NEXT GENERATION LEARNING

2016 ANNUAL MEETING

March 12-18 Seattle, Washington

USCAP
Creating a Better Pathologist
Assessment of PD-L1 Expression in Lung Cancer

David L. Rimm MD-PhD
Professor
Departments of Pathology and Medicine (Oncology)
Disclosures:

- In the last 24 months I have been engaged in the following relationships:
  - I am a consultant to Amgen, Applied Cellular Diagnostics, Astra Zeneca, Bethyl Labs, Biocept, BMS, Cernostics, Genoptix/Novartis, Metamark Genetics, MDAgree, OptraScan, and Perkin Elmer
  - I have received honoraria from Genentech/Roche and Ventana
  - I hold equity in MDAgree and Metamark Genetics
  - Cepheid, Genoptix, Gilead Sciences, Kolltan, Perkin Elmer and OncoplexDx fund research in my lab.
Pembrolizumab for the Treatment of Non–Small-Cell Lung Cancer

Edward B. Garon, M.D., Naiyer A. Rizvi, M.D., Rina Hui, M.B., B.S., Natasha Leighl, M.D., Ani S. Balmanoukian, M.D., Joseph Paul Eder, M.D., Amita Patnaik, M.D., Charu Agarwal, M.D., Matthewhuber, M.D.

Garon EB et al. NEJM 2015 372:2018-2028
The Merck Assay

Pembrolizumab DAKO-22c3 Ab
Epithelial measurement

- Used ROC curves to optimize predictive value
- Found no value to interface pattern
- Settled on a percentage score, (potentially the easiest)
- Qualtek- Dako

Figure 1. PD-L1 Expression in Non-Small-Cell Lung Cancers.

Results were reported as the percentage of neoplastic cells showing membranous staining of programmed cell death ligand 1 (PD-L1) (proportion score). Shown are tumor samples obtained from patients with a proportion score of less than 1% (Panel A), a score of 1 to 49% (Panel B), and a score of at least 50% (Panel C) (all at low magnification). Tumor samples with the corresponding proportion scores are shown at a higher magnification in Panels D through F. PD-L1 staining is shown by the presence of the brown chromogen. The blue color is the hematoxylin counterstain.

Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients


Median CI Range

<table>
<thead>
<tr>
<th>IHC 0 (n = 60)</th>
<th>8.14</th>
<th>5.57 to 17.57</th>
<th>4.14 to 73.14+</th>
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</thead>
<tbody>
<tr>
<td>IHC 1 (n = 34)</td>
<td>17.14</td>
<td>6.00 to 43.29</td>
<td>0.14+ to 50.57+</td>
</tr>
<tr>
<td>IHC 2 (n = 23)</td>
<td>18.14</td>
<td>6.00 to 48.14</td>
<td>1.00+ to 48.57+</td>
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<tr>
<td>IHC 3 (n = 33)</td>
<td>37.28</td>
<td>18.29 to 59.00</td>
<td>1.86 to 59.00</td>
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<tr>
<td>Unknown (n = 25)</td>
<td>19.71</td>
<td>6.29 to NE</td>
<td>0.14+ to 48.00+</td>
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Number at risk

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<tr>
<th></th>
<th>IHC 0</th>
<th>IHC 1</th>
<th>IHC 2</th>
<th>IHC 3</th>
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<tr>
<td>n</td>
<td>60</td>
<td>34</td>
<td>23</td>
<td>33</td>
<td>25</td>
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<tr>
<td>2 weeks</td>
<td>29</td>
<td>19</td>
<td>16</td>
<td>23</td>
<td>16</td>
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<tr>
<td>4 weeks</td>
<td>20</td>
<td>12</td>
<td>11</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>6 weeks</td>
<td>14</td>
<td>11</td>
<td>8</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>8 weeks</td>
<td>7</td>
<td>9</td>
<td>3</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>10 weeks</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>5</td>
<td>0</td>
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<td>14 weeks</td>
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<td>0</td>
<td>0</td>
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<tr>
<td>16 weeks</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>
**Atezolizumab**

