New Era of Cancer Therapy
Immuno-Oncology: PD1/PD-L1 inhibitors

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Kaiser Permanente

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Kaiser Permanente
Disclosure

Farah Brasfield and Jennifer Chang report having no financial relationships with any commercial interests during the past 12 months.
Arming the Immune System Against Cancer

How the Promise of Immunotherapy Is Transforming Oncology
Learning Objectives

1. Describe the significant development of cancer immunotherapy.

2. Explain the mechanism of action of immune checkpoint inhibitors, e.g., PD-1/PD-L1 inhibitors.


4. Identify the impact of PD-1/PD-L1 inhibitors for treatment of melanoma and NSCLC.

5. Summarize the clinical implications of PD1/PDL-1 inhibitors for practicing pharmacists.
What is Cancer Immunotherapy?

- Stimulates body’s immune system by utilizing T-cells to attack and eliminate cancer cells
- Restores patient’s own antitumor immune response
- Improves antitumor function of the immune system
- Attenuates immunosuppressive microenvironment of the tumor

FDA-Approved Cancer Immunotherapy

- BCG vaccine
- Cytokine IFN-α
- Cytokine Aldesleukin (IL-2)
- Cancer Vaccine Sipuleucel-T (Provenge)
- CTLA-4 inhibitor Ipilimumab (Yervoy)
- PD-1 inhibitor pembrolizumab nivolumab
- PD-L1 inhibitor atezolizumab


KEY: IFN-α = interferon alpha; CTLA-4 = cytotoxic T lymphocyte antigen-4; PD-1 = programmed death-1; PD-L1 = programmed death ligand 1

Oncolytic virus therapy
Talimogene laherparepvec (Imlygic)
Cytotoxic T Lymphocyte Antigen 4 Checkpoint

Key: CTLA-4= cytotoxic T lymphocyte-associated antigen 4

Programmed Death-1 (PD-1) Checkpoint
## FDA-Approved PD-1 Inhibitor

<table>
<thead>
<tr>
<th>Pembrolizumab (Keytruda)</th>
<th>Nivolumab (Opdivo)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Indications</strong></td>
<td></td>
</tr>
<tr>
<td>- Unresectable or metastatic melanoma</td>
<td>- BRAF V600 wild-type or mutation-positive unresectable or metastatic melanoma, as a single agent</td>
</tr>
<tr>
<td>- Metastatic NSCLC with disease progression on or after platinum-containing chemotherapy and TKI if EGFR/ALK mutation positive in patients whose tumors express PD-L1 as determined by and FDA-approved test</td>
<td>- Unresectable or metastatic melanoma, in combination with ipilimumab</td>
</tr>
<tr>
<td>- Recurrent or metastatic HNSCC with disease progression on or after platinum-containing chemotherapy</td>
<td>- Metastatic non-small cell lung cancer and progression on or after platinum-based chemotherapy and TKI if EGFR/ALK mutation positive</td>
</tr>
<tr>
<td></td>
<td>- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy</td>
</tr>
<tr>
<td></td>
<td>- Classical Hodgkin lymphoma that has relapsed or progressed after autologous HSCT</td>
</tr>
</tbody>
</table>

**KEY:**
- HNSCC = head and neck squamous cell carcinoma
- HSCT = hematopoietic stem cell transplantation
- NSCLC = non-small cell lung cancer
- TKI = tyrosine kinase inhibitor

Atezolizumab (Tecentriq)

- Approved on May 18, 2016
- First Programmed Death Ligand 1 (PD-L1) inhibitor
- FDA Indication: Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy; have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Lung cancer indication (approved on 10/18/2016): Metastatic non-small cell lung cancer who have disease progression during or following chemotherapy


KEY: PDUFA= prescription drug user fee action
# Lung Cancer: New Cases and Deaths

