Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

Christine M. Walko, Pharm.D., BCOP, FCCP, Activity Chair
Associate Member, Individualized Cancer Management
H. Lee Moffitt Cancer Center
Tampa, Florida

Shetal A. Patel, M.D., Ph.D.
Assistant Professor of Medicine: Thoracic and Head/Neck Oncology
UNC Lineberger Comprehensive Cancer Center
University of North Carolina Hospitals
Chapel Hill, NC

Disclosures

In accordance with ACCME and ACPE Standards for Commercial Support, ASHP policy requires that all faculty, planners, reviewers, staff, and others in a position to control the content of this presentation disclose their relevant financial relationships. In this activity, only the individuals below have disclosed a relevant financial relationship. No other persons associated with this presentation have disclosed any relevant financial relationships.

Christine M. Walko, Pharm.D., BCOP, FCCP
• Consultant for Jackson Genetic Laboratories

Shetal A. Patel, M.D., Ph.D.
• AstraZeneca, Principle Investigator
Learning Objectives

• Explain the rationale, place in therapy, and mechanism of action of immune checkpoint inhibitors with focus on lung cancer and melanoma treatments.

• Determine patient characteristics and companion diagnostic tests that identify patients with lung cancer or melanoma who may benefit from immune checkpoint inhibitor therapy.

• Recommend strategies to recognize and manage adverse events associated with immune checkpoint inhibitors use in patients with melanoma and lung cancer.

• Develop strategies to educate patients and caregivers on the adverse events associated with the use of immune checkpoint inhibitors.

On average how many cancer patients being treated with immunotherapies for lung cancer or melanoma do you provide care to each month?

a. None-I am not directly involved in patient care
b. 1-10 patients/month
c. 11-30 patients/month
d. 31-50 patients/month
e. More than 50 patients/month
Current Immune Checkpoint Inhibitors and Mechanism of Action in Cancer Therapy

Shetal A. Patel, M.D., Ph.D.
Assistant Professor of Medicine
Thoracic and Head/Neck Oncology

History of Immunotherapy

- Immunotherapy: use of the immune system to treat cancer
- Long history with recent rapid progress
- 1890s: William Coley observed correlation between concomitant infection and tumor regression
- 1980s: Early immune therapies included vaccines, nonspecific immune activation (high dose IL-2 [Interleukin-2], interferon-α)
- 2000s: Cancer immune surveillance hypothesis
- 2010s: Antibodies targeting T cell inhibitory receptors approved by FDA
- Chimeric antigen receptor (CAR) T cells
- Bispecific antibodies
- Oncolytic viruses

Cancer Research Institute https://www.cancerresearch.org/immunotherapy/timeline-of-progress
CTLA-4 and PD-1 Pathways

- CTLA-4 and PD-1 pathways are T cell checkpoint receptors
- Ipilimumab: blocks CTLA-4 on T-cells


PD-1/PD-L1 Blockade

- Pembrolizumab and nivolumab: block interaction of PD-1 with ligands
- Atezolizumab, durvalumab, avelumab: block PD-L1 interaction with PD-1 on T cells
- PD-1/PD-L1 blockade reinvigorates T cell function

# Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

## Currently Approved Immune Checkpoint Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
<th>Initial FDA Approval Date (month/year)</th>
<th>Number of Approvals for Different Cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipiilimumab</td>
<td>CTLA-4</td>
<td>3/2011</td>
<td>3</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>PD-1</td>
<td>12/2014</td>
<td>9</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1</td>
<td>9/2014</td>
<td>15</td>
</tr>
<tr>
<td>Cemiplimab-rwlc</td>
<td>PD-1</td>
<td>9/2018</td>
<td>1</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>PD-L1</td>
<td>5/2016</td>
<td>4</td>
</tr>
<tr>
<td>Avelumab</td>
<td>PD-L1</td>
<td>3/2017</td>
<td>3</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>PD-L1</td>
<td>5/2017</td>
<td>2</td>
</tr>
</tbody>
</table>

www.fda.gov accessed 10/9/2019

## FDA-Approved PD-1 Antibody: Nivolumab

- **Nivolumab**
  - Melanoma (adjuvant and metastatic settings)
  - Metastatic non-small cell lung cancer (NSCLC)
  - Metastatic small cell lung cancer (SCLC)
  - Advanced renal cell carcinoma (RCC)
  - Relapsed classical Hodgkin lymphoma
  - Metastatic squamous cell carcinoma of the head and neck
  - Metastatic bladder cancer after platinum therapy
  - MSI-H/dMMR colorectal cancer (CRC)
  - Advanced hepatocellular carcinoma (HCC)

