Immunotherapy and PD-1 Inhibitors in the Treatment of Cancer
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Disclosures
• I have no conflicts of interest to disclose

Learning Objectives
• Define the role of immunotherapy in the treatment of cancer with PD1 inhibitors being the main focus
• Recall the mechanism of action for PD1 inhibitors and list the most common side effects

Immunotherapy
• Immune system plays important role in recognizing and destroying damaged cells
• T cells are primary effector cells for this process
• Tumor cells often evade immune response

2. La-Beck NM et al. Pharmacotherapy. 2015.

Immunotherapy
• Immunotherapy
  “A type of cancer treatment designed to boost the body’s natural defenses to fight the cancer”
• American Society of Clinical Oncology (ASCO) definition
Immunotherapy in Cancer Treatment

• Immune system is slow to respond
  ▫ Needs to “ramp up”
• May see initial worsening of disease
  ▫ “tumor flare”
• Longer time to response than traditional chemotherapy
  ▫ Caution against stopping treatment early
• May not have decrease in tumor size
  ▫ Prolonged stabilization of disease

Research

• Activating immune response to fight cancer cells
  ▫ Cytokines
  ▫ T cells
    ▪ Checkpoint inhibitors
    ▫ Costimulatory receptors
    ▫ Oncolytic viruses
    ▫ Vaccines

Programmed Cell Death 1 (PD-1) Inhibitors

• Nivolumab (Opdivo*)
  ▫ Unresectable or metastatic melanoma
    ▪ Single agent
    ▪ In combination with ipilimumab (Yervoy*)
  ▫ Metastatic non-small cell lung cancer (NSCLC)
    ▪ Single agent
• Pembrolizumab (Keytruda*)
  ▫ Unresectable or metastatic melanoma
  ▫ Metastatic NSCLC
    ▪ With PD-L1 expression based on FDA approved test

Normal Immune Response

Mechanism of Action

Tumor Immune Evasion

Mechanism of Action
**Mechanism of Action**

- **Programmed Cell Death 1 (PD-1) receptors**
  - Found on T cells
  - Programmed Cell Death Ligand 1 and 2 (PD-L1 and PD-L2)
  - Overexpressed by tumor cells
  - Binding of PD-L1 or PD-L2 to PD-1 results in:
    - T cell apoptosis
    - Downregulation of cytokine production
    - Suppression of anti-tumor response

**PD-1 Inhibitors – Restoration of Immune Response**

*Early studies showed increased tumor growth through PD-1 immune checkpoint inhibition. While having an effect on the tumor, this could affect normal cells.*

- **Opdivo**
  - Website. 2015.
- **Keytruda**
  - Prescribing information. 2015.
- **La-Beck NM et al. Pharmacotherapy.** 2015.

**PD-1 Inhibitors**

- **Bind to PD-1 receptor on T cells**
  - Block interaction of PD-1 receptor with PD-L1 and PD-L2
  - Releases the inhibition of the anti-tumor immune response
  - Results in decreased tumor growth

**Mechanism of Action**

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  - Bind to PD-1 receptor on T cells
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**Mechanism of Action**

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  - Bind to PD-1 receptor on T cells
    - Block interaction of PD-1 receptor with PD-L1 and PD-L2
  - Releases the inhibition of the anti-tumor immune response
    - Results in decreased tumor growth

**Dosing and Administration**

- **Single agent**
  - 3 mg/kg every 2 weeks
    - Unresectable or metastatic melanoma
    - NSCLC
  - In combination with ipilimumab
    - 1 mg/kg every 3 weeks for 4 doses → 3 mg/kg every 2 weeks
      - Unresectable or metastatic melanoma
  - 60 minute infusion

**Pharmacokinetics**

- **Half life** – 26.7 days
- **Time to steady state** – 12 weeks
- **Renal impairment** –
  - Mild to severe – no dosage adjustment necessary
  - Hepatic impairment
    - Mild – no dosage adjustment needed
    - Moderate to severe – not evaluated
Warnings and Precautions

- Immune-mediated reactions
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Endocrinopathies
  - Nephritis and renal dysfunction
  - Rash
  - Encephalitis
- Embryofetal Toxicity

Adverse Reactions

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Melanoma Rate (%)</th>
<th>NSCLC Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>24</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>Nausea</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Pruritus</td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

Clinical Trials

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Melanoma</th>
<th>NSCLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial Design</td>
<td>Single Agent</td>
<td>In Combination</td>
</tr>
<tr>
<td>Treatment</td>
<td>Nivolumab</td>
<td>Nivolumab + ipilimumab</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Treatment naive</td>
<td>Recurrence after one prior platinum-containing regimen</td>
</tr>
</tbody>
</table>

CheckMate 037

<table>
<thead>
<tr>
<th>Result</th>
<th>Nivolumab n=120</th>
<th>ICC n=47</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response n (%, 95% CI)</td>
<td>38 (31.7, 23.5–40.8)</td>
<td>5 (10.6%, 3.5–23.1)</td>
</tr>
<tr>
<td>BRAF wild-type (n=94, 36) n (%)</td>
<td>6 (23.1)</td>
<td>4 (11.1)</td>
</tr>
<tr>
<td>BRAF mutated (n=26, 11) n (%)</td>
<td>32 (34.0)</td>
<td>1 (9.1)</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Result</th>
<th>Nivolumab + ipilimumab</th>
<th>ipilimumab n=27</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response n (%, 95% CI)</td>
<td>44 (61, 49-72)</td>
<td>4 (11, 3-25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete Response n (%)</td>
<td>16 (22)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>BRAF wild-type n=23</td>
<td>Objective Response n (95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete Response n (%)</td>
<td>12 (52, 31-73)</td>
<td>1 (10, 0-45)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete Response n (%)</td>
<td>5 (22)</td>
<td>0 (0)</td>
<td></td>
</tr>
</tbody>
</table>
### CheckMate 017