## Figure 3. Leading Sites of New Cancer Cases and Deaths – 2016 Estimates

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated New Cases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>180,890 (21%)</td>
<td>160,680 (21%)</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>117,920 (14%)</td>
<td>106,470 (13%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>70,820 (8%)</td>
<td>63,670 (8%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>58,950 (7%)</td>
<td>60,050 (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>46,870 (6%)</td>
<td>49,350 (6%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>40,170 (5%)</td>
<td>32,410 (4%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>39,650 (5%)</td>
<td>29,510 (3%)</td>
</tr>
<tr>
<td>Oral cavity &amp; pharynx</td>
<td>34,780 (4%)</td>
<td>26,050 (3%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>34,090 (4%)</td>
<td>25,400 (3%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>28,410 (3%)</td>
<td>23,050 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>841,390 (100%)</td>
<td>843,820 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated Deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>85,920 (27%)</td>
<td>72,160 (26%)</td>
</tr>
<tr>
<td>Prostate</td>
<td>26,120 (8%)</td>
<td>23,170 (8%)</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>26,020 (8%)</td>
<td>21,450 (7%)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>21,450 (7%)</td>
<td>20,330 (7%)</td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>18,280 (6%)</td>
<td>14,240 (5%)</td>
</tr>
<tr>
<td>Leukemia</td>
<td>14,130 (4%)</td>
<td>10,470 (4%)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>12,720 (4%)</td>
<td>10,270 (4%)</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>11,820 (4%)</td>
<td>8,890 (3%)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>11,520 (4%)</td>
<td>8,630 (3%)</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>9,440 (3%)</td>
<td>9,120 (3%)</td>
</tr>
<tr>
<td>All sites</td>
<td>314,290 (100%)</td>
<td>281,400 (100%)</td>
</tr>
</tbody>
</table>

Estimates are rounded to the nearest 10, and cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

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Non-Small Cell Lung Cancer: Rates of 5-Year Survival by Stage

Figure. Rates of 5-Year Survival in NSCLC by Stage

NSCLC indicates non-small cell lung cancer.
Nivolumab in Non-Small Cell Lung Cancer

**CheckMate 057 Study**  
*Borghaei et al.*  
Phase 3, randomized, OL, International  
**Nonsquamous** NSCLC  
All had prior platinum-based therapy  
Median age: 62 years  
Most had ECOG PS of 1; stage IV cancer and were current or former smokers

**CheckMate 017 Study**  
*Brahmer et al.*  
Phase 3, randomized, OL, International  
**Squamous** NSCLC  
All had prior platinum-based therapy  
Median age: 63 years  
Most had ECOG PS of 1; stage IV cancer and were current or former smokers

- **Nivolumab 3 mg/kg every 2 weeks**
- **Docetaxel 75 mg/m² every 3 weeks**

**Primary endpoint:** Overall survival

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KEY: NSCLC = non-small cell lung cancer; ECOG = Eastern Cooperative Oncology Group; OL = open-label; PS = performance status
Nivolumab in Non-Small Cell Lung Cancer

Advanced NSCLC - After Progression of 1st line Chemotherapy


Nivolumab in Non-Small Cell Lung Cancer

**Borghaei et al.: Nonsquamous NSCLC**
Nivolumab vs. Docetaxel
Median time to response: 2.1 months vs. 2.6 months
Median duration of response: 17.2 months (1.8 to 22.6+) vs. 5.6 months (1.2+ to 15.2+)

**Brahmer et al.: Squamous NSCLC**
Nivolumab s. Docetaxel
Median time to response: 2.2 months vs. 2.1 months
Median duration of response: not reached (2.9 to 20.5+) vs. 8.4 months (1.4+ to 15.2+)