- **Nivolumab + ipilimumab**
  - Melanoma (adjuvant and metastatic settings)
  - Metastatic MSI-H/dMMR colorectal cancer (CRC)
  - Advanced renal cell carcinoma (intermediate or poor risk)

MSI-H: microsatellite instability high  
dMMR: deficient mismatch repair

Opdivo package insert (Sept 2019)
FDA-Approved PD-1 Antibody: Pembrolizumab

- **Pembrolizumab**
  - Melanoma (adjuvant and metastatic settings)
  - Metastatic NSCLC
    - Also stage IIIIB non-resectable NSCLC
  - Metastatic small cell lung cancer (SCLC)
  - Metastatic squamous cell carcinoma of the head and neck
  - Relapsed classical Hodgkin lymphoma
  - Primary mediastinal large B-cell lymphoma
  - Metastatic bladder cancer after platinum therapy or not eligible for platinum therapy
  - MSI-H/dMMR solid tumors
  - Advanced HCC
  - Recurrent/metastatic gastric cancer
  - Recurrent/metastatic esophageal cancer
  - Recurrent/metastatic cervical cancer
  - Recurrent/locally advanced Merkel cell carcinoma

- **Pembrolizumab + carboplatin + pemetrexed**
  - Metastatic non-squamous NSCLC

- **Pembrolizumab + carboplatin + paclitaxel**
  - Metastatic squamous NSCLC (can also use paclitaxel protein-bound particles)

- **Pembrolizumab + axitinib**
  - First line therapy for advanced RCC

- **Pembrolizumab + lenvatinib**
  - Advanced endometrial cancer

Keytruda package insert (Sept 2019)

FDA-Approved PD-L1 Antibody: Atezolizumab

- **Atezolizumab**
  - Locally advanced or metastatic bladder cancer not eligible for platinum therapy or after progression on platinum therapy
  - Metastatic NSCLC

- **Atezolizumab + carboplatin + etoposide**
  - First line extensive-stage small cell lung cancer

- **Atezolizumab + carboplatin + paclitaxel + bevacizumab**
  - First line metastatic non-squamous NSCLC, with no EGFR or ALK mutations

- **Atezolizumab + paclitaxel protein-bound particles (Abraxane)**
  - Advanced/metastatic triple negative breast cancer (TNBC)

EGFR: Epidermal growth factor receptor; ALK: Anaplastic lymphoma kinase

Tecentriq package insert (2019 May)

©2020 American Society of Health-System Pharmacists, Inc. All rights reserved.
## Other FDA-Approved PD-1 and PD-L1 Antibodies

<table>
<thead>
<tr>
<th>Checkpoint Inhibitor</th>
<th>Drug Target</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cemiplimab-rwlc</td>
<td>PD-1</td>
<td>• Metastatic and locally advanced cutaneous squamous cell carcinoma</td>
</tr>
</tbody>
</table>
| Avelumab             | PD-L1       | • Metastatic Merkel cell carcinoma  
|                      |             | • Metastatic urothelial carcinoma after platinum-based therapy  
|                      |             | • In combination with axitinib for advanced RCC |
| Durvalumab           | PD-L1       | • Unresectable stage III NSCLC following platinum-based therapy  
|                      |             | • Metastatic urothelial carcinoma after platinum-based therapy |


## Approved Adult Dosing Regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>IV Dose</th>
<th>Infusion Time (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab*</td>
<td>240 mg every 2 weeks or 480 mg every 4 weeks</td>
<td>30 for both doses</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>200 mg every 3 weeks</td>
<td>30</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>1200 mg every 3 weeks</td>
<td>60 for first infusion then 30 subsequently</td>
</tr>
<tr>
<td>Avelumab</td>
<td>10 mg/kg every 2 weeks</td>
<td>60</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>10 mg/kg every 2 weeks</td>
<td>60</td>
</tr>
</tbody>
</table>

