Post-ASCO Immunotherapy Highlights (Part 2): Biomarkers for Immunotherapy

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Objectives

To discuss:

• PD-L1 as a biomarker for PD-1/PD-L1 inhibitors
• Tumor mutation burden as a predictor of response
• Checkpoint inhibition in colorectal cancer with high microsatellite instability or mismatch-repair deficiency
• Role of oncogenic viruses in predicting immunotherapeutic response
ASCO 2016: Biomarkers for Immunotherapy

- Checkpoint inhibitors have demonstrated unprecedented rates of durable responses; however, only a minority of patients respond.
- Goal of biomarkers:
  - To predict clinical outcomes
  - To select appropriate patients for immunotherapy

Types of biomarkers for immunotherapy

- Immunologic (eg, PD-L1)
- Viral (eg, HPV, MCPyV)
- Genetic (eg, mutation burden, MSI, dMMR)

dMMR: mismatch repair deficiency; MCPyV: Merkel Cell Polyomavirus; MSI: microsatellite instability.
PD-L1 as Biomarker
Complexities/Challenges of PD-L1 as Biomarker for Anti-PD-1/PD-L1 Therapies

- Multiple cell types in the tumor microenvironment can express PD-L1
  - Both tumors cells and tumor infiltrating lymphocytes (TIL)
  - IHC tests can score tumor cells and/or immune infiltrating cells
- Heterogeneity even within a single patient
  - PD-L1 expression can change over time
  - PD-L1 expression may differ at different locations
- Focal PD-L1 expression
  - Can result in sampling error

PD-L1 Expression correlated with Response to Pembrolizumab in NSCLC: KEYNOTE-010

• Analysis of outcomes with PD-L1 categorized as a tumor proportion score (TPS)\textsuperscript{1}
  – Phase III randomized study: pembrolizumab improved OS over docetaxel in previously-treated, PD-L1+ NSCLC\textsuperscript{2}

<table>
<thead>
<tr>
<th>Pembro/Doce</th>
<th>TPS 1%-24%</th>
<th>TPS 25%-49%</th>
<th>TPS 50%-74%</th>
<th>TPS ≥75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS (mo)</td>
<td>9.7/8.5</td>
<td>9.8/9.9</td>
<td>15.8/8.2</td>
<td>16.6/8.2</td>
</tr>
<tr>
<td>mPFS (mo)</td>
<td>2.6/4.0</td>
<td>2.9/3.8</td>
<td>4.3/4.3</td>
<td>6.2/4.0</td>
</tr>
<tr>
<td>ORR (%)</td>
<td>8.6/10.9</td>
<td>15.8/9.1</td>
<td>22.6/9.6</td>
<td>33.7/7.0</td>
</tr>
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• Increasing PD-L1 expression was associated with more favorable outcomes with pembrolizumab, but not with docetaxel
• Pembrolizumab improved OS over docetaxel even at the lowest TPS category
• PD-L1- patients were excluded in the study

Doce: docetaxel; mOS: median overall survival; mPFS: median progression-free survival; ORR: objective response rate.

Nivolumab and Pembrolizumab Showed High Response in Hodgkin Lymphoma

- Reed-Sternberg cells uniformly demonstrate copy number alterations of the PD-L1 and PD-L2 loci on 9p24.1
- 2 phase II studies in relapsed/refractory classical Hodgkin lymphoma: CheckMate-025 (nivolumab) and KEYNOTE-087 (pembrolizumab)

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3mg/kg Q2W (n=80)</th>
<th>Pembrolizumab 200 mg Q3W (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS</td>
<td>10.0 mo</td>
<td>-</td>
</tr>
<tr>
<td>ORR</td>
<td>66%</td>
<td>73%-83%</td>
</tr>
<tr>
<td>mDOR</td>
<td>7.8 mo</td>
<td>-</td>
</tr>
<tr>
<td>Grade 3/4 TRAE</td>
<td>25%</td>
<td>4%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
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Nivolumab approved by the FDA on May 17, 2016 for cHL that has relapsed or progressed after autologous HSCT and post-transplant brentuximab vedotin

cHL: classical Hodgkin lymphoma; HSCT: hematopoietic stem cell transplantation; mDOR: median duration of response; mPFS: median progression-free survival; ORR: objective response rate; TRAE: treatment-related adverse event.