Nivolumab in Non-Small Cell Lung Cancer

CheckMate-026 Study: First-line monotherapy

- Phase 3, open-label, randomized study
- Nivolumab monotherapy vs investigator's-choice chemotherapy in 541 patients with untreated, advanced, squamous/non-squamous NSCLC; biomarker PD-L1 at 5% or greater
- Until disease progression, unacceptable toxicity, or completion of 6 cycles
- Nivolumab failed to achieve primary outcome of improvement of progression free survival compared to chemotherapy
- Phase 3 CheckMate-227 study: Combination of nivolumab plus ipilimumab for PD-L1 positive patients, and nivolumab plus ipilimumab, or nivolumab plus chemotherapy in PD-L1 negative patients

Nivolumab in Non-Small Cell Lung Cancer: Place in Therapy

• As **single therapy** in the **second-line** treatment of advanced stage Non-Small Cell Lung Cancer (NSCLC)

• Upon disease progression on or after platinum-based chemotherapy

• Upon disease progression on FDA-approved EGFR inhibitors (e.g., erlotinib, gefitinib) or ALK inhibitors (e.g. crizotinib), in patients with EGFR or ALK mutations

**KEY:** ALK=anaplastic lymphoma kinase; EGFR= epidermal growth factor receptor
Pembrolizumab in Non-Small Cell Lung Cancer

**KEYNOTE-001 Study**
Phase 1, OL, biomarker assessment trial

495 patients with locally advanced or metastatic NSCLC
80% had nonsquamous histology and had more than 2 prior lines of chemotherapy

**RESULTS**

- **ORR:** 19.4%
  - Previously treated ORR: 18%
  - Previously untreated: 24.8%
- Median duration of response: 12.5 months
  - Previously treated: 10.4 months
  - Previously untreated: 23.3 months

**CONCLUSION**
Prevalence of PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy

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KEY: OL= open label; ORR= overall response rate
Pembrolizumab in Non-Small Cell Lung Cancer

**KEYNOTE-010 Study**

- Phase 2/3, randomized, OL, 24 countries
- 1043 patients with previously treated advanced NSCLC (70% nonsquamous; 20% squamous) with PD-L1 expression on at least 1% of tumor cells
- 28% with PD-L1 expression on at least 50% of tumor cells

**Pembrolizumab 2 mg/kg every 3 weeks**
- Median OS: 10.4 months (vs. docetaxel, HR 0.71, 95% CI 0.85-0.88; p=0.0008)

**Pembrolizumab 10 mg/kg every 3 weeks**
- Median OS: 12.7 months (vs. docetaxel, HR 0.61, 95% CI 0.49-0.75; p<0.0001)

**Docetaxel 75 mg/m² every 3 weeks**
- Median OS: 8.5 months


KEY: CI= confidence interval; HR= hazard ratio; OS= overall survival
Pembrolizumb in Non-Small Cell Lung Cancer

KEYNOTE-024 Study: 1st line Treatment

- Randomized, pivotal, Phase 3
- Advanced non-small cell lung cancer (NSCLC) whose tumors expressed high levels of PD-L1 (tumor proportion score of 50 percent or more)
- Pembrolizumab 200 mg every three weeks monotherapy compared to standard of care platinum-based chemotherapies. The primary endpoint is PFS; secondary endpoints are OS and overall response rate (ORR).
- 6/16/2016: Patients in the standard chemotherapy arms are now offered pembrolizumab due to it meeting the primary endpoints. Full study results are not published yet.

Available at: http://www.streetinsider.com/Corporate+News/Merck+(MRK)+Announces+Superior+Data+on+KEYTRUDA+vs.+Chemotherapy+in+Untreated+NSCLC/11745836.html
Pembrolizumb in Non-Small Cell Lung Cancer

Place in Therapy

• As **single therapy** in the **second-line** treatment of advanced stage Non-Small Cell Lung Cancer (NSCLC) in patients whose tumors express PD-L1

• Upon disease progression on or after platinum-based chemotherapy

• Upon disease progression on FDA-approved EGFR inhibitors (e.g., erlotinib, gefitinib) or ALK inhibitors (e.g. crizotinib), in patients with EGR or ALK mutations.

