Precision Oncology Approaches for Immunotherapy

Eric H. Rubin, M.D.
MSD
Disclosures

• Employee of MSD
• Will discuss indications for pembrolizumab that are approved in U.S. but not E.U.
Using Predictive Biomarkers (Companion Diagnostics) to Select Patients for Treatment

- Cancer therapeutics are increasingly being developed together with tests that enable identification of patients most likely to benefit from the treatment
- “No test is perfect, but some tests are useful”
  - Histology is an imperfect biomarker that is used to select cancer patients for treatment
- Companion diagnostics increasingly used to select among treatment options
  - For both “targeted” therapeutics as well as immuno-oncology agents
- Companion diagnostic development typically lags behind therapeutics, creating scientific and regulatory complexity
The PD-1 and PD-L1/L2 Pathway

- PD-1 is an immune checkpoint receptor
- Binding of PD-1 by its ligands PD-L1 or PD-L2 leads to downregulation of T-cell function
- This mechanism is usurped by many tumors
- PD-1 blockade through mAb therapy can restore and reveal effective anti-tumor immunity

**Potential Mechanism-based Predictive Biomarkers for Checkpoint Inhibitors**

**Tumor Inflammation**
- PD-L1 Expression
- Immune-Related Gene Expression (GEP) Signature

**Tumor Antigenicity**
- Microsatellite instability, DNA Mismatch Repair Deficiency, Tumor Mutation Burden (TMB)

**Goal is to identify patients most likely to benefit from treatment**
### Predictive Biomarkers Important for Several Pembrolizumab Approvals

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Approval Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Melanoma</strong></td>
<td>✓ 1&lt;sup&gt;st&lt;/sup&gt; approval of a PD-1 inhibitor (US)</td>
</tr>
<tr>
<td></td>
<td>✓ 1L and 2L – full approval</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>✓ Approved for 2L TPS (\geq 1%) (US/EU/JPN)</td>
</tr>
<tr>
<td></td>
<td>✓ Approved for 1L TPS (\geq 50%) (US/JPN/EU)</td>
</tr>
<tr>
<td></td>
<td>✓ Approved 1L non-squamous NSCLC, combination with pemetrexed and carboplatin (US)</td>
</tr>
</tbody>
</table>

**Other Tumors**

- ✓ Approved for Head & Neck 2L (US)
- ✓ Approved for Relapsed or Refractory Hodgkin Lymphoma (US/EU)
- ✓ Approved for 1L Cis-ineligible Bladder Cancer and 2L Metastatic Bladder Cancer (US/EU)
- ✓ Approved for Microsatellite Instability High/Deficient in Mismatch Repair Cancer (US)
- ✓ Approved for Recurrent or Advanced Gastric or GE Junction Adenocarcinoma CPS \(\geq 1\) (US)
- ✓ Approved for Previously Treated Patients with Recurrent or Metastatic Cervical CPS \(\geq 1\) (US)

Blue text indicates predictive biomarker required for approval
First PD-1/L1 Companion Diagnostic Approved - 22C3 pharmDx IHC Assay for Use in NSCLC

Correlation with Improved Outcomes to Pembrolizumab

Adapted from presentation by Garon EB AACR 2015
Utility of 22C3 pharmDx IHC Assay for Monotherapy Pembrolizumab in 1L NSCLC

October 2016

US FDA approves pembrolizumab in the first-line treatment of patients with NSCLC (PD-L1 TPS≥50% tumor proportion score)

Updated data show median OS of 30 months for pembrolizumab versus 14.2 months for chemotherapy

Updated by Brahmer J, et al at WCLC 2017
Use of Combinations to Expand the Population that Benefits

Risk of death for chemotherapy halved by combining pembrolizumab with chemotherapy in 1L metastatic NSCLC (KEYNOTE-189)

Ghandi L, et al. 2018 AACR Annual Meeting
Overall Survival Benefit Observed Irrespective of PD-L1 TPS (Keynote 189)

Data cutoff date: Nov 8, 2017.

Ghandi L, et al. 2018 AACR Annual Meeting
On May 23, 2017, the US Food and Drug Administration (FDA) approved pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) solid tumors, regardless of tumor site or histology.
DNA Microsatellites

- Small, repetitive sequences, principally of polyadenine tracts\(^1\)

- Abundant throughout the genome; polymorphic between individuals, but unique and uniform in length in each person\(^1\)

- Microsatellites are prone to mutations when there are deficiencies in DNA mismatch repair (dMMR)\(^2\)

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Microsatellite Mutations are Usually Corrected by MMR Machinery

- During replication, incorrect DNA alignment and polymerase errors can lead to insertions/deletions\(^1\)
- Mismatch repair proteins **MLH1, MSH2, MSH6, PMS2** correct these errors\(^2\)
- MMR deficiency due to loss of repair protein expression or function causes MSI phenotype\(^1\)