* FDA-approved dosing for single-agent treatment only

FDA-approved prescribing information for each agent
Combination Ipilimumab and Nivolumab Dosing

- FDA-approved combination dosing for metastatic melanoma:
  - Nivolumab 1 mg/kg followed by ipilimumab 3 mg/kg on the same day, every 3 weeks x 4 doses
  - Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 3 weeks

- NCT 02714218 enrolling to assess different doses in metastatic melanoma:
  - Nivolumab 3 mg/kg + Ipilimumab 1 mg/kg
  - Nivolumab 1 mg/kg + Ipilimumab 3 mg/kg
  - Nivolumab 6 mg/kg + Ipilimumab 1 mg/kg

- FDA-approved combination dosing for RCC and MSI-H CRC:
  - Nivolumab 3 mg/kg followed by ipilimumab 1 mg/kg on the same day, every 3 weeks x 4 doses
  - Nivolumab 240 mg IV every 2 weeks or Nivolumab 480 mg IV every 3 weeks

Optimizing the Use of Immune Checkpoint Inhibitors with Biomarkers

Shetal A. Patel, M.D., Ph.D.
Assistant Professor of Medicine:
Thoracic and Head/Neck Oncology
Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

Potential Biomarkers for Response to Immune Checkpoint Inhibitors

- **PD-L1 expression by immunohistochemistry**
- **Microsatellite instability**
- Numerous investigational factors being tested in trials:
  - Tumor mutational burden (TMB)
  - T-cell-inflamed gene expression profile
  - HLA genotype and class I diversity
  - Gut microbiome
  - Mutations in JAK2, β2-microglobulin, STK11/KEAP1, and the β-catenin pathway


PD-L1 Expression

**Benefits**
- Immunohistochemistry (IHC) is readily available, can be performed quickly, and correlates with response to PD-1/PD-L1 inhibitors in multiple tumor types
- Response rates vary by tumor type
- PD-L1 expression can be used to prioritize treatment options

**Challenges**
- PD-L1 expression can vary over time and between tumor sites in a given patient
- Different tests may produce different results because antibodies have different affinities and specificities
- Specimen processing techniques may decrease sensitivity
- Unclear threshold values across tests, malignancies, and PD-1/PD-L1 agents

PD-L1 Companion Diagnostics: Pembrolizumab

**TPS: Tumor Proportion Score**
- Measures the % of viable tumor cells showing partial or complete membrane staining of any intensity
- PD-L1 TPS threshold:
  - TPS ≥ 1%: First and second line for non-small cell lung cancer (single-agent therapy)

**CPS: Combined Positive Score**
- Measures the % of PD-L1 staining cells (tumor cells, lymphocytes, and macrophages) relative to the total number of viable tumor cells
- May be > 100 but the maximum score reported is 100
- PD-L1 CPS thresholds:
  - CPS > 1: certain cervical, head and neck, and gastric/gastroesophageal junction cancer indications
  - CPS > 10: first line bladder cancer in patients who cannot tolerate cisplatin

Keytruda package insert (Sept 2019)

PD-L1 Companion Diagnostics: Atezolizumab

- VENTANA PD-L1 (SP142) Assay reports both:
  - The proportion of tumor area occupied by PD-L1 expressing tumor-infiltrating immune cells (% IC) of any intensity
  - Percentage of PD-L1 expressing cells (% TC) of any intensity
  - PD-L1 % IC thresholds
    - IC > 1%: Combination therapy with paclitaxel protein-bound for unresectable locally advanced or metastatic TNBC
    - IC > 5%: first line bladder cancer in patients who cannot tolerate cisplatin

Tecentriq package insert (2019 May)
KEYNOTE-042 Trial

Pembrolizumab vs. platinum doublet for first-line NSCLC (EGFR and ALK wild-type)

- Pembrolizumab is now approved as first line therapy for patients with stage III NSCLC who are not candidates for surgical resection or definitive chemoradiation or metastatic NSCLC with PD-L1 TPS ≥1% determined by an FDA-approved test.