*Genentech/Roche*

**POPLAR: PD-L1 Expression Subgroups**

- **TC3 or IC3**
  - **ORR: 44%**
  - **ORR: 50%**

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>Atezo ORR&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>TC3 (TC High)</td>
<td>44% (14%, 79%)</td>
</tr>
<tr>
<td>IC3 (IC High)</td>
<td>50% (21%, 79%)</td>
</tr>
<tr>
<td>TC3 or IC3</td>
<td>48% (26%, 70%)</td>
</tr>
<tr>
<td>All Treated Patients</td>
<td>23% (14%, 33%)</td>
</tr>
</tbody>
</table>

- **TC3 and IC3** represent non-overlapping populations, each benefiting from treatment with atezolizumab (anti-PDL1)

*GPA A et al. ASCO 2015*

*M. Kowanetz, Dx Summit 2015*
Nivolumab/BMS

OS by PD-L1 Expression

≥1% PD-L1 expression level

mOS (mo)

Hivo 17.2
Doc 9.0

HR (95% CI) = 0.59 (0.43, 0.82)

<1% PD-L1 expression level

mOS (mo)

Hivo 19.4
Doc 10.4

HR (95% CI) = 0.90 (0.56, 1.24)

≥5% PD-L1 expression level

mOS (mo)

Hivo 18.2
Doc 8.1

HR (95% CI) = 0.43 (0.30, 0.63)

<5% PD-L1 expression level

mOS (mo)

Hivo 9.7
Doc 16.1

HR (95% CI) = 1.01 (0.77, 1.34)

≥10% PD-L1 expression level

mOS (mo)

Hivo 19.4
Doc 8.0

HR (95% CI) = 0.40 (0.26, 0.59)

<10% PD-L1 expression level

mOS (mo)

Hivo 9.9
Doc 16.3

HR (95% CI) = 1.00 (0.76, 1.31)

Symbols represent censored observations.

From Paz-Ares at ASCO 2015
Dako/Abcam 28-8 Assay

Development of an Automated PD-L1 Immunohistochemistry (IHC) Assay for Non–Small Cell Lung Cancer

Therese Phillips, MA,* Pauline Simmons, BS,* Hector D. Inzunza, MD, PhD,† John Cogswell, PhD,‡ James Novotny, Jr, PhD,‡ Clive Taylor, MD, PhD,‡ and Xiaoling Zhang, PhD*

FIGURE 1. Positive PD-L1 membrane staining in NSCLC tumor tissues illustrating intensity grades (top, ×20) and PD-L1 tumor scores (bottom, ×40). NSCLC indicates non–small cell lung cancer; PD-L1, programmed cell death 1 ligand 1.
Summary of PD-1 axis Trials by Biomarker

Nivolumab (anti-PD-1)  Pembrolizumab (anti-PD-1)  MEDI4736 (anti-PD-L1)  MPDL3280A (anti-PD-L1)

Response rate

Sunshine and Taube, Curr Opin Pharma, 2015
# The Candidate Predictive PD-L1 Antibodies For Companion Dx Assays

<table>
<thead>
<tr>
<th>PD-L1 Drug and Vendor</th>
<th>Nivolumab BMS</th>
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<th>Atezolizumab Roche/Genentech</th>
<th>Durvalumab AstraZeneca</th>
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<td>Clone and Source</td>
<td>28-8 Abcam - ECD</td>
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<td>Scoring Method</td>
<td>% cells with membrane staining at any intensity</td>
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<td>&gt;25%</td>
</tr>
<tr>
<td>Method</td>
<td>Pathologist/Subjective</td>
<td>Pathologist/Subjective</td>
<td>Pathologist/Subjective</td>
<td>Pathologist/Subjective</td>
</tr>
</tbody>
</table>
## Antibody Validation: The Antibodies that Failed

<table>
<thead>
<tr>
<th>Antibody supplier</th>
<th>clone</th>
<th>Species</th>
<th>Validation* failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abcam</td>
<td>Pab ab 5880</td>
<td>rabbit</td>
<td>Non-specific binding activity in non-expressing cell lines</td>
</tr>
<tr>
<td>BioLegend</td>
<td>29E.2A3</td>
<td>mouse</td>
<td>Background noise signal higher than specific signal</td>
</tr>
<tr>
<td>eBioscience</td>
<td>MIH1</td>
<td>mouse</td>
<td>No signal</td>
</tr>
<tr>
<td>MBL international</td>
<td>27A2</td>
<td>mouse</td>
<td>No signal</td>
</tr>
<tr>
<td>GeneTex</td>
<td>Pab GTX89590</td>
<td>rabbit</td>
<td>Non-specific binding activity in non-expressing cell lines</td>
</tr>
<tr>
<td>Sino Biological</td>
<td>015</td>
<td>rabbit</td>
<td>Non-specific binding activity in non-expressing cell lines</td>
</tr>
</tbody>
</table>