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Adapted from Chung et al. 2003; Kirkpatrick et al. 1997,\(^3,4\)
MSI-H Phenotype May Confer Responsiveness to PD-1 Inhibition Independent of Histology

- Hypothesis: Since the target is immune cells, PD-1 inhibition is effective in treating any MSI-H cancer

  - Regardless of tumor histology high neoantigen expression leads to autologous immune recognition of cancer cells, and cytotoxic T-lymphocyte rich microenvironment within the tumor

  - Blocking PD-1 on tumor neoantigen-specific T cells may activate anti-tumor immune responses

Results from an MSD-Supported Investigator-Initiated Trial of Pembrolizumab in MSI-H Cancer

- MSD-supported, investigator-initiated trial (KN-016) at Johns Hopkins University – initial detection of consistent efficacy signal in a biomarker-defined population across tumor histologies
### KN-016 Study Design

<table>
<thead>
<tr>
<th>Colorectal Cancers</th>
<th>Non-Colorectal Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort A</strong></td>
<td><strong>Cohort B</strong></td>
</tr>
<tr>
<td>Deficient in</td>
<td>Proficient in</td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td>Mismatch Repair</td>
</tr>
<tr>
<td>(n=25)</td>
<td>(n=25)</td>
</tr>
<tr>
<td><strong>Cohort C</strong></td>
<td></td>
</tr>
<tr>
<td>Deficient in</td>
<td></td>
</tr>
<tr>
<td>Mismatch Repair</td>
<td></td>
</tr>
<tr>
<td>(n=21)</td>
<td></td>
</tr>
</tbody>
</table>

- Mismatch repair testing was performed locally using standard IHC for MMR deficiency or PCR-based test for microsatellite instability.
KN-016 CRC: Best Radiographic Response

% Change from Baseline SLD

-100
-50
0
50
100

MMR-proficient CRC
MMR-deficient CRC
KN-016 MSI-H/dMMR non-CRC: Best Radiographic Response
Pembrolizumab Response by Tumor Type - FDA Filing (15 tumor types)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N</th>
<th>n (%)</th>
<th>95% CI</th>
<th>DOR range</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC</td>
<td>90</td>
<td>32 (36%)</td>
<td>(26%, 46%)</td>
<td>(1.6+, 22.7+)</td>
</tr>
<tr>
<td>Non-CRC</td>
<td>59</td>
<td>27 (46%)</td>
<td>(33%, 59%)</td>
<td>(1.9+, 22.1+)</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>5 (36%)</td>
<td>(13%, 65%)</td>
<td>(4.2+, 17.3+)</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27%)</td>
<td>(6%, 61%)</td>
<td>(11.6+, 19.6+)</td>
</tr>
<tr>
<td>Gastric or GE junction cancer</td>
<td>9</td>
<td>5 (56%)</td>
<td>(21%, 86%)</td>
<td>(5.8+, 22.1+)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (83%)</td>
<td>(36%, 100%)</td>
<td>(2.6+, 9.2+)</td>
</tr>
<tr>
<td>Small intestinal cancer</td>
<td>8</td>
<td>3 (38%)</td>
<td>(9%, 76%)</td>
<td>(1.9+, 9.1+)</td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Source: USPI
<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>N</th>
<th>n (%)</th>
<th>95% CI</th>
<th>DOR range (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CRC (continued)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>PR, PR</td>
<td>(7.6, 15.9)</td>
<td>9.8+</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>PR, SD</td>
<td>(18.2+)</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophageal cancer</td>
<td>1</td>
<td>PR</td>
<td>(18.2+)</td>
<td></td>
</tr>
<tr>
<td>Sarcoma</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid cancer</td>
<td>1</td>
<td>NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retroperitoneal adenocarcinoma</td>
<td>1</td>
<td>PR</td>
<td>(7.5+)</td>
<td></td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>1</td>
<td>CR</td>
<td>(8.9+)</td>
<td></td>
</tr>
<tr>
<td>Renal cell cancer</td>
<td>1</td>
<td>PD</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable.

Source: USPI
Pooled DOR Results for Patients with MSI-H/dMMR Cancer

Confirmed responses are durable

Median DOR (mos): Not reached (1.6+ - 22.7+)
Number (KM %) responders ≥6 mos: 46 (78%)
Pembrolizumab MSI-H/dMMR Efficacy Conclusions

- MSI-H phenotype represents a unique immunobiology that implicates the roles of high mutational load and responsiveness to immune checkpoint blockade regardless of cancer histology
- MSI-H cancer patients treated with chemotherapy in the second-line and later settings - associated with poor clinical outcomes, including low ORRs, brief DORs (< 6 m) and significant toxicity
- Durable clinical responses were demonstrated in 5 pembrolizumab studies in 149 subjects with 15 different types of MSI-H cancer
  - Pooled ORR across all trials: ORR 39.6% (95% CI: 31.7, 47.9); 7.4% of subjects achieved a CR
  - DOR range (range 1.6+ - 22.7+ months)
- In second-line and later settings, pembrolizumab provides meaningful clinical benefit to patients with MSI-H cancer
Increasing Complexity of Companion/Complementary Diagnostics in Immuno-Oncology
Multiple FDA-Approved PD-L1 IHC Assays and Cutoffs: 22-C3, 28-8, SP-263, and SP-142 Assays