<table>
<thead>
<tr>
<th>Median Overall Survival (months) Based on PD-L1 TPS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study</strong></td>
</tr>
<tr>
<td>TPS ≥ 1</td>
</tr>
<tr>
<td>TPS ≥ 20</td>
</tr>
<tr>
<td>TPS ≥ 50</td>
</tr>
</tbody>
</table>


Chemotherapy and Immunotherapy Combinations

- KEYNOTE-189 nonsquamous NSCLC
- KEYNOTE-407 squamous NSCLC
- OS improved across TPS subsets for chemotherapy + pembrolizumab

<table>
<thead>
<tr>
<th>Study</th>
<th>Pembrolizumab + chemotherapy</th>
<th>Placebo + chemotherapy</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonsquamous (KN-189)</td>
<td>69.2% OS 2 years</td>
<td>49.4% OS 2 years</td>
<td>0.49 (0.38-0.64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Squamous (KN-407)</td>
<td>15.9</td>
<td>11.3</td>
<td>0.64 (0.49-0.85)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

OS = overall survival
Chemotherapy = platinum doublet

Chemotherapy and Immunotherapy Combinations

- Adding immune checkpoint blockade to anti-VEGF therapy
- IMpower 150 study of patients with nonsquamous NSCLC
- Preliminary activity in patients with EGFR mutations, liver metastases

<table>
<thead>
<tr>
<th></th>
<th>ABCP</th>
<th>BCP</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>19.2</td>
<td>14.7</td>
<td>0.78 (0.64-0.96)</td>
<td>0.02</td>
</tr>
<tr>
<td>Baseline Liver Metastases</td>
<td>13.3</td>
<td>9.4</td>
<td>0.52 (0.33-0.82)</td>
<td></td>
</tr>
<tr>
<td>Sensitizing EGFR mutations</td>
<td>NE</td>
<td>17.5</td>
<td>0.41 (0.23-0.75)</td>
<td></td>
</tr>
</tbody>
</table>

ABCP = atezolizumab + bevacizumab + carboplatin/paclitaxel
BCP = bevacizumab + carboplatin/paclitaxel
VEGF = Vascular endothelial growth factor


Microsatellite Instability (MSI)

- DNA mismatch repair (MMR) enzymes correct errors that occur during normal DNA replication
- Inactivation of MMR enzymes results in more somatic mutations
  - Inactivation of MLH1, MSH2, MSH6, or PMS2
  - Can be germline or somatic (occurring only in the tumor)
- Frequency in solid tumors:
  - Colorectal cancer: 15%
  - Endometrial cancer: 22-33%
  - Other tumors: 5% or less

- Correlated with increased number of mutations/neoantigens

Current MSI-High Approvals

Pembrolizumab

- Treatment of adult and pediatric patients with unresectable or metastatic MSI-high or MMR deficient:
  - Solid tumors following prior therapy with no satisfactory alternatives
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan
  - Not yet established for pediatric patients with MSI-high central nervous system (CNS) tumors

Nivolumab

- Treatment of adult and pediatric patients with unresectable or metastatic MSI-high or MMR deficient:
  - Colorectal cancer following prior therapy with fluoropyrimidine, oxaliplatin, and irinotecan

Keytruda package insert (Sept 2019).
Opdivo package insert (Sept 2019).

Mutation Load and Immunotherapy

**Biomarker Findings**

- Tumor mutational burden indicates the number of non-synonymous mutations reported per megabase (Mb)
  - Cancers secondary to environmental exposures (Ultraviolet [UV] light, cigarette smoking) or certain DNA damage-related deficiencies have higher mutation burdens
  - Correlation with neoantigens: mutations can generate novel antigens that are recognized as non-self by T cells
- Improved median progression free survival (mPFS) in lung cancer patients with high tumor mutation burden, regardless of PD-L1 status

TMB and Immune Checkpoint Inhibitor Survival Across Solid Tumors

- Clinical and genomic data for 1662 patients with advanced cancer who were treated with immune checkpoint inhibitors were analyzed
  - 5,371 patients not treated with immune checkpoint inhibitors
- Utilized the MSK-IMPACT next generation sequencing assay
  - Clinical assay that assesses somatic exonic mutation in 468 cancer-related genes
  - Includes comparison with matched germline normal DNA
  - Prior studies determine mutation load by whole exome sequencing (not commonly used in clinical care)