<table>
<thead>
<tr>
<th>Result</th>
<th>Nivolumab n=131</th>
<th>Docetaxel n=129</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective Response n (%, 95% CI)</td>
<td>27 (20, 14-28)</td>
<td>12 (9, 5-15)</td>
<td>0.008</td>
</tr>
<tr>
<td>Median Time to Response n (range)</td>
<td>2.2 (1.6–11.8)</td>
<td>2.1 (1.8–9.5)</td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response n (range)</td>
<td>Not yet reached</td>
<td>8.4 months (1.4–15.2+)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median Progression Free Survival n (95% CI)</td>
<td>3.5 months (2.1–4.9)</td>
<td>2.8 months (2.1–3.5)</td>
<td></td>
</tr>
</tbody>
</table>

### Pembrolizumab (Keytruda®)

- **Dosing and Administration**
  - Single agent
    - 2 mg/kg every 3 weeks
  - 30 minute infusion

- **Pharmacokinetics**
  - Half life – 28 days
  - Time to steady state – 18 weeks
  - Renal impairment –
    - Mild to severe – no dosage adjustment necessary
  - Hepatic impairment
    - Mild – no dosage adjustment needed
    - Moderate to severe – not evaluated
Warnings and Precautions

- Immune-mediated Reactions
  - Pneumonitis
  - Colitis
  - Hepatitis
  - Endocrinopathies
  - Nephritis
- Infusion-related reactions
- Embryofetal Toxicity

Adverse Reactions

### Melanoma

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<tr>
<th>Reaction</th>
<th>Rate (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>17.9</td>
<td>2. Keytruda [prescribing information]. 2015.</td>
</tr>
</tbody>
</table>

### NSCLC

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Rate (%)</th>
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Clinical Trials

**Melanoma**

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Prescribing Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Randomised, multicenter, international study; Dose expansion of KEYNOTE-001; Cohort of KEYNOTE-001</td>
</tr>
<tr>
<td>Arms</td>
<td>Pembrolizumab 2 mg/kg; Pembrolizumab 10 mg/kg; Pembrolizumab 2 mg/kg; Pembrolizumab 10 mg/kg</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>Progressive, measurable, unresectable melanoma; Previously treated with at least two doses of ipilimumab; If BRAF mutation positive; Progression after anti-BRAF therapy</td>
</tr>
</tbody>
</table>

**NSCLC**

<table>
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<tr>
<th>Clinical Trial</th>
<th>Prescribing Information</th>
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<tbody>
<tr>
<td>Design</td>
<td>Multicenter, open-label multi-cohort, activity-estimating study</td>
</tr>
<tr>
<td>Arms</td>
<td>Pembrolizumab 2 mg/kg; Pembrolizumab 10 mg/kg</td>
</tr>
<tr>
<td>Inclusion Criteria</td>
<td>NSCLC with progression after platinum-based therapy; Evidence of PD-L1 expression</td>
</tr>
</tbody>
</table>

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**Melanoma**

<table>
<thead>
<tr>
<th>Result</th>
<th>Pembrolizumab 2 mg/kg</th>
<th>Pembrolizumab 10 mg/kg</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate (n=81, 76)</td>
<td>21 (26, 17-37)</td>
<td>20 (26, 17-38)</td>
<td>0.96</td>
</tr>
<tr>
<td>Median Time to Response (range)</td>
<td>12 weeks (11-16)</td>
<td>12 weeks (7-17)</td>
<td></td>
</tr>
<tr>
<td>Median Duration of Response (range)</td>
<td>Not yet reached</td>
<td>Not yet reached</td>
<td></td>
</tr>
<tr>
<td>Median Progression Free Survival (n=89, 84) (95% CI)</td>
<td>22 weeks (12-36)</td>
<td>14 weeks (12-24)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
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**NSCLC**

<table>
<thead>
<tr>
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<th>Pembrolizumab</th>
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</thead>
<tbody>
<tr>
<td>Overall response rate n (95% CI)</td>
<td>25 (41, 29-54)</td>
</tr>
<tr>
<td>Ongoing response at final analysis n (9%)</td>
<td>21 (84)</td>
</tr>
<tr>
<td>Ongoing response ≥ 6 months n (9%)</td>
<td>11 (44)</td>
</tr>
</tbody>
</table>

**Note:** The tables and figures are based on the provided data and references. The values and references may need to be updated for the most current information.
Immunotherapy

- Activates patients immune system
- May see tumor burden worsen before seeing benefit
- Even if no objective response, may see prolonged stabilization of disease

PD-1 Inhibitors

- FDA approved for use in Melanoma and NSCLC
- Immune Mediated Reactions

References


Summary

- Immunotherapy
  - Activates patients immune system
  - May see tumor burden worsen before seeing benefit
  - Even if no objective response, may see prolonged stabilization of disease

- PD-1 Inhibitors
  - FDA approved for use in Melanoma and NSCLC
  - Immune Mediated Reactions

Questions??