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pembrolizumab</th>
<th>Nivolumab</th>
<th>Durvalumab</th>
<th>Atezolizumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic Platform</td>
<td>Dako</td>
<td></td>
<td>Ventana</td>
<td></td>
</tr>
<tr>
<td>Antibody</td>
<td>22-C3</td>
<td>28-8</td>
<td>SP-263</td>
<td>SP-142</td>
</tr>
<tr>
<td>Cut-off(s) being tested</td>
<td>TC$^1$ 1%, 50%</td>
<td>TC 1%, 5% or 10%</td>
<td>TC$^1$ 25%</td>
<td>TC$^1$ or IC$^2$ 1%, 5%, 10%</td>
</tr>
</tbody>
</table>

1) TC = tumor cell staining.  
2) IC = infiltrating immune cell staining  
3) Combined positive score (tumor and immune cell staining)

AACR-sponsored “Blueprint” project designed to compare the 4 assays
### Multiple Assays under Development for Evaluation of Tumor Mutational Burden (TMB)

<table>
<thead>
<tr>
<th>Company</th>
<th>Panel Name</th>
<th>Regulatory Status</th>
<th>Panel Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foundation Medicine</td>
<td>FoundationOne (F1) CDx</td>
<td>IVD</td>
<td>324 genes</td>
</tr>
<tr>
<td>Foundation Medicine</td>
<td>Blood TMB assay</td>
<td>LDT</td>
<td>394 genes</td>
</tr>
<tr>
<td>Caris Life Sciences</td>
<td>Molecular Intelligence Profile</td>
<td>LDT</td>
<td>592 genes</td>
</tr>
<tr>
<td>NeoGenomics</td>
<td>NeoTYPE Discovery Profile</td>
<td>LDT</td>
<td>Various, Unspecified</td>
</tr>
<tr>
<td></td>
<td>NeoTYPE Solid Tumor Profiles</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NeoTYPE Solid Tumor Profiles Standalone</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quest Diagnostics</td>
<td>Watson Genomics</td>
<td>LDT</td>
<td>50 genes</td>
</tr>
<tr>
<td>Memorial Sloan Kettering</td>
<td>MSK-IMPACT</td>
<td>510(k)</td>
<td>468 genes</td>
</tr>
<tr>
<td>Illumina</td>
<td>TruSight Tumor 170</td>
<td>RUO</td>
<td>170 genes</td>
</tr>
<tr>
<td>ThermoFisher</td>
<td>Oncomine Tumor Mutation Load</td>
<td>RUO</td>
<td>1.7 Mb</td>
</tr>
</tbody>
</table>

- Various studies evaluating TMB as a predictive marker for IO treatments have used different scoring approaches and cutoffs, making direct comparisons of the assays difficult.
- Ongoing effort led by the Friends of Cancer Research, with inclusion of FDA, and several Pharma and Diagnostics companies, to create a set of standards for the calculation and reporting of TMB.
The Ultimate in Precision Oncology - Personalized Cancer Vaccines?

A personalized cancer vaccine

mRNA encoding 20 neoantigens

Tissue Samples
Tumor (biopsy) and normal (blood)

Next Generation Sequencing (NGS)
What are the mutations?

Vaccine Design
Which mutations are predicted to be the most immunogenic?
What is the best design for a drug to present these mutations to the immune system?

Manufacturing
One manufacturing batch per patient rather than one batch for many patients

Administration
By health care professionals

Slide courtesy of Tal Zaks
Modernova’s mRNA Vaccines Designed to Direct T Cells towards Cancer Killing

**What is mRNA-4157?**

- Up to 20 different neoantigens for each patient in a single mRNA construct based on mutations identified by NGS sequencing of tumor
- Encapsulated in formulated lipid nanoparticles
- Designed to express neoantigens that will instruct the immune system to recognize cancerous tissue as foreign

Moderna-Merck Phase I study ongoing – Keynote 603
Summary

- Multiple biomarkers have potential to help identify patients most likely to benefit from immuno-oncology treatments.
- PD-L1 IHC is most advanced (approved as companion/complementary diagnostics) and widely available.
- MSI-H/dMMR assays provided a basis for the first tissue/site agnostic indication approved by FDA.
- Multiple additional potential predictive biomarkers, including TMB, are under investigation.
- Personalized cancer vaccines are under investigation and represent an exemplar of precision immuno-oncology approaches.