<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Number of Patients</th>
<th>Top 20% TMB Cut Off (mutations/Mb)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder</td>
<td>214</td>
<td>17.6</td>
<td>0.040</td>
</tr>
<tr>
<td>Colorectal</td>
<td>110</td>
<td>52.2</td>
<td>0.031</td>
</tr>
<tr>
<td>Esophagogastric</td>
<td>126</td>
<td>8.8</td>
<td>0.221</td>
</tr>
<tr>
<td>Primary glioma</td>
<td>117</td>
<td>5.9</td>
<td>0.465</td>
</tr>
<tr>
<td>Head and neck</td>
<td>138</td>
<td>10.3</td>
<td>0.007</td>
</tr>
<tr>
<td>Melanoma</td>
<td>321</td>
<td>30.7</td>
<td>0.067</td>
</tr>
<tr>
<td>Non-small cell lung</td>
<td>350</td>
<td>13.8</td>
<td>0.0002</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>151</td>
<td>5.9</td>
<td>0.569</td>
</tr>
</tbody>
</table>

TMB Biomarker Summary

- An association between higher TMB and improved overall survival with immune checkpoint inhibitor therapy was seen in most solid tumors
  - Notable exceptions included primary gliomas and renal cell carcinoma
- The TMB cutpoints for association with response varied between cancer types
  - There may not be a universal “high” TMB for solid tumors in general
  - Difficulty of harmonizing TMB cutoffs across assays


Challenges and Novel Therapies

- Tumor microenvironment is complex
- Numerous positive/negative regulators, unique to each patient
- Novel treatments:
  - Oncolytic viruses
  - Immune checkpoint antibodies
  - Agonists
  - Chimeric antigen receptor (CAR) T cells
  - Tumor infiltrating lymphocyte (TIL) therapy
Case Presentation 1: LP

- LP is a 62-year-old female former light smoker who began experiencing persistent cough and intermittent abdominal pain
- Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland
- Biopsy of the RUL lesion demonstrated an adenocarcinoma consistent with primary lung malignancy
  - EGFR, ALK, ROS1, BRAF, MET, and RET all negative
  - Microsatellite stable and intermediate mutation burden (10 Mutations/Mb)

**PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)**

Tumor Proportion Score (TPS) (%) 70

CT=computerized tomography
EGFR, ALK, ROS1, BRAF, MET, and RET refer to specific gene rearrangements that have been linked to lung cancer.

Which of the following is NOT an acceptable treatment for this patient?

a. Pembrolizumab monotherapy
b. Docetaxel monotherapy
c. Carboplatin/pemetrexed + pembrolizumab
d. Carboplatin/paclitaxel/bevacizumab + atezolizumab
Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

Nonsquamous NSCLC: Choosing a first-line regimen

• Pembrolizumab monotherapy or chemotherapy + PD-1/PD-L1 blockade and bevacizumab are approved for first-line treatment

• Patient considerations for choosing a regimen:
  – Baseline neuropathy - avoid paclitaxel
  – Baseline liver metastases, may benefit from bevacizumab?
  – Renal insufficiency (CrCl < 45 mL/min, cannot use pemetrexed)
  – Is patient highly symptomatic? Consider chemotherapy + PD-1/PD-L1 ± bevacizumab combination regimens because of higher response rates

Case Presentation 1: LP

• LP is a 62-year-old female former light smoker who began experiencing persistent cough and intermittent abdominal pain

• Chest CT showed a right upper lobe (RUL) lung lesion and masses involving the liver and right adrenal gland

• Biopsy of the RUL lesion showed adenocarcinoma consistent with primary lung malignancy
  – EGFR, ALK, ROS1, BRAF, MET, and RET all negative
  – Microsatellite stable and intermediate mutation burden (10 Mutations/Mb)

**PD-L1 IMMUNOHISTOCHEMISTRY (IHC) ANALYSIS (Dako 22C3 pharmDx™)**

Tumor Proportion Score (TPS) (%) 70

• **Should this patient be treated with first-line PD-1/PD-L1 blockade?**

CT=computerized tomography

EGFR, ALK, ROS1, BRAF, MET, and RET refer to specific gene rearrangements that have been linked to lung cancer.
Immune-Related Adverse Effects: Identification, Management, and Monitoring

