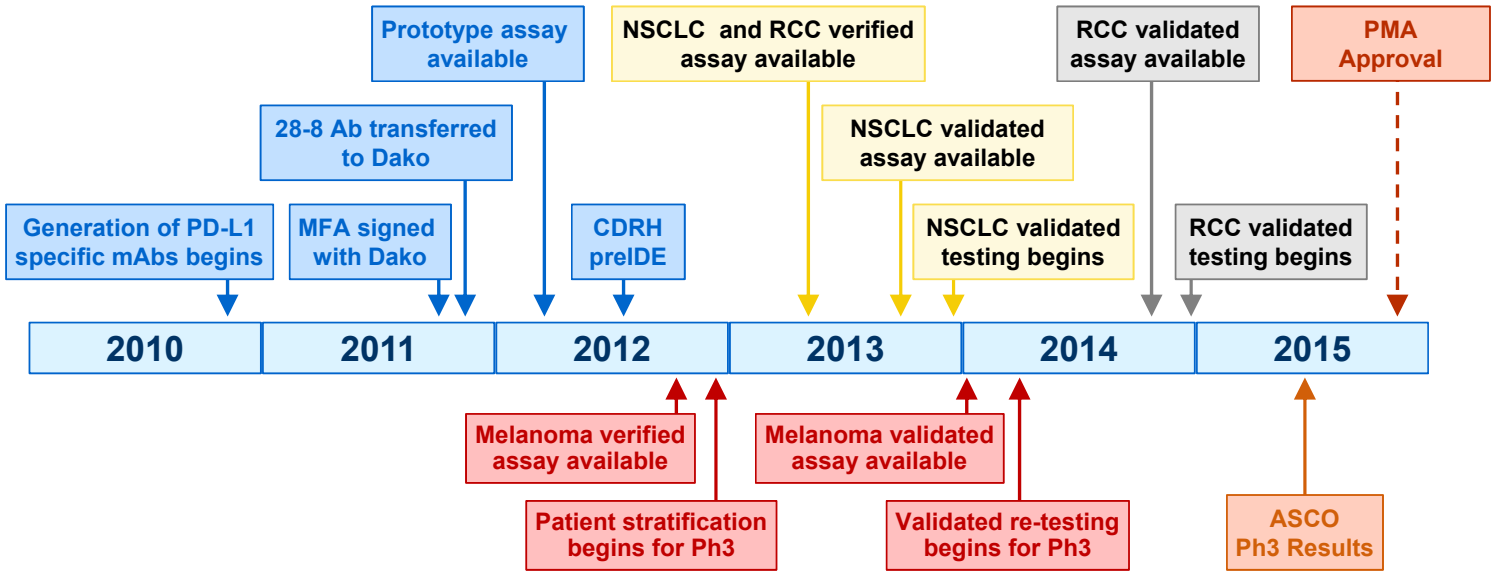
- Percentage of viable tumor cells that exhibit PD-L1 plasma membrane staining at any intensity

1. FDA-approved October, 2015 . Dako PD-L1 IHC 28-8 pharmDX IFU. http://www.dako.com/download.pdf?objectid=128371002. Accessed October 29, 2015.

2. Phillips T et al. *Appl Immunohistochem Mol Morphol*. 2015;23:541-549.

BMS Nivolumab PD-L1 Assay: Comprehensive, Fully Integrated, Co-Development

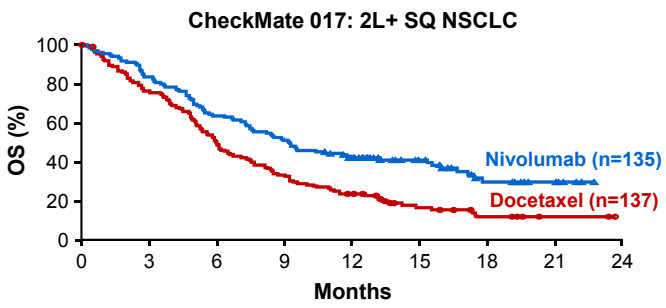
Incorporation of PD-L1 IHC testing into all registrational studies

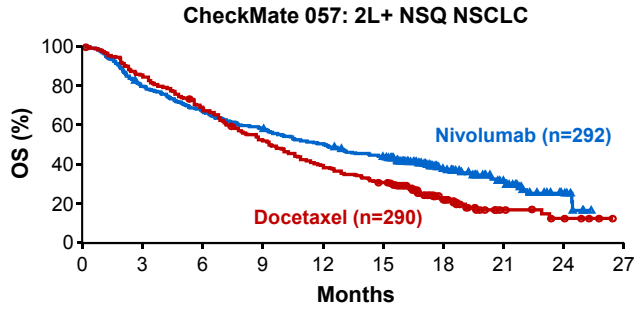


Over 12,000 clinical samples have been tested with the analytically validated assay

