The Role of Immuno-Oncology Biomarkers in Lung Cancer

Vamsidhar Velcheti, MD, FACP
Staff Physician, Associate Director
Center for Immuno-Oncology Research
Taussig Cancer Institute | Cleveland Clinic

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I will be discussing off-label indications and usage of drugs or biomarker assays that are currently FDA approved for other indications, or not FDA approved.

• Consultant/Advisory Board
  – Merck
  – Bristol-Myers Squibb
  – Genentech
  – Celgene
  – AstraZeneca
  – Navigate BioPharma
  – Foundation Medicine
  – Takeda Oncology
  – Fulgent Genetics
Treatment of Advanced Stage Non-small Cell Lung Cancer

Survival (%)

Month

- Cisplatin and paclitaxel
- Cisplatin and gemcitabine
- Cisplatin and docetaxel
- Carboplatin and paclitaxel

Treatment of Advanced Stage Non-small Cell Lung Cancer

Treatment of Advanced Stage Non-small Cell Lung Cancer

- Targeted therapy
- Immunotherapy

Survival (%) vs. Month
- Cisplatin and paclitaxel
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- Targeted therapy
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accc-cancer.org
I-O: Evolving Cancer Treatment Modality

• I-O is a fundamentally different approach to fighting cancer that harnesses the body’s own immune system\(^1\)

Through I-O research, therapies are being investigated in an attempt to utilize the body’s own immune system to fight cancer\(^1\)\(^-\)\(^3\)

Emerging Challenge in Cancer Immunotherapy

"Bridging the Gap" Requires

- Identifying patients that would benefit the most from immunotherapy
- Identifying patients at high risk for serious irAEs
- Rational combinations based on sound mechanistic principles

Significant Gap to Bridge

\[ \approx 20-30\% \]

PD-1 Monotherapy ORR %

acs-cancer.org
The Immune Response to Cancer: Very Complex Balance Between Continuous Activation and Suppression


accc-cancer.org
Approved Biomarkers for Immuno-oncology Diagnostics

Phenotype markers
- PD-L1 IHC
- TILs
- Th1/IFN-γ
- Microbiome
- Other: IPRES/MDSC

Genomic markers
- MSI
- Mutational burden
- APM/IFN mut.
- DNA FISH
- TCRβ clonality

Approved by the FDA

Kurt Schalper ASCO 2017
Current FDA-approved PD-1 Inhibitors and Diagnostic Biomarkers in Lung Cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA Approval</th>
<th>Indication</th>
<th>Companion Diagnostic</th>
<th>Complementary Diagnostic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>March 2015</td>
<td>2nd Line advanced stage NSCLC (Squamous Cell Carcinoma)</td>
<td>None required</td>
<td>DAKO- 28.8 PD-L1 IHC (1%, 5% and 10%)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>October 2015</td>
<td>2nd Line advanced stage NSCLC (Non-Squamous Cell Carcinoma)</td>
<td>None required</td>
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</tr>
<tr>
<td>Pembrolizumab</td>
<td>October 2015</td>
<td>2nd Line advanced stage NSCLC</td>
<td>DAKO- 22C3 PD-L1 IHC &gt;1% TPS, 1-49%</td>
<td>Ventana- SP142, TC=Tumor cell IC = Immune cell Combine both Percentage and Subjective intensity++</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>April 2016</td>
<td>2nd Line advanced stage NSCLC</td>
<td>None required</td>
<td>Ventana- SP263, TC=Tumor cell Membrane staining</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>October 2016</td>
<td>1st Line advanced stage NSCLC</td>
<td>DAKO-22C3 PD-L1 IHC &gt;50% TPS*</td>
<td>Ventana- SP142, TC=Tumor cell Membrane staining</td>
</tr>
<tr>
<td>Pembrolizumab with Carboplatin/Pemetrexed</td>
<td>May 2017</td>
<td>1st Line advanced stage NSCLC (Non-Squamous Cell Carcinoma)</td>
<td>None required</td>
<td>Ventana- SP263, TC=Tumor cell Membrane staining</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Stage III Non-small cell lung cancer maintenance</td>
<td>none</td>
<td>Ventana- SP263, TC=Tumor cell Membrane staining</td>
<td></td>
</tr>
</tbody>
</table>

TC3=TC>50%  
IC3= IC>10%  
TC2/IC2=TC or IC>5%  
TC1/IC1=TC or IC>1%  
* Tumor proportion score

++

PD-1 Inhibitors and Diagnostic Biomarkers in Lung Cancer

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Association of Community Cancer Centers
Current Biomarker Approach for Selecting Patients for Immunotherapy