Christine M. Walko, Pharm.D., BCOP, FCCP, Activity Chair
Associate Member, Individualized Cancer Management
H. Lee Moffitt Cancer Center

Immune-Related Adverse Events (irAEs)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Clinical Effects</th>
<th>Time of Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Rash, pruritus</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Diarrhea, colitis</td>
<td>6-8 weeks</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Dyspnea, cough, fever, chest pain</td>
<td>10 weeks</td>
</tr>
<tr>
<td>Liver</td>
<td>Elevated enzymes, bilirubin, hepatitis</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypophysitis, hypothyroidism</td>
<td>After 6 weeks but can be prolonged</td>
</tr>
</tbody>
</table>

Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

PD-1 and PD-L1 Toxicities


<table>
<thead>
<tr>
<th>Duration of treatment (weeks)</th>
<th>Grade of Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>Skin Toxicity</td>
</tr>
<tr>
<td>6</td>
<td>Diarrhea/Colitis</td>
</tr>
<tr>
<td>8</td>
<td>Pneumonitis</td>
</tr>
<tr>
<td>10</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td></td>
</tr>
<tr>
<td>delayed</td>
<td></td>
</tr>
</tbody>
</table>

Phase III Nivolumab +/- Ipilimumab Toxicity

<table>
<thead>
<tr>
<th>Toxicity (%)</th>
<th>Nivolumab</th>
<th>Ipilimumab</th>
<th>Nivolumab and Ipilimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grade</td>
<td>Grade 3 and 4</td>
<td>All grade</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>2.2</td>
<td>33.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>34.2</td>
<td>1.3</td>
<td>28</td>
</tr>
<tr>
<td>Rash</td>
<td>25.9</td>
<td>0.6</td>
<td>32.8</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>3.8</td>
<td>1.3</td>
<td>3.9</td>
</tr>
<tr>
<td>Increased AST</td>
<td>3.8</td>
<td>1.0</td>
<td>3.5</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.6</td>
<td>0</td>
<td>4.2</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.3</td>
<td>0.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7.7</td>
<td>0</td>
<td>6.1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4.5</td>
<td>0.3</td>
<td>4.2</td>
</tr>
</tbody>
</table>


©2020 American Society of Health-System Pharmacists, Inc. All rights reserved.
Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

ASCO/NCCN Joint Guidelines: Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- Purpose: To increase awareness, outline strategies and offer guidance on the recommended management of immune-related adverse effects (irAE) in patients treated with immune checkpoint inhibitors (ICPi)
- Multidisciplinary panel across medical specialties
- Systematic review of 204 publications from 2000 to 2017

ASCO: American Society of Clinical Oncology
NCCN: National Comprehensive Cancer Network


Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- Skin toxicities
  - Rash
  - Bullous dermatoses
  - Severe cutaneous adverse reactions
- Gastrointestinal toxicities
  - Colitis
  - Hepatitis
- Lung toxicities
  - Pneumonitis
- Endocrine toxicities
  - Primary hypothyroidism
  - Hyperthyroidism
  - Primary adrenal insufficiency
  - Hypophysitis
  - Diabetes mellitus


©2020 American Society of Health-System Pharmacists, Inc. All rights reserved.
Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- Musculoskeletal toxicities
- Renal toxicities
- Nervous system toxicities
- Hematologic toxicities
- Cardiovascular toxicities
  - Myocarditis, arrhythmias, heart failure, vasculitis
  - Venous thromboembolism
- Ocular toxicities


Case Presentation 2

- DD is a 71-year-old male former smoker diagnosed with locally advanced head and neck squamous cell cancer (larynx)
- He is initially treated with chemotherapy and radiation but has disease progression within 2 months of treatment completion and is started on pembrolizumab
- After 2 cycles he presents with pruritus, erythematous patches on his arms, upper chest, and back
- He is initially started on a mid-potency topical steroid, however the lesions progress and he returns with multiple tense bullae overlying the areas of erythema
- What is the appropriate next step?

https://www.nhs.uk/conditions/bullous-pemphigoid
**Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma**