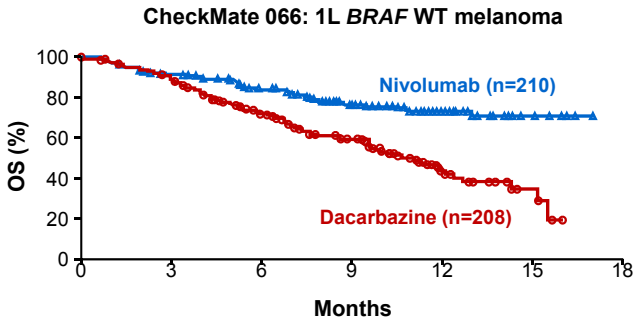
Nivolumab Demonstrates Consistent Overall Survival Benefit in an Unselected Population Across Four Tumor Types in Phase III Trials

NSCLC

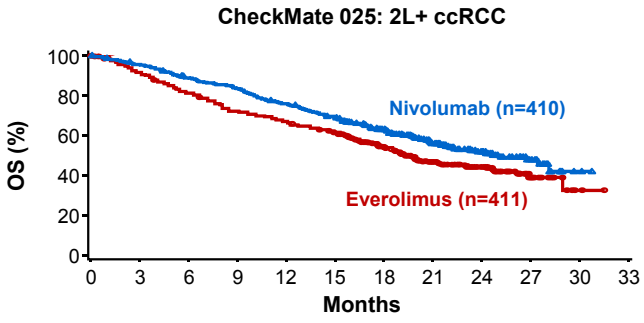




Melanoma



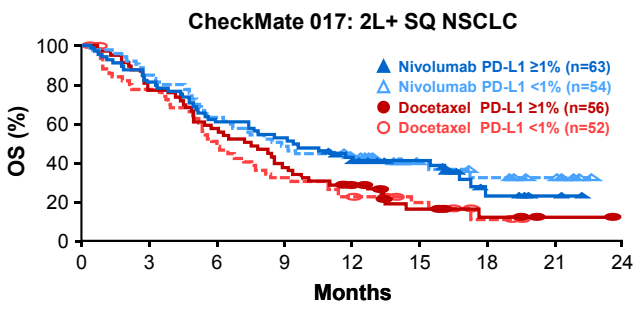
RCC

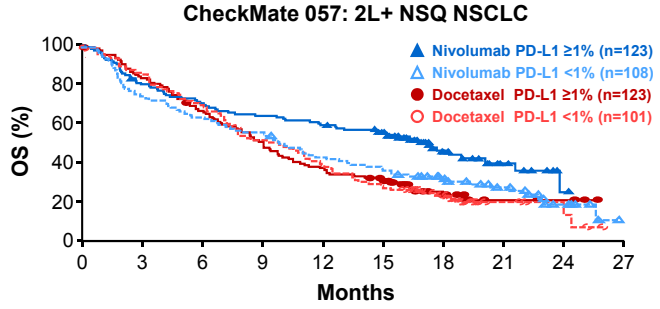


1. Long V et al. Oral presentation at SMR 2014. 2. Paz-Ares L et al. Oral presentation at ASCO 2015. Abstract LBA109. 3. Sharma P et al. Oral presentation at ESMO 2015. Abstract 3LBA. 4. Spigel DR et al. Oral presentation at ASCO 2015. Abstract 8009.

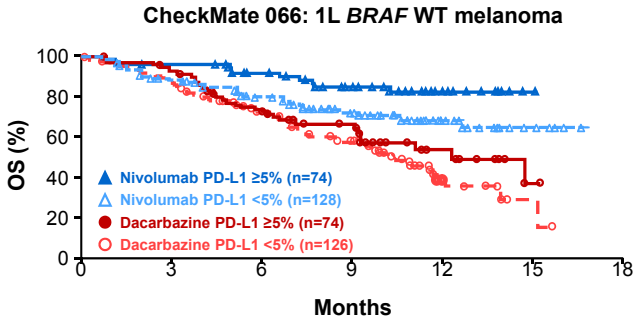
Nivolumab Monotherapy Demonstrates OS Benefit Across PD-L1 Expression Subgroups