• Potential first-line option in advanced stage NSCLC whose tumors expresses high level of PD-L1
Atezolizumab (MPDL3280A) Clinical Trials

• A phase III study of MPDL3280A in combination chemotherapy for patients with chemotherapy-naïve stage IV non-squamous NSCLC (NCT02367781)

• A phase III study of MPDL3280A in combination with chemotherapy and bevacizumab (Avastin) in patients with chemotherapy-naïve stage IV non-squamous NSCLC (NCT02366143)

• A phase III study of MPDL3280A versus chemotherapy for patients with PD-L1-positive chemotherapy-naïve stage IV non-squamous NSCLC (NCT02409342)

• A phase III study of MPDL3208A in combination with chemotherapy in patients with chemotherapy-naïve stage IV squamous NSCLC (NCT02367794)

• A phase III study of MPDL3280A versus chemotherapy in patients with PD-L1-positive chemotherapy-naïve stage IV squamous NSCLC (NCT02409355)

Available at: www.clinicaltrial.gov
Impact of PD-1/PD-L1 Inhibitors in Lung Cancer

• Are we expecting to see PD-1/PD-L1 inhibitors change the landscape of lung cancer treatment?
• What is the role of PD-1/PD-L1 inhibitor as second-line treatment for Non-Small Cell Lung Cancer?
• Are we ready to move PD-1 inhibitors to the front-lines in Non-Small Cell Lung Cancer?
Melanoma- Statistics

• 5th most common cancer among men and 7th most common cancer in women

• Estimated 76,380 adults (46,870 men and 29,510 women) in the United States will be diagnosed with melanoma of the skin

• Estimated 10,130 deaths (6,750 men and 3,380 women) from melanoma


AJCC TNM stages and overall survival of patients with cutaneous melanoma
Melanoma: Nivolumab combination

**CheckMate 067**: Phase 3, RCT, DB

945 patients with previously untreated stage III, IV unresectable or metastatic melanoma

- Nivolumab 1 mg/kg + ipilimumab 3 mg/kg every 3 weeks for 4 doses followed by nivolumab 3 mg/kg every 2 weeks for cycle 3 and beyond
- Nivolumab 3 mg/kg every 2 weeks
- Ipilimumab 3 mg/kg every 3 weeks for 4 doses

Coprimary endpoint: progression-free survival

# Melanoma: Nivolumab combination

**Key Outcome Comparisons in CheckMate 067**

<table>
<thead>
<tr>
<th>KEY ENDPOINTS</th>
<th>Nivolumab+Ipilimumab</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>11.5 months</td>
<td>6.9 months</td>
<td>2.9 months</td>
</tr>
<tr>
<td><strong>HR vs. ipilimumab</strong></td>
<td>0.42</td>
<td>0.57</td>
<td>---</td>
</tr>
<tr>
<td>Median OS</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1 expression ≥ 5% Median PFS</td>
<td>14 months</td>
<td>14 months</td>
<td>3.9 months</td>
</tr>
<tr>
<td><strong>HR vs. ipilimumab</strong></td>
<td>0.4</td>
<td>0.4</td>
<td>--</td>
</tr>
<tr>
<td>PD-L1 expression ≤ 5 % median PFS</td>
<td>11.2 months</td>
<td>5.3 months</td>
<td>2.8 months</td>
</tr>
<tr>
<td><strong>HR vs. ipilimumab</strong></td>
<td>0.42</td>
<td>0.6</td>
<td>--</td>
</tr>
</tbody>
</table>


KEY: HR= hazard ratio; PFS= progression free survival
Nivolumab in Melanoma

**CheckMate 037**
Randomized, controlled, open-label, Phase 3
Unresectable or metastatic melanoma and progressed after ipilimumab or ipilimumab and a BRAF inhibitor if they are BRAF V600 mutation positive