*Validation is defined as single band specificity on Western, staining of B7H1 transfected Mel624 cells and no staining of non-transfected cells and staining of placental syncytiotrophoblast, but not placental stroma.
Expressio
with poor

S. Muenst · A.
M. G. Muraro
S. D. Soysal

Fig. 1 Representative photographs of PD-L1 expression in breast cancer tissue punches. a Tissue punch negative for PD-L1 expression. Magnification × 200. b Tissue punch with strong PD-L1 expression in 100% of cells. Magnification × 200. c Same tissue punch as in b magnification × 400. d Tissue punch with strong PD-L1 expression in 40% of cells. Magnification × 200
Strong Expression of PD-L1
(Tumor and Stromal)
The Challenge of Scoring PD-L1 – Stromal Staining
Is this tumor or stromal?
Planned Studies of the PD-L1 Companion Diagnostic Test

• The “Blue Print” stimulated by FDA/ASCO/AACR meeting, led by Fred Hirsch. Round robin assessment of untreated patients with FDA approved or submitted Companion Dx tests.

• The NCCN/BMS study, led by Ignascio Wistuba and I. A round robin study (8 institutions) of E1L3N on Leica Bond and 3 of the 4 FDA CDx (excluding SP263)
An NCCN/BMS Sponsored Multi-institutional Analysis of Programed Cell Death Ligand-1 (PD-L1) Expression in Lung Cancer

Yale Archives

Selection of about 100 cases of NSCLC including Adenocarcinoma and Squamous Cell Carcinoma

Objective 1:
90 cases from one block
6 cuts from each, 3 required, 3 backup (one for each site)

Objective 2a:
86 cases each with 3 blocks from the same tumor
2 cuts from each block (1 stained, 1 backup)

MDACC Archives

Selection of about 40 core needle biopsies of NSCLC including 20 Adenocarcinoma and 20 Squamous Cell Carcinoma

Objective 2b:
40 cases cut with 2 sections per slide from each tumor
2 cuts from each block (1 stained, 1 backup)
Yale Internal Study of Heterogeneity and Pathologist Scoring Concordance

- 35 cases of Lung Cancer selected from SRC archives
  - Each case must have included at least 3 tumor blocks
  - Each case must be at least a square cm of tumor
- All cases stained in 3 batches on a Lab Vision Autostainer (similar to Dako) using SP142 at optimal titration with recommended antigen retrieval conditions and protocol.
- All cases read by 5 pathologists (David, Brad, Daniel, Kurt and Vasso)
- All cases scored by % cells stained Tumor and % cells stained stroma (immune cells)
- Statistical Analysis by Gang Han
35 NSCLC cases x 3 blocks / case

Block 1
- Tumor and Stroma
  - SP142: DAB (max %)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5
  - SP142: QIF (max AQUA score)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5

Block 2
- Tumor and Stroma
  - SP142: DAB (max %)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5
  - SP142: QIF (max AQUA score)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5

Block 3
- Tumor and Stroma
  - SP142: DAB (max %)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5
  - SP142: QIF (max AQUA score)
    - Pathologist 1
    - Pathologist 2
    - Pathologist 3
    - Pathologist 4
    - Pathologist 5
Distribution of Cases by Pathologist for Tumor Staining (first 5 sets)
Distribution of Cases by Pathologist for Tumor Staining (All 35 sets)
Tumor Cell Expression using SP142 (n=35)

Distribution of Maximum PD-L1 (SP142) Tumor Cell Positivity for 5 Pathologists
Distribution of Cases by Pathologist for Immune Cell Staining (first 5 sets)
Distribution of Cases by Pathologist for Immune Cell Staining (All 35 sets)
Immune Cell Expression using SP142 (n=35)