PD-L1 Expression Did Not Predict for Clinical Benefit of Nivolumab in RCC

- CheckMate-025: Phase III randomized study
  - Advanced RCC after 1-2 antiangiogenic therapy (n=821)
  - Nivolumab significantly improved ORR and OS over everolimus

<table>
<thead>
<tr>
<th>PD-L1 ≥1% (n = 24%)</th>
<th>PD-L1 &lt;1% (n = 76%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median OS, months (95% CI)</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>21.8 (16.5–28.1)</td>
</tr>
<tr>
<td>Everolimus</td>
<td>18.8 (11.9–19.9)</td>
</tr>
<tr>
<td>HR (95% CI): 0.79</td>
<td>(0.53–1.17)</td>
</tr>
</tbody>
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PD-L1 Negative Patients Can Respond to Anti-PD-1/PD-L1 Therapies

- Across cancer types:
  Although PD-L1 expression is associated with higher response rates, PD-L1- patients can still respond

Data presented at ASCO 2016 on solid tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Therapy</th>
<th>ORR for PD-L1 &lt;1%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNSCC</td>
<td>2L Nivolumab(^1)</td>
<td>12%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1L+ Pembroliزumab + ipilimumab(^2)</td>
<td>45%</td>
</tr>
</tbody>
</table>
| NSCLC                 | 1L Nivolumab\(^3\)  
                        | 1L Nivolumab + ipilimumab\(^3\)             | 14%  
                        | 0-30%            |
| Urothelial carcinoma  | 2L Atezolizumab\(^4\)  
                        | 2L Durvalumab\(^5\)                          | 8%  
                        | 7%               |

Cannot exclude PD-L1- patients from anti-PD-1/PD-L1 therapies


Tumor Mutation Burden as Biomarker
Tumor Mutation Burden (TMB) in Different Cancer Types

Somatic mutation frequencies observed in exomes from 3,083 tumor-normal pairs

Each dot corresponds to a tumor-normal pair, with vertical position indicating the total frequency of somatic mutations in the exome.

Determining TMB by Limited Gene Sets vs. Whole Exome Sequencing (WES)

- Profiling a smaller fraction of the genome could serve as an accurate surrogate for TMB
- HC NGS of the coding sequence of 236-315 genes compared with WES

Mutations in limited gene set vs. WES

HC NGS: hybrid capture-based next-generation sequencing; TMB: tumor/total mutation burden.

TMB Correlated with Immunotherapy Response in Melanoma

- 65 melanoma patients treated with anti-PD-1/PD-L1 (nivolumab, pembrolizumab, atezolizumab)
- Initial cohort and validation cohort

<table>
<thead>
<tr>
<th>TMB (mut/MB)</th>
<th>Response</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>High: &gt;23.1</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>Intermediate: 3.3-23.1</td>
<td>29%</td>
<td>71%</td>
</tr>
<tr>
<td>Low: &lt;3.3</td>
<td>14%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Responders to anti-PD-1/PD-L1 had higher mutation burden than non-responders

Node NGS: hybrid capture-based next-generation sequencing; TMB: tumor/total mutation burden.

Patients with high TMB had higher PFS and OS compared with patients with intermediate and low TMB.