Primary Endpoints: objective response and overall survival

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Nivolumab 3 mg/kg every 2 weeks

Objective Response Rate: 31.7%
Overall Survival: Not available
Progression Free Survival: Data not yet mature

Dacarbazine 1000 mg/m² every 3 weeks or paclitaxel 175 mg/m² combined with carboplatin AUC of 6 every 3 weeks

Objective Response Rate: 10.6%
Overall Survival: Not available
Progression Free Survival: Data not yet mature

Phase 3 Controlled Study
Previously untreated metastatic melanoma without a BRAF mutation (N=418)
nivolumab 3 mg/kg every 2 weeks or dacarbazine 1000 mg/m2 every 3 weeks
Primary end point: overall survival

Nivolumab in Melanoma: Place in Therapy

• BRAF V600 wild-type or mutation-positive unresectable or metastatic melanoma, as a single agent

• Unresectable or metastatic melanoma, in combination with ipilimumab
Melanoma- Pembrolizumab

KEYNOTE- 006
Ipilimumab-Naïve population

Randomized, controlled, Phase 3
834 patients with advanced
melanoma who had received no
more than one previous treatment

Primary Endpoints: progression free
survival and overall survival

Pembrolizumab 10 mg/kg every 2 weeks

Median PFS: 5.5 months (HR: vs. ipilimumab 0.58)
Estimated 1-year survival rate*: 74% (HR vs. ipilimumab 0.63)

Pembrolizumab 10 mg/kg every 3 weeks

Median PFS: 4.1 months
Estimated 1-year survival rate*: 68.4% (HR vs. ipilimumab 0.69)

Ipilimumab 3 mg/kg every 3 weeks

Median PFS: 2.8 months
Estimated 1-year survival rate*: 58.2%

*Because the overall survival results for the two pembrolizumab groups were
superior than ipilimumab, the independent data and safety monitoring
Committee recommended stopping the study early to allow patients in the
ipilimumab group the option of receiving pembrolizumab
Immune-Related Adverse Events

• Inflammatory side effects caused by increasing immune system function, immune-checkpoint blockade
• Different side effects than traditional chemotherapy
• Important to recognize and understand how to manage these side effects
• Early diagnosis, high suspicion, excellent patient-provider communication and adequate use of corticosteroids are crucial
• Can affect any organ system (e.g., skin, gastrointestinal, hepatic, endocrine systems)
Immune-Related Adverse Events

- General symptoms include fevers, chills and lethargy
- Most common adverse events are fatigue, nausea and decreased appetite
- Side effects can occur anytime; some side effects occur early while some side effects may occur much later or even after discontinuation of therapy
- Check adrenocorticotropic hormone cortisol, and testosterone (men) in patients who develop fatigue and nonspecific symptoms
- Routine monitoring of thyroid function tests, complete blood counts, liver function tests and metabolic panels at each treatment and at intervals of 6 to 12 weeks for the first 6 months after finishing treatment
## Immune-Related Adverse Events

<table>
<thead>
<tr>
<th>Type of Immunotherapy</th>
<th>REMS</th>
<th>Skin Toxicity</th>
<th>Endocrinopathy</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD-1 Inhibitor</td>
<td>No</td>
<td>Rash</td>
<td>Hypopysitis, thyroiditis more common, adrenal insufficiency</td>
<td>Pneumonitis not common; neuropathy, Guillain-Barre, myasthenia gravis, nephritis, all rare</td>
</tr>
<tr>
<td>PD-L1 Inhibitor</td>
<td>No</td>
<td>Rash</td>
<td>Hypopysitis, thyroiditis more common, adrenal insufficiency</td>
<td>Pneumonitis rare, anemia rare</td>
</tr>
<tr>
<td>CTLA-4 Inhibitor</td>
<td>Yes</td>
<td>Rash Common</td>
<td>Hypophysitis, thyroiditis, and adrenal insufficiency</td>
<td>Neuropathy, nephritis, Guillaine-Barre, myasthenia gravis, sarcoid, and thrombocytopenia all rare</td>
</tr>
<tr>
<td>PD-1 + CTLA-4</td>
<td>No</td>
<td>Rash Common</td>
<td>Hypopysitis, thyroiditis more common, adrenal insufficiency</td>
<td>Pneumonitis not common; neuropathy, Guillain-Barre, myasthenia gravis, nephritis, all rare</td>
</tr>
</tbody>
</table>