KEYNOTE-24: I-L Metastatic NSCLC w/ PDL-1 IHC > 50% TPS (Dako 22C3)

Overall Survival: Updated Analysis

Keynote-024 updated OS analysis: Brahmer J, et al. WCLC October 2017, Yokohama Japan
Challenges with clinical PD-L1 biomarker evaluation

1. How different are these PD-L1 IHC assays when compared to each other, in terms of their staining characteristics

2. Can these assays be interchanged when used to determine the PD-L1 status of patient’s tumor

3. Is PD-1 status reproducible, i.e., spatial and temporal heterogeneity
Challenges with clinical PD-L1 biomarker evaluation

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Comparability among Five PD-L1 IHC Assays Based on Tumor Cell Staining

Each circle represents the mean of all scores (glass slide & digital combined)

Blueprint phase-2 study: M.S. Tsao. et al. WCLC October 2017, Yokohoma Japan
Real-world Distribution of PD-L1 Tumor Expression by Assay Type

PD-L1 biomarker IHC assay results (N=1728*)

<table>
<thead>
<tr>
<th>PD-L1 tumor expression, categorized †</th>
<th>FDA-approved IHC assay, n (%)</th>
<th>Laboratory-developed tests, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dako 22C3 (N=1335)</td>
<td>Dako 28-8 (N=90)</td>
</tr>
<tr>
<td>&lt;1%</td>
<td>478 (35.8)</td>
<td>37 (41.1)</td>
</tr>
<tr>
<td>1–49%</td>
<td>376 (28.2)</td>
<td>25 (27.8)</td>
</tr>
<tr>
<td>≥50%</td>
<td>481 (36.0)</td>
<td>28 (31.1)</td>
</tr>
</tbody>
</table>

*Some patients had >1 test and are represented in >1 column
†p<0.0001 for $\chi^2$ test comparing results across the 4 assay types, and
p=0.053 for $\chi^2$ test comparing results across 3 assay types, excluding the Ventana SP142

Velcheti et al. WCLC October 2017, Yokohoma Japan

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Challenges with clinical PD-L1 biomarker evaluation

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Tumor PD-L1 Heterogeneity

- Heterogeneity – multiple tumors and multiple passes within a tumor
- Interval between biopsy and treatment
- Primary versus metastatic disease
- Antibody and staining conditions

- Defining a positive result (cut-offs):
  - Cell type expressing PD-L1 (immune cell versus tumor or both)
  - Location of expression – cell surface versus intracellular versus stromal
  - Intensity, percent of cells ‘positive’
  - Distribution - patchy versus diffuse, intratumoral versus peripheral

Immunofluorescence shows stroma and epithelial staining are often concordant and adjacent

Green = Cytokeratin
Blue = Nuclei
Red = PD-L1 (SP142)

McLaughlin J et al JAMA Oncol 2016
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Novel Quantitative Techniques for Evaluation of PD-L1

PD-1/PD-L1 INTERACTION SCORE

Interaction Score = PD-1+ cells co-localized with PD-L1+ cells

Velcheti, et al. WCLC October 2017, Yokohoma Japan
Novel Quantitative Techniques for Evaluation of PD-L1

A

Type 1 = Low CD3

Type 2 = High CD3/low GZB & Ki-67

Type 3 = High CD3/high GZB or Ki-67

B

Progression-free survival

Log-rank P = 0.043

Surviving probability

Time (years)

C

Overall survival

Log-rank P = 0.003

Surviving probability

Time (years)

Schalper, et al. WCLC October 2016, Vienna Austria
NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Pembrolizumab

NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Pembrolizumab

NSCLC Tumor Mutation Burden Associated with Clinical Benefit with Nivolumab in First-line NSCLC

Peters S, et al. AACR 2017
NSCLC ctDNA based Tumor Mutation Burden Associated with Clinical Benefit with Atezolizumab (OAK trial)

Gandara D, et al. ESMO 2017
Microbiome and Immunotherapy

Patients with metastatic melanoma, PD-1
~45 patients

Responders to PD-1 had higher gut microbiota diversity than non-responders.

Wargo, et al. ASCO 2017

Conclusion

• PDL-1 testing and MSI are the only approved diagnostic tests for selecting patients for PD-1 axis inhibitors.

• Interrogating the tumor microenvironment using phenotype/immunology and genomic metrics could provide future strategies for selecting patients for single agent and combination I-O therapy.
Thank you for participating in the webinar. Presentation slides and archived recording will be available at accc-iclio.org