NSCLC

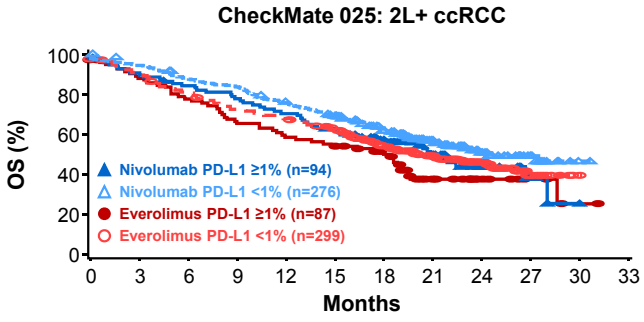




Melanoma



RCC



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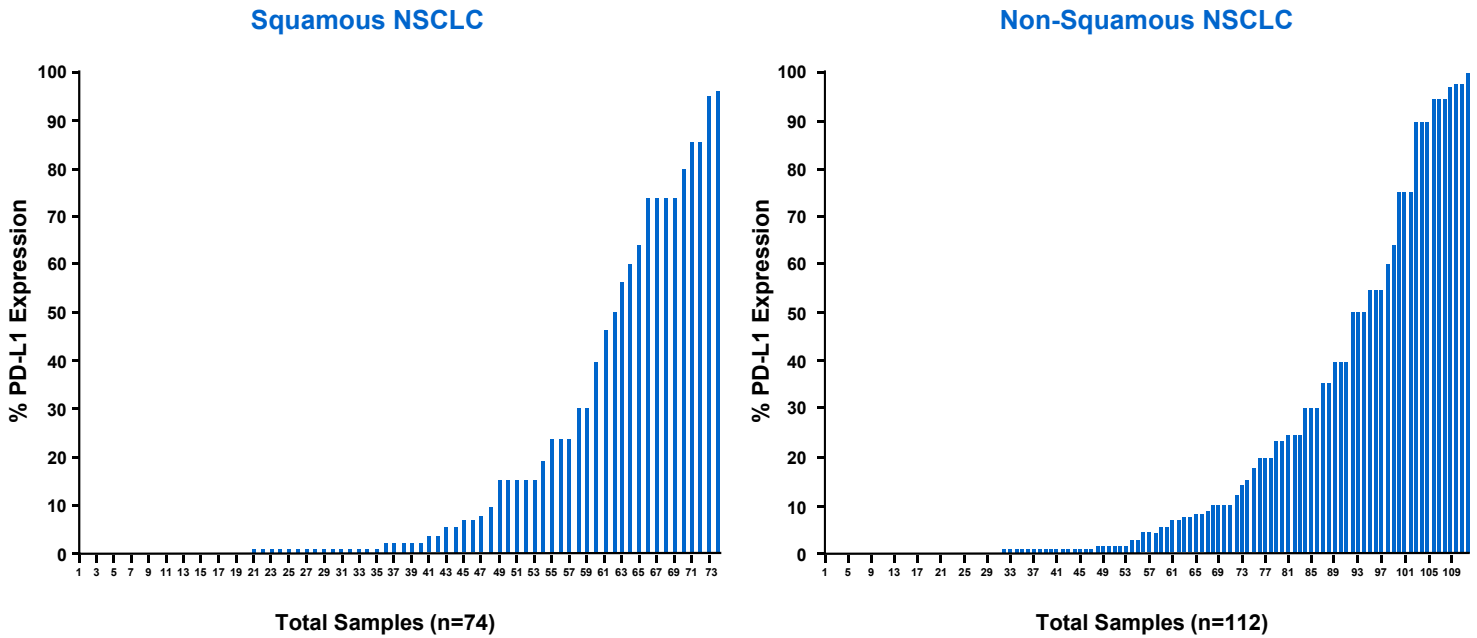
Where Should the Cutoff Be?

Tumor PD-L1 Expression Across the Patient Population Is a Continuum



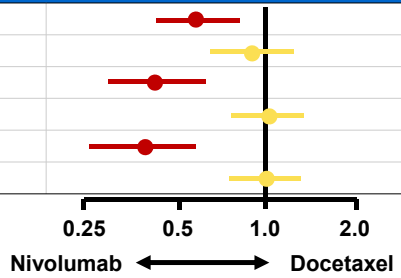
Dako 28-8 PD-L1 IHC pharmDx assay on detection of PD-L1 in NSCLC FFPE biopsy specimens:

Phillips T et al. *Appl Immunohistochem Mol Morphol*. 2015;23:541-549.

