KEYTRUDA (pembrolizumab) Case Study
PD-1 Targeted Immunotherapy for MSI-H Cancer

FDA-ASCO-Friends Tissue-Agnostic Indications Workshop
• Small, repetitive sequences, principally of polyadenine tracts\textsuperscript{1}

• Abundant throughout the genome; polymorphic between individuals, but unique and uniform in length in each person\textsuperscript{1}

• Microsatellites are prone to mutations when there are deficiencies in DNA mismatch repair (dMMR)\textsuperscript{2}

During replication, incorrect DNA alignment and polymerase errors can lead to insertions/deletions\(^1\). Mismatch repair proteins \textit{MLH1, MSH2, MSH6, PMS2} correct these errors\(^2\). MMR deficiency due to loss of repair protein expression or function causes MSI phenotype\(^1\). DNA mutations cause protein neo-antigens, detected as ‘foreign’ & destroyed by T- cells\(^5\).

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
MSI-H Cancer: Disease Background and Testing Guidelines
Cancers that are more likely to be MSI-H (i.e., prevalence ~5% or higher) include those of the gastrointestinal and gynecological organ systems.

Le, 2017
NCCN Guidelines version 1.2016 for Colorectal Cancer: Lynch Syndrome, Stage II disease, and all patients with metastatic disease

- IHC for dMMR and PCR for MSI are different assays measuring the same biologic effect
- IHC/MMR & PCR/MSI tests are widely used, and readily available in the US (EU)
- NGS platforms available more recently for Colorectal Cancer and Lynch Syndrome testing
- Class II assays cleared for IHC and NGS
- These testing guidelines informed the testing approach used in Merck MSI-H cancer trials:

<table>
<thead>
<tr>
<th>Test</th>
<th>Reagents to targets</th>
<th>Result Indicative of MSI-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>IHC</td>
<td>Antibodies to: MLH1/MSH2/MSH6/PMS2</td>
<td>Any 1 (or more) of 4 proteins absent</td>
</tr>
<tr>
<td>PCR</td>
<td>PCR probes to: BAT25, BAT26, NR21, NR24, Mono27 OR BAT25, BAT26, Di 5S346, Di 2S123, Di 17S250</td>
<td>≥ 2 of 5 loci differ in size from corresponding normal loci</td>
</tr>
</tbody>
</table>
dMMR when at least one of four MMR proteins are absent

- MLH1
- PMS2
- MSH2
- MSH6
PCR-Based MSI Assay

MSI-H if $\geq 2$ of 5 loci differ in size from corresponding normal loci

![Diagram of the PCR-Based MSI Assay process]

**Normal**
- NR-21
- BAT-25
- Mono-27

**Tumor**
- BAT-26
- NR-24
- Penta C, D

Courtesy: James Eshleman
sBLA Submission, Approval, and Post-marketing Commitments
• May 2015, FDA meeting for KEYNOTE-164
  – To discuss design of KEYNOTE-164 with FDA:
  – FDA encouraged Merck to enroll patients with MSI-H small intestinal and other gastrointestinal malignancies in a dedicated protocol, in order to expedite development in this population

• July 2015, FDA meeting for KEYNOTE-158 (Basket Trial)
  – To discuss design of KEYNOTE-158 with FDA
  – Included cohort of MSI-H solid tumors (except colorectal cancer)

• On May 23, 2017, the U.S. FDA granted accelerated approval to pembrolizumab for adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or with MSI-H or dMMR colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan
Development Timeline of KEYTRUDA in MSI-H Cancer

2013
- Type B Meeting KN164 MSI-H CRC May 2015
- KN016 IND#118566 submitted to IND June 2013
- First patient enrolled in KN016 Sept 2013

2015
- Type B Meeting KN158 MSI-H Non CRC July 2015
- KN016 NEJM pub May 2015
- First patient enrolled in KN164 Aug 2015

2016
- BTD Granted MSI-H CRC Oct 2015
- Type B: Pre-sBLA July 2016
- First patient enrolled in KN158 Dec 2015
- sBLA submitted Sept 2016
- BTD Granted MSI-H Non-CRC Aug 2016

2017
- FDA Meeting Feb 2017
- Application Orientation Meeting Oct 2016
- sBLA Approval 23 May 2017

PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

## 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
### Objective response rate and DOR range

<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><strong>Non-CRC (continued)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>PR, PR</td>
<td></td>
<td>(7.6, 15.9)</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>PR, SD</td>
<td></td>
<td>9.8+</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></td>
<td>18.2+</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></td>
<td>7.5+</td>
</tr>
<tr>
<td>Small cell lung cancer</td>
<td>1</td>
<td>CR</td>
<td></td>
<td>8.9+</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
Pediatric Strategy, PMRs, and PMC
• Expectation that disease biology of MSI-H cancer in adults will be similar to disease biology in children (e.g., children with congenital dMMR syndromes) → extrapolation of pembrolizumab efficacy to the pediatric population

• Accepted pediatric dose

• A ongoing study which is enrolling pediatric patients is being conducted to satisfy a requirement for accelerated approval
• Longer follow-up with pembrolizumab in MSI-H cancer patients

• Greater number and variety of tumor types, including at least 124 patients with CRC and 300 patients with non-CRC, including a sufficient number of patients with prostate cancer, thyroid cancer, small cell lung cancer; and ovarian cancer; and 25 children

• To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response
• Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of an immunohistochemistry based *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are mismatch repair deficient.

• Commitment to support the availability through an appropriate analytical and clinical validation study using clinical trial data that will support labeling of a nucleic acid-based *in vitro* diagnostic device that is essential to the safe and effective use of pembrolizumab for patients with tumors that are microsatellite instability high.
CDx development after drug approval: Rationale, challenges

• Lemery, et al., 2017 [link]

• CDx test(s) were not co-developed.
  – MSI-H / dMMR as a prognostic determinant for colorectal cancer recurrence was available for decades in medical practice
  – FDA approved this indication without approved CDx tests….because of the high unmet medical need…the high response rate, and the known safety profile

• 2 CDx assays to be developed as part of PMCs
  – Tests are clinically, biologically synonymous, but measure different substrates
    • IHC, to support dMMR
    • nucleic acid-based, to support MSI-H

• Post-trial development of a CDx is challenging
  – sample availability is a major hurdle as limited tumor tissue was collected from trials, limited number of tumor blocks for IHC
Harmonization with other National Health Authorities
MSI-H Pan Tumor Approval in Japan

- Approved on December 21, 2018 by PMDA
- Approved under Conditional Early Approval System (CEAS)
# MSI-H Pan Tumor Worldwide Registration Status

(22 approvals)

<table>
<thead>
<tr>
<th>Country</th>
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<tr>
<td>United States</td>
<td>5/23/2017</td>
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</table>
Clear interest in scientific concept
The concept of histology-independent indications

- Requires in-depth knowledge about the mechanism of and at least strong plausibility across subgroups
- Need to explore heterogeneity of effects (interactions, resistance mechanisms)
- Multiple therapeutic contexts, evidence of positive benefit-risk balance
- Easier when high unmet need across subgroups
- Challenging when competing against available options with established clinical utility (e.g. survival) in some subgroups; indirect comparisons (rare diseases, lack of historical data); extrapolation

Challenges to translate scientific concept into current regulatory framework
Thank You