Approval of pembrolizumab for the treatment of MSI-H/dMMR cancers, agnostic of cancer type

FDA approval on May 23, 2017
Traditional paradigm for approvals for in oncology

• Based on tumor type, e.g.,
  – Previously untreated pancreatic cancer
  – HCC after previous sorafenib treatment

• Based on a biomarker within a tumor type, e.g.,
  – HER-2 positive breast or gastric cancer
  – RAS wild-type colorectal cancer
MSI-H/dMMR, not the organ, defines the indication.
What is MSI-H/dMMR?

• MSI-H = microsatellite instability
• dMMR = deficient mismatch repair
• Causes of dMMR/MSI-H:
  – Mutation in DNA repair proteins
    • Can occur in Lynch syndrome
  – Inactivation of DNA repair proteins
Why does this matter?

• Impairment in mismatch repair causes
  – Greatly increased number of mutations in tumors
  – Some mutations (neo-antigens) may be targeted by immune system

• Pembrolizumab can facilitate immune system attack in some MSI-H/dMMR cancers
Mechanism of Action

A. Signaling Mechanism of PD-1 and PD-L1

- Tumor cell
- MHCI
- Cancer neoantigen
- T-cell receptor
- PD-L1
- Inhibitory signaling
- PD-1

B. Inhibition of PD-1 Signaling in Microsatellite-Instability–High Cancers

- Pembrolizumab inhibits PD-1 signaling
- Mutant peptide

As compared with microsatellite-stable tumors, tumors with high mutation burden due to deficient mismatch repair have increased probability that neoantigens susceptible to recognition by high-avidity T cells will be present.

Tumors are more susceptible to immunotherapy

Increased proliferation and activation of T cells

Lemery et al., NEJM, 2017
MSI-H in different tumor types

Bonneville et al., JCO Precision Oncology, 2017
## Data supporting pembrolizumab approval

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No. of Tumors</th>
<th>Patients with a Response</th>
<th>Range of Response Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no. (%)</td>
<td>mo</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>90</td>
<td>32 (36)</td>
<td>1.6+ to 22.7+</td>
</tr>
<tr>
<td>Endometrial cancer</td>
<td>14</td>
<td>5 (36)</td>
<td>4.2+ to 17.3+</td>
</tr>
<tr>
<td>Biliary cancer</td>
<td>11</td>
<td>3 (27)</td>
<td>11.6+ to 19.6+</td>
</tr>
<tr>
<td>Gastric or gastroesophageal junction</td>
<td>9</td>
<td>5 (56)</td>
<td>5.8+ to 22.1+</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>6</td>
<td>5 (83)</td>
<td>2.6+ to 9.2+</td>
</tr>
<tr>
<td>Small-intestine cancer</td>
<td>8</td>
<td>3 (38)</td>
<td>1.9+ to 9.1+</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2</td>
<td>2 (100)</td>
<td>7.6 to 15.9</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>2</td>
<td>1 (50)</td>
<td>9.8+</td>
</tr>
<tr>
<td>Other cancers</td>
<td>7</td>
<td>3 (43)</td>
<td>7.5+ to 18.2+</td>
</tr>
</tbody>
</table>

*Response was as defined by RECIST. “Other cancers” includes one patient each with the following tumor types: bladder, esophageal, sarcoma, thyroid, retroperitoneal, small-cell lung cancer, and renal cell cancer (includes two patients who could not be evaluated and were considered not to have had a response). A + sign indicates that the response was ongoing at the time of data cutoff.*

Lemery, NEJM, 2017
Pembrolizumab MSI-H approval considerations

• Strong scientific/biological rationale
• Compelling clinical data
• Extensive history of clinical use / safety profile
• Favorable risk/benefit profile with similar ORR in other indications
• Approved for patients without available therapies
Post-approval

• Accelerated approval requirement
  – Assess clinical effects in larger number of patients and longer duration
    • Including children

• Approval commitments
  – Develop tests to identify MSI-H and dMMR in tumor samples
Ongoing questions / issues

• What is the best test?
  – IHC, PCR, NGS (or combination)

• Identification of more people with Lynch syndrome

• Will benefit continue to endure after stopping pembrolizumab?

• Adjuvant use?

• GBM?