Managing Immune-Mediated Rash

Grade 1-2 (covering ≤30% BSA)
- Continue treatment
- Administer topical corticosteroid creams and antihistamines (e.g., hydroxyzine, diphenhydramine)

Grade 3-4 (Covering >30% BSA; life-threatening consequences)
- Grade 3: Withhold treatment
- Grade 4: permanently discontinue treatment
- 1 to 2 mg/kg/day of prednisone or equivalent
- Consider skin biopsy and dermatology consult

If symptoms persist >1-2 weeks or recur:
- Withhold treatment, consider 0.5-1 mg/kg/day methylprednisolone or equivalent.
- Once improving, taper steroids over at least 1 month and resume treatment

If improved to <Grade 2, taper steroids over at least 1 month before resuming treatment

# Immune-Mediated Endocrinopathies

<table>
<thead>
<tr>
<th></th>
<th>All Grades n/N (%)</th>
<th>Grade 2 n/N</th>
<th>Grade 3-5 n/N</th>
<th>Median Time to onset, months (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypophysitis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma: Opdivo</td>
<td>7/787 (0.9%)</td>
<td>3 /787</td>
<td>2/787 (Gr 3)</td>
<td>5.5 (1.6-11)</td>
</tr>
<tr>
<td>Melanoma: Opdivo + Yervoy</td>
<td>36/407 (9%)</td>
<td>25 /407</td>
<td>8/407 (Gr 3)</td>
<td>2.7 (27 days- 5.5 months)</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>2/406 (0.5%)</td>
<td>1/406</td>
<td>--</td>
<td>3.2, 9.2</td>
</tr>
<tr>
<td><strong>Hypothyroidism or thyroiditis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Melanoma: Opdivo</td>
<td>73/787 (9%)</td>
<td>37/787</td>
<td>1/787</td>
<td>2.8 (15 days-13.8 months)</td>
</tr>
<tr>
<td>Melanoma: Opdivo + Yervoy</td>
<td>89/407 (22%)</td>
<td>47/407</td>
<td>6/407</td>
<td>2.1 (1 day-10.1 months)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>20/287 (7%)</td>
<td>--</td>
<td>--</td>
<td>2.9 (1.4-11.8)</td>
</tr>
</tbody>
</table>

Managing Immune-Mediated Endocrinopathies

**Symptomatic Endocrinopathy**
(eg., hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism)
- Continue treatment for hypothyroidism or hyperthyroidism
- Initiate hormone replacement therapy for hypothyroidism
- Initiate medical treatment for hyperthyroidism

**Hypophysitis**
- Grade 2 or 3: Withhold treatment; 1 mg/kg/day prednisone equivalents
- Grade 4: Permanently discontinue treatment

**Adrenal Insufficiency**
- Grade 2: Withhold treatment
- Grade 3-4: Permanently discontinue treatment; 1-2 mg/kg/day prednisone equivalents

**Other Endocrinopathies**
Withhold treatment for other endocrinopathies with abnormal lab/pituitary scan

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Managing Immune-Mediated Endocrinopathies

• For asymptomatic TSH elevations (e.g., hypothyroidism, hyperthyroidism), continue treatment

• Consider endocrinology consult; evaluate endocrine function and consider pituitary scan

• Repeat labs in 1 to 3 weeks, MRI in 1 month if symptoms persist but normal lab/pituitary scan

• Continue standard monitoring in patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