OS: overall survival; PFS: progression-free survival; TMB: tumor/total mutation burden.
TMB Correlated with Time on Immunotherapy in NSCLC

- Comprehensive genomic profiling (CGP) to assess TMB and MSI status
- Analysis of 64 NSCLC patients

<table>
<thead>
<tr>
<th>TMB (mut/MB)</th>
<th>Median time on anti-PD-1/PD-L1</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥15</td>
<td>64 weeks</td>
<td>0.396 (0.190-0.825; P=0.010)</td>
</tr>
<tr>
<td>&lt;15</td>
<td>17 weeks</td>
<td></td>
</tr>
<tr>
<td>≥12.1</td>
<td>27 weeks</td>
<td>0.619 (0.339-1.127; P=0.117)</td>
</tr>
<tr>
<td>&lt;12.1</td>
<td>17 weeks</td>
<td></td>
</tr>
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- High TMB correlated with longer duration of anti-PD-1/PD-L1 therapy (nivolumab/pembrolizumab/avelumab)
- MSI-H status strongly correlated with high TMB

MSI-H: microsatellite instability high; mut: mutations; NSCLC: non-small cell lung cancer; TMB: tumor/total mutation burden.

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer

- **Exploratory analysis of biomarkers of response to atezolizumab**
  - IMvigor210 study: metastatic urothelial cancer (n=310)
  - Focus on PD-L1, Cancer Genome Atlas (TCGA) subtype, TMB

**PD-L1 status and outcome**

<table>
<thead>
<tr>
<th>PD-L1 status</th>
<th>ORR</th>
</tr>
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<tbody>
<tr>
<td>IC2/3</td>
<td>28%</td>
</tr>
<tr>
<td>IC0/1</td>
<td>10%</td>
</tr>
<tr>
<td>All</td>
<td>16%</td>
</tr>
</tbody>
</table>

IC: immune cells; TMB: tumor/total mutation burden

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer (continued)

- ORR significantly higher in luminal II vs. other subtypes \((P=0.0072)\)

TCGA subtype and outcome

Biomarkers of Outcome to Atezolizumab in Urothelial Cancer (continued)

- Highest TMB quartile was associated with improved OS with atezolizumab
- Both in pretreated (cohort 2) and previously untreated patients (cohort 1)

TMB and outcome

PD-L1, TCGA subtype, and TMB are significant independent predictors of response to atezolizumab

Microsatellite Instability and Mismatch Repair Deficiency as Biomarkers
Microsatellite Instability (MSI) and Mismatch Repair Deficiency (dMMR)

MSI: hypermutable phenotype with changes in microsatellites (short, tandem repeat sequences of DNA)\(^1\)
- Categories: MSI-high, MSI-low, MSS (microsatellite stable)

MSI caused by DNA mismatch repair (MMR) deficiency (dMMR)\(^2\)
- dMMR due to inactivating mutations of MMR genes: \textit{MLH1}, \textit{MLH3}, \textit{MSH2}, \textit{MSH3}, \textit{MSH6}, \textit{PMS1}, \textit{PMS2}
- MSI-H mainly due to inactivation of \textit{MLH1}

MSI-H represents 15% of colorectal cancer (CRC)\(^3\)
- MSI-H associated with improved OS in CRC

Nivolumab ± Ipilimumab Showed Activity in mCRC with MSI-H: CheckMate-142

- In CRC, MSI-H is associated with increase in immune infiltration and expression of checkpoint regulators
- Interim analysis of CheckMate-142: phase 2 study
  - MSI-H cohort and MSS cohort treated by nivolumab ± ipilimumab

<table>
<thead>
<tr>
<th></th>
<th>MSI-H cohort (n=100)</th>
<th>MSS cohort (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo 3</td>
<td>Nivo 3 + ipi 1</td>
</tr>
<tr>
<td>ORR</td>
<td>25%</td>
<td>33%</td>
</tr>
<tr>
<td>mPFS</td>
<td>5.3 mo</td>
<td>Not reached</td>
</tr>
<tr>
<td>mOS</td>
<td>17.1 mo</td>
<td>Not reached</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>5.7%</td>
<td>13.3%</td>
</tr>
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Nivolumab and ipilimumab demonstrated durable responses in MSI-H mCRC

Ipi: ipilimumab; mCRC: metastatic colorectal cancer; MSI-H: microsatellite instability high; MSS: microsatellite stable; nivo: nivolumab.