Distribution of Maximum PD-L1 (SP142) Stromal Cell Positivity for 5 Pathologists
Intraclass Correlation Coefficient (ICC) to Assess Reproducibility of Each Variable

• Variables:
  – 5 pathologists
  – 3 block per tumor
  – N=35 tumors in the cohort

• Calculate ICC to determine reproducibility between blocks and between pathologists for the 35 Lung Cancer Case cohort

<table>
<thead>
<tr>
<th></th>
<th>ICC for readers*</th>
<th>ICC for blocks**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor</td>
<td>94.2%</td>
<td>93.7%</td>
</tr>
<tr>
<td>Stromal</td>
<td>19.5%</td>
<td>77.7%</td>
</tr>
</tbody>
</table>

* based on max % among blocks (N=175 for both tumor and stroma)
** based on all % (N=525=35*5*3 for both tumor and stroma)
Generating the AQUA® score

Combine DAPI image and cytokeratin image then cluster to assign each pixel to a subcellular compartment

\[ \Sigma \text{target intensity in compartment pixels} = \Sigma \text{compartment pixel area} \]

\[ \Sigma \text{compartment pixel area} = \text{AQUA score} \]
Case06838

Tumor Mask

Stromal Mask

Median = 3467.1
Minimum = 2396.7
Maximum = 6970.5

Median = 2584.5
Minimum = 1923.1
Maximum = 8070.6
PD-L1 by IHC and QIF on 3 blocks from the same specimen

Block H6

Block H7

Block H8
Tumor PD-L1 QIF scores according to percentage tumor cell positivity estimation

- Blue: < 1%
- Red: 1-50%
- Green: > 50%

Cases
Stromal PD-L1 QIF scores according to percentage stromal cell positivity estimation

- Blue: < 1%
- Red: 1-50%
- Green: > 50%

QIF score (AU)

Cases
Tumor vs Stromal PD-L1

Case 11966-2

\[ y = 0.4794x + 280.23 \]
\[ R^2 = 0.3151 \]

Case 6226-4

\[ y = 0.5984x + 276.07 \]
\[ R^2 = 0.5153 \]
Treated Cohort: E1L3N Tumor and Stromal FOV AQUA Scores for Each Case Sorted by Tumor Mean Score

Blue Dots = Tumor FOV
Red Dots = Stromal FOV
Green Line = visual detection threshold
Black bar = mean
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<td>Pathologist/Subjective</td>
</tr>
</tbody>
</table>
Antibodies are Not Identical: 25% Discordant

- 46 NSCLC cases
- Serial sections
- 588 FOVs measured with QIF with each antibody
- E1L3N = 43.8% Positive
  - Cell Signaling (~DAKO)
- SP142 = 34.4% Positive
  - Ventana (~Roche/Genentech)

FOV = field of view; QIF = quantitative immunofluorescent.

Quantitative Assessment of the Heterogeneity of PD-L1 Expression in Non-Small-Cell Lung Cancer

Joseph McLaughlin, MD; Gang Han, PhD; Kurt A. Schalper, MD, PhD; Daniel Carvajal-Hausdorff, MD; Vasiliki Pelakou, MD, PhD; Jamsai Rehman, MD; Vamsidhar Velcheti, MD; Roy Herbst, MD, PhD; Patricia LoRusso, DO; David L. Rimm, MD, PhD

*IMPORTANT* Early-phase trials with monoclonal antibodies targeting PD-1 (programmed cell death protein 1) and PD-L1 (programmed cell death 1 ligand 1) have demonstrated durable clinical responses in patients with non-small-cell lung cancer (NSCLC). However, current assays for the prognostic and/or predictive role of tumor PD-L1 expression are not standardized with respect to either quantity or distribution of expression.
# PD-L1 Antibody Comparison Study