Increased PD-L1 Expression May Predict for Higher Magnitude of Overall Survival Benefit in Some Cases

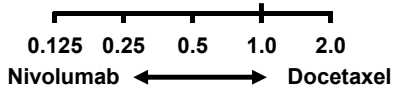
CheckMate 057: Non-Squamous NSCLC[1]

PD-L1 expression level	Patients, n	Median OS (months)		
		Unstratified HR	Nivolumab	Docetaxel
≥1%	246	0.59	17.1	9.0
<1%	209	0.90	10.4	10.1
≥5%	181	0.43	18.2	8.1
<5%	274	1.01	9.7	8.0
≥10%	165	0.40	19.4	10.3
>10%	290	1.00	9.9	10.3



CheckMate 017: Squamous NSCLC[2]

PD-L1 expression level	Patients, n		Unstratified HR (95% CI)	Interaction *P*-value
	Nivolumab	Docetaxel		
≥1%	63	56	0.69 (0.45, 1.05)	0.56
<1%	54	52	0.58 (0.37, 0.92)	
≥5%	42	39	0.53 (0.31, 0.89)	0.47
<5%	75	69	0.70 (0.47, 1.02)	
≥10%	36	33	0.50 (0.28, 0.89)	0.41
<10%	81	75	0.70 (0.48, 1.01)	
Not quantifiable	18	29	0.39 (0.19, 0.82)	



1. OPDIVO [prescribing information]. Bristol-Myers Squibb Company: Princeton, NJ; 2015. 2. Spigel DR et al. Oral presentation at ASCO 2015. Abstract 8009.

Frequency of Treatment-Related Adverse Events Was Similar Across PD-L1 Subgroups

	Nivolumab		Docetaxel	
	Any Grade, %	Grade 3–4, %*	Any Grade, %	Grade 3–4, %*
Treatment-related AEs reported in ≥10% of patients				
Total patients with an event	**69**	**10**	**88**	**54**
Fatigue	16	1	29	5
Nausea	12	1	26	1
Decreased appetite	10	0	16	1
Asthenia	10	<1	18	2
Diarrhea	8	1	23	1
Peripheral edema	3	0	10	<1
Myalgia	2	<1	11	0
Anemia	2	<1	20	3
Alopecia	<1	0	25	0
Neutropenia	<1	0	31	27
Febrile neutropenia	0	0	10	10
Leukopenia	0	0	10	8
Any treatment-related adverse event				
<1% PD-L1 expression	**61**	**8**	**85**	**58**
≥1% PD-L1 expression	**74**	**13**	**90**	**53**

* No grade 5 events were reported at database lock; 1 grade 5 event was reported for nivolumab post-database lock.
AE=adverse event.
Borghaei H et al. *N Engl J Med.* 2015. doi:10.1056/NEJMoa1507643.

PD-L1 as a Selection Biomarker: Clinical and Regulatory Position for Nivolumab as of Nov. 8, 2015

- Nivolumab demonstrates OS benefit in Phase III trials
  - Across studied tumor types
  - Regardless of PD-L1 expression
  - **FDA-approved indications do not depend on PD-L1 expression**
    - Metastatic melanoma, NSCLC

- While PD-L1 expression level is not required to begin treatment with nivolumab, this information may help inform treatment expectations
  - Dako 28-8 PD-L1 IHC
    - FDA-approved class III IVD
    - Available to physicians as a complementary diagnostic to guide the management of patients with non-squamous NSCLC treated with nivolumab

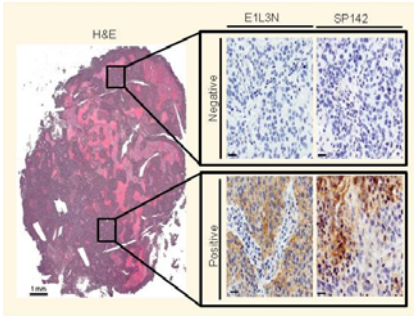
PD-L1 as a Biomarker:
"There is still a lot to learn…"

Challenges Surrounding Biomarker

Biology: PD-L1[1-3]

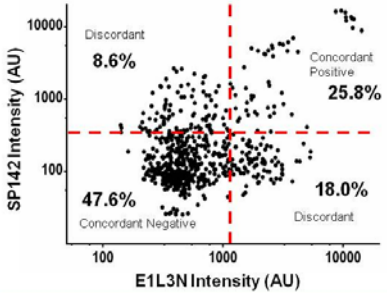
- Inter and intratumor heterogeneity
- Inducible and dynamic (IFN, post-treatment)
- Cell type (immune cell versus tumor versus both)
- Location (membrane versus cytoplasm)

Expression of PD-L1 is heterogeneous[1]



Technical: Assay[1,4,5]

- Epitope stability
- Distribution (patchy versus diffuse)
- Different antibodies and platforms
- Different thresholds for expression
- Interobserver readability



Abs are not identical: >25% discordant[1,6,7]

Logistics: Tissue[1,8,9]

- Interval between tissue and treatment (archived versus fresh)
- Primary versus metastatic disease
- Some circumstances not amenable to obtaining any tissue
- Certain biopsy methods result in poor tissue quality/quantity

IFN=interferon; PD-L1=programmed death ligand 1.