• Taper steroids over at least 1 month before resuming treatment

• Resume treatment if symptoms improved with or without hormone replacement
Gastrointestinal Toxicity and Hepatotoxicity

- **PD-1 Inhibitor**
  - Diarrhea and colitis with ulceration: Uncommon
  - Elevated LFTs: Uncommon

- **PD-L1 Inhibitor**
  - Diarrhea and colitis with ulceration: Rare
  - Elevated LFTs: Rare

- **CTLA-4 Inhibitor**
  - Diarrhea and colitis with ulceration: Common
  - Elevated LFTs: Common

- **PD-1 + CTLA-4**
  - Diarrhea and colitis with ulceration: (Boxed Warning)
  - Elevated LFTs: (Boxed Warning)

## Frequency and Onset of GI Adverse Reactions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diarrhea or colitis</th>
<th>Immune mediated colitis (All Grades)</th>
<th>Immune mediated colitis Grades 3-5</th>
<th>Median time to onset (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma Opdivo</td>
<td>31%</td>
<td>4.1%</td>
<td>20 pts/787</td>
<td>5.6 (3 days-13.1 months)</td>
</tr>
<tr>
<td>Melanoma Opdivo + Yervoy</td>
<td><strong>56%</strong></td>
<td><strong>26%</strong></td>
<td>62 pts/407</td>
<td><strong>1.6</strong> (3 days-15.2 months)</td>
</tr>
<tr>
<td>NSCLC Opdivo</td>
<td>17%</td>
<td>2.4%</td>
<td>3 pts/287</td>
<td>2.7 (4 weeks-19 months)</td>
</tr>
<tr>
<td>Renal Opdivo</td>
<td>25%</td>
<td>3.2%</td>
<td>5 pts/406</td>
<td>4.8 (2 days-15.6 months)</td>
</tr>
</tbody>
</table>

Managing Immune-Mediated GI Toxicity

Grade 1
- Continue treatment
- Symptomatic treatment

If symptoms worsen or persist, treat as Grade 2 or 3/4

Grade 2
- Withhold treatment
- Symptomatic treatment
- If persists > 5-7 days or recurs: 0.5 to 1 mg/kg/day prednisone equivalents

If symptoms worsen or persist >3-5 days with oral steroids, treat as Grade 3-4
- If improved, resume treatment; if steroids have been administered, taper steroids over at least 1 month

Grade 3/4
- Grade 3: Withhold until Grade 0-1
- Grade 4: Permanently discontinue
  - 1-2 mg/kg/day prednisone equivalents
  - Consider lower GI endoscopy
  - Permanently discontinue for Grade 3/4 in Opdivo + Yervoy combination

If persists >3-5 days or recurs: Add non-corticosteroid immunosuppressive medication (e.g., infliximab)
- If improved from Grade 3, when at Grade 1, taper steroids over at least 1 months before resuming treatment

## Dosing and Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Opdivo)</td>
<td><strong>Updated dosing (9/13/16):</strong> 240 mg IV infusion every 2 weeks for all indications except Hodgkin Lymphoma</td>
<td>Over 60 minutes</td>
</tr>
<tr>
<td></td>
<td><strong>Monotherapy</strong> 3 mg/kg IV infusion every 2 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Combination with ipilimumab in melanoma</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Opdivo 1 mg/kg IV infusion, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then Opdivo 240 mg every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>2 mg/kg IV infusion every 3 weeks (melanoma &amp; NSCLC)</td>
<td>Over 30 minutes</td>
</tr>
<tr>
<td></td>
<td>200 mg IV infusion every 3 weeks (HNSCC)</td>
<td></td>
</tr>
<tr>
<td>Atezolizumab (Tencentriq)</td>
<td>1,200 mg IV infusion every 3 weeks</td>
<td>Over 60 minutes, if first infusion is tolerated, subsequent infusion can be delivered over 30 minutes</td>
</tr>
</tbody>
</table>
Biomarkers of PD1/PD-L1 Inhibitors: To Test or Not To Test