Pembrolizumab Showed Activity in MMR-Deficient CRC

- Genetic and epigenetic defects in MMR lead to MSI-H
  - MMR deficiency associated with Lynch Syndrome
- Phase II study: pembrolizumab in refractory MMR deficient (dMMR) and MMR proficient (pMMR) CRC

<table>
<thead>
<tr>
<th>CRC cohort (n=53)</th>
<th>dMMR</th>
<th>pMMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>57%</td>
<td>0%</td>
</tr>
<tr>
<td>mPFS</td>
<td>Not reached</td>
<td>2.3 mo</td>
</tr>
<tr>
<td>mOS</td>
<td>Not reached</td>
<td>6.0 mo</td>
</tr>
<tr>
<td>Grade 3/4 AE</td>
<td>&lt;5%</td>
<td></td>
</tr>
</tbody>
</table>

Complete and durable responses seen in more than 50% of patients

AE: adverse events; CRC: colorectal cancer; MMR: mismatch repair; MSI-H: microsatellite instability high.

Oncogenic Viruses as Biomarkers
Trend Towards Higher Benefit of Nivolumab for HPV-Positive HNSCC

- **CheckMate 141**: phase III randomized study of nivolumab vs. investigator’s choice
  - Recurrent or metastatic HNSCC ($n=361$)
- **Documentation p16 for HPV status (oropharyngeal)**

HNSCC: head and neck squamous cell carcinoma.

**Trend Towards Higher Response to Pembrolizumab for HPV-Positive HNSCC**

- **KEYNOTE-055**: single-arm phase II
  - Pembrolizumab for recurrent or metastatic HNSCC after progression on platinum and cetuximab (n=172)

<table>
<thead>
<tr>
<th></th>
<th>HPV + (n=18)</th>
<th>HPV – (n=74)</th>
</tr>
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<tbody>
<tr>
<td>ORR</td>
<td>4 (22%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>PR</td>
<td>4 (22%)</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (17%)</td>
<td>14 (19%)</td>
</tr>
<tr>
<td>PD</td>
<td>9 (50%)</td>
<td>42 (57%)</td>
</tr>
</tbody>
</table>

- Preliminary data show trend towards higher response or benefit of anti-PD-1 therapy in HPV positive patients
- More data is warranted

HNSCC: head and neck squamous cell carcinoma; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

MCPyV Status and PD-L1 Expression Did Not Impact Response to Avelumab in MCC

- Merkel Cell Polyomavirus (MCPyV) negative tumors have higher mutation burden
- JAVELIN Merkel 200: phase 2 study of avelumab (anti-PD-L1) in MCC (n=88)

Avelumab showed activity in MCC regardless of MCPyV or PD-L1 status

MCC: Merkel cell carcinoma.

• PD-L1 expression correlated with response to pembrolizumab in NSCLC
• Nivolumab and pembrolizumab showed high response in Hodgkin Lymphoma
• PD-L1 expression did not predict for clinical benefit of nivolumab in RCC
• PD-L1 negative patients can respond to anti-PD-1/PD-L1 therapies
2016 ASCO Annual Meeting: Summary (Continued)

• TMB correlated with immunotherapy outcome in melanoma and with time on immunotherapy in NSCLC
• PD-L1, TCGA subtype, and TMB are significant independent predictors of response to atezolizumab
• Nivolumab and ipilimumab demonstrated durable responses in MSI-H mCRC
• Pembrolizumab showed activity in MMR-deficient CRC
• Preliminary data show trend towards higher response or benefit of anti-PD-1 therapy in HPV positive patients
• Avelumab showed activity in MCC regardless of MCPyV or PD-L1 status
Questions?
Register for the ICLIO National Conference
September 30, 2016
Philadelphia

www.accc-iclio.org
Thank you for participating in the ICLIO e-Course. Presentation slides and archived recording will be available at accc-icl.io
References