1. Herbst RS. Presented at ASCO 2015 Annual Meeting. Post-057 discussion. 2. Heskamp S et al. *Cancer Res.* 2015. [Epub ahead of print]. 3. Pardoll DM. *Nat Rev Cancer*. 2012;12:252-264. 4. Wilson BE et al. *J Immunol Methods*. 1991;139:55-64. 5. Phillips T et al. *Appl Immunohistochem Mol Morphol.* 2015;23(8):541-549. 6. Rimm D et al. *Breast Cancer Res Treat.* 2014;147(2):457-458. 7. Velcheti V et al. *Lab Invest*. 2014;94(1):107-116. 8. Check W. *Cap Today*. 2010. 9. Warth A et al. *Recent Results Cancer Res.* 2015;199:71-84.

Multiple Diagnostics, Different Development Strategies and Trial Designs Complicate Assessment of PD-L1 Expression

	BMS	Merck[1-3]	Roche[4-6]	AstraZeneca[7]
Ab clone/ anti-PD-1/PD-L1/ company	28-8 Nivolumab Abcam	22C3 Pembrolizumab Dako	SP142 Atezolizumab Spring Bioscience	SP263 Durvalumab Spring Bioscience
IVD Class III diagnostic partner	Dako	Dako	Ventana	Ventana
Trial Design	**057:** All comers	**KN-001:** All comers	**POPLAR:** all comers **FIR:** TC2/3 or IC2/3	**NCT01693562:** all comers
Sample source and collection	Archival or fresh tissue	Phase I: Fresh tissue Phase II/III: Archival or fresh tissue	Archival or fresh tissue	Archival or fresh tissue
Staining location	Membrane	Membrane	Membrane	Membrane
Cell type scored	Tumor cells	Tumor cells	Tumor cells and immune cells	Tumor cells
Scoring method	Percentage of cells with membrane staining at any intensity	**Tumor Proportion score (TPS):** % of cells with membrane staining at any intensity	**Tumor cell (TC) score:** staining % of tumor cells **Immune cell (IC) score:** staining % in tumor area	Percentage of cells with membrane staining
Thresholds (Prospective, retrospective analyses)	<1% or ≥1%, <5% or ≥5%, <10% or ≥10%	≥50%	**TC3 or IC3:** TC ≥50% or IC ≥10% **TC2/3 or IC2/3:** TC or IC ≥5% **TC1/2/3 or IC1/2/3:** TC or IC ≥1% **TC0 and IC0:** TC and IC <1%	≥25%

1. Dolled-Filhart M et al. Poster presentation at ASCO 2015. 11065. 2. Rizvi N et al. Poster presentation at ASCO 2015. 8026. 3. Rizvi NA et al. Oral presentation at ASCO 2014. 8007. 4. Spira AI et al. Oral presentation at ASCO 2015. 8010. 5. Spigel DR et al. Poster presentation at ASCO 2015. 8028. 6. Liao Z et al. Poster presentation for Spring Bioscience. 7. Rebelatto MC et al. Poster presentation at ASCO 2015. 8033.

Should Biomarkers Be Used to Select Patients for Cancer Immunotherapy? Mirage or Oasis

Mirage?

No

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Mirage?

No

Oasis?

Not yet . . .

Debate Questions

Panel Discussion

Moderator: Maria Karasarides, PhD – AstraZeneca

Panelists:

- Steve Averbuch, MD – Bristol-Myers Squibb
- Daniel S. Chen, MD, PhD – Genentech
- Marc Theoret, MD – US Food and Drug Administration
- Thomas Gajewski, MD, PhD – University of Chicago
- Jeffrey Weber, MD, PhD – New York University

Blueprint Project Collaboration May Provide Insight Into Assay Concordance

- A **collaboration** between different stakeholders
  - Evaluate and compare the analytical performance of 4 IUO assays (manufactured by Dako and Ventana) that are currently being used for PD-L1 diagnostic purposes under controlled conditions
- **Goal:** deliver results on assay performance to the larger clinical and diagnostic community