• Pembrolizumab is approved for use with a companion diagnostic test for PD-L1 expression
• Pembrolizumab trials were done in patients who were PD-L1 positive
• PD-L1 expression is not a requirement for nivolumab
• Level of PD-L1 expression is clinically relevant
• Front-line treatment as a prognostic test to prioritize therapy
## Cost of PD-1/PD-L1 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost for 6 Weeks*</th>
<th>Cost per Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>$17,785</td>
<td>$154,130</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>$17,500</td>
<td>$151,840</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>$17,240</td>
<td>$149,400</td>
</tr>
</tbody>
</table>

*Based on Wholesale Acquisition Cost (WAC); patient weight of 80 kg

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**Combination of nivolumab + Ipilimumab for metastatic melanoma**

**Estimated Annual Cost for the Combination:** $250,000
Economic Impact of PD1/PD-L1 Inhibitors: Value Assessment

• Institute for Clinical and Economic Review (ICER): Treatment Options for Advanced Non-Small Cell Lung Cancer (Draft Evidence Report, August 19, 2016)
  • Nivolumab, pembrolizumab and atezolizumab vs. docetaxel in second-line NSCLC
  • Cost-effectiveness of the PD-1/PD-L1 inhibitors exceed the quality-adjusted life year (QALY) benchmark of $150,000
  • Cost effectiveness ratio ranges from $208,000 per QALY for atezolizumab to $250,000 for the PD-1 inhibitors

• American Society of Clinical Oncology (ASCO) Value Framework
  • Prospective randomized comparative trial: Total Net Health Benefit score vs. drug acquisition cost

• National Comprehensive Cancer Network (NCCN) Evidence Blocks

Available at: https://icer-review.org/meeting/nsclc/
Ongoing Important Questions

• Identify patients that are most likely to benefit and those who are unlikely to benefit
• Identify optimal duration of treatment
• Determine the best sequence or combination of these agents with other chemotherapy or targeted agents
• Single vs. combination immunotherapy
• PD-1 vs. PD-L1 inhibitors, which one is better?
Optimal Utilization of PD-1/PD-L1 Inhibitors

• Role of the health system Pharmacy and Therapeutics Committee
• Formulary management and development of appropriate guidelines
• Role of the clinical oncology pharmacists in managing immune-mediated adverse events
• Oncology subcommittee work in collaboration with P&T Committee to address high cost medications
• Understand the evidence on the FDA-labeled indications and address off-labeled indications
Summary

• Cancer immunotherapy, i.e., PD-1, PD-L1 inhibitors changes the paradigm of how we treat some most difficult to treat cancers

• Personalized medicine and upfront biomarker results have become increasingly important

• Numerous ongoing questions are important to address how we can best utilize these agents

• Role of pharmacists in managing these high cost agents are critical
Test Questions

1) Which of the following is an FDA-Approved Indication for both nivolumab and pembrolizumab?

A. As a single agent for unresectable/metastatic melanoma
B. As a single first-line agent for treatment of advanced non-small cell lung cancer
C. In combination with ipilimumab for the treatment of first-line unresectable/metastatic melanoma
D. Advanced renal cell carcinoma who have received prior anti-angiogenic therapy
2) Which of the following statement is true regarding the use of combination nivolumab and ipilimumab?

A. Combination of nivolumab and ipilimumab is approved for use in lung cancer
B. Combination of nivolumab and ipilimumab has lower treatment related adverse event than nivolumab alone
C. **Combination of nivolumab and ipilimumab reduced patient risk by 58% compared with ipilimumab alone in untreated metastatic melanoma**
D. A & C are true
Test Questions

3) Diarrhea and colitis are more common with PD-1/PDL-1 inhibitors than CTLA-4 inhibitor.
   True/False
References