<table>
<thead>
<tr>
<th>Antibody Name</th>
<th>PD-L1</th>
<th>PD-L1</th>
<th>PD-L1</th>
<th>PD-L1</th>
<th>PD-L1</th>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clone</td>
<td>SP142</td>
<td>E1L3N</td>
<td>SP263*</td>
<td>E1J2</td>
<td>9A11</td>
<td>28_8*</td>
</tr>
<tr>
<td>Isotype and Host species</td>
<td>Rabbit IgG</td>
<td>Rabbit IgG</td>
<td>Rabbit IgG</td>
<td>Rabbit IgG</td>
<td>Mouse</td>
<td>Rabbit IgG</td>
</tr>
<tr>
<td>Company</td>
<td>Spring Bioscience</td>
<td>CST</td>
<td>Ventana</td>
<td>CST</td>
<td>CST</td>
<td>Abcam</td>
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<tr>
<td>Catalog #</td>
<td>M4420</td>
<td>#13684</td>
<td>790-4905</td>
<td>15765</td>
<td>29122</td>
<td>ab20591</td>
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<th>PD-L1</th>
<th>PD-L1</th>
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<th>PD-L1</th>
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</table>

<table>
<thead>
<tr>
<th>Lot</th>
<th>Applications</th>
<th>Concentration</th>
<th>Recommended dilution</th>
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</thead>
<tbody>
<tr>
<td>150420D</td>
<td>IHC-P</td>
<td>77 μg/ml</td>
<td>1:100</td>
</tr>
<tr>
<td>6</td>
<td>IHC-P, IF, WB, IP, Flow</td>
<td>1010 μg/ml</td>
<td>1:200</td>
</tr>
<tr>
<td>F023122</td>
<td>IHC-P</td>
<td>1.16 μg/ml</td>
<td>Pre-dilute</td>
</tr>
<tr>
<td>RM3</td>
<td>IHC-P</td>
<td>5700 μg/ml</td>
<td>1:100</td>
</tr>
<tr>
<td>1</td>
<td>WB, IHC-P, IF-IC</td>
<td>100 μg/ml</td>
<td>1:200</td>
</tr>
<tr>
<td>GR234653-3</td>
<td>IHC-P, WB, Flow</td>
<td>967 μg/ml</td>
<td>1:500</td>
</tr>
</tbody>
</table>

1) Dako would NOT sell the 22.3 antibody to our lab since we did not have a Link48 stainer

2) After purchasing 6 tubes of 28.8 from Abcam with 2 different operators we were unable to get reproducible results, so this antibody was eliminated from the study
PD-L1 Index TMA (YTMA-337)
Example of Quantitative Optimization of Titration

SP142 EDTA pH8 20min Titration Curve

- AQUA scores
- Dilution
- Ratio

*Only patient tumor cores included
Example of Inter-Run Regression
(SP263 - 3 different days)

All other antibodies showed similar inter-run and inter-operator regressions.
**SP142 vs 9A11**

- **Overall Regression**
  - $y = 1.0374x + 594$
  - $R^2 = 0.6909$

- **Tumour core Regression**
  - $y = 0.6627x + 384.48$
  - $R^2 = 0.8879$

- **Cell Line Regression**
  - $y = 1.0271x + 3203.3$
  - $R^2 = 0.7296$

**SP263 vs 9A11**

- **Overall Regression**
  - $y = 0.5222x + 285.83$
  - $R^2 = 0.9169$

- **Tumour core Regression**
  - $y = 0.8664x + 2188$
  - $R^2 = 0.8848$

- **Cell Line Regression**
  - $y = 0.8378x - 30.619$
  - $R^2 = 0.766$
Antibody Comparison on Horizon Discovery PD-L1 Developmental TMA
Conclusions

• When tested on Cell Lines (Yale or HD) the antibodies are almost indistinguishable.

• There was essentially no difference between ECD (SP263) and ICD (SP142, E1L3N and 9A11) antibodies.

• When tested on tumors, there is some variation, but that may be due to heterogeneity in the TMA.
Thanks to:

**Rimm Group:**
Kurt Schalper  
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John McGuire  
Vasiliki Pelakanou  
Nikita Mani  
Yan Song  
Maria Toki  
Jamaal Rehman  
Patricia Gaule  
Nick Goel  
Yuting Lui  
Brad Wasserman

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Elsa Anagnostou  
Anastasios Dimou  
Alley Welsh  
Robert Camp  
Maria Vassilikapoulou  
Huan Cheng  
Jennifer Bordeaux  
Elizabeth Zarrella  
Hallie Wimberly  
Jason Brown

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Sudha Kumar  
Veronique Neumeister  
Yalai Bai  
(Google YPTS)

**Yale Collaborators**
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