### Cutaneous irAEs
- Any grade seen in about 30-50% of patients receiving immune checkpoint inhibitors
  - Most commonly manifest as maculopapular rash, pruritus and vitiligo
  - Typically low grade
  - Resolve within 1-2 months with treatment
  - T-cell infiltrate seen on biopsy specimens of the skin
- Grade ≥ 3 are rare but often require systemic corticosteroids
- PD-1 or PD-L1 cutaneous irAE may be more diverse and occur later than with ipilimumab
  - Combination nivolumab and ipilimumab is associated with more common cutaneous irAEs that occur earlier than with single agents


### Rash/Inflammatory Dermatitis

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
</table>
| **G1**: No effect on QOL or controlled with topical or oral antipruritic | • Topical emollients and/or mild/moderate topical corticosteroids  
• Avoid irritants and sun exposure |
| **G2**: Affects QOL and requires intervention | • Consider withholding ICPI  
• Consider prednisone (or equivalent) 1 mg/kg tapering over at least 4 weeks  
• Topical emollients and/or moderate/high potency topical corticosteroids and oral antihistamines |
| **G3**: G2 but failure to respond to G2 interventions | • Withhold ICPI and consult dermatology  
• Methylprednisolone 1-2 mg/kg, taper over > 4 weeks  
• Topical emollients, high potency topical corticosteroids |
| **G4**: All severe rashes not manageable with prior interventions and intolerable | • Hold ICPI, consult dermatology, admit patient  
• Methylprednisolone 1-2 mg/kg, slow taper when toxicity resolves  
• Consider permanent discontinuation |

CTCAE: Common Terminology Criteria for Adverse Events

Case Management for Skin Toxicity

- Patient is referred to dermatology who performs a biopsy
- Biopsy demonstrates ulceration and direct immunofluorescence reveals complement and IgG deposition
- He is started on 1 mg/kg prednisone and lesions begin to improve
- Steroid was tapered over 6 weeks with input from dermatology
- Patient was rechallenged with PD-1 blockade and had a response for over 14 months

Case Presentation 3

- MA is a 61-year-old male former smoker diagnosed with metastatic squamous NSCLC, PD-L1 TPS 5%
- Treated with carboplatin/paclitaxel and pembrolizumab
- Restaging scans after 2 cycles show a partial response
- Develops cellulitis on his leg and is started on clindamycin
- 2 weeks later he develops watery diarrhea, 7-8 episodes daily with mild abdominal cramping
- Differential diagnosis/workup for his diarrhea?
Gastrointestinal irAEs

- Can occur anywhere in the gastrointestinal tract (mucositis, colitis, enteritis)
  - With single-agent immunotherapy, mostly commonly seen about 6-8 weeks after start of treatment
  - Rare cases reported even after being off therapy for several months
- Colitis most common with ipilimumab alone or with nivolumab
- Endoscopic exam typically shows:
  - Diffuse ulceration and edema (can affect the entire colon)
  - Lymphocytic and neutrophilic infiltration
- Novel prevention and treatment strategies:
  - Earlier use of biologic agents such as infliximab
  - Manipulation of gut microbiome

Colitis (highlights)

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
</table>
| **G1**: Increase of < 4 stools /day or mild increase in ostomy output | • May continue ICPI or hold until < G1  
• Monitor for dehydration |
| **G2**: Increase in 4-6 stools/day, moderate increase in ostomy output | • Hold ICPI until ≤ G1 (may permanently stop CTLA-4 inhibitors)  
• Consult with Gastroenterology, consider esophagogastroduodenoscopy (EGD)/colonoscopy to stratify for need for infliximab  
• Initiate prednisone 1 mg/kg/day, taper over 4-6 weeks when ≤ G1 |
| **G3**: Increase in ≥ 7 stools/day, incontinence, severe ostomy output, hospitalization needed | • As above for G3, with hospitalization for electrolyte replacement, prednisone 1-2 mg/kg/day  
• If symptoms ≥ 3-5 days or recur after improvement, consider IV methylprednisolone or infliximab |
| **G4**: Life threatening consequences | • Permanently discontinue ICPI  
• Methylprednisolone 1-2 mg/kg/day  
• **Infliximab** 5-10 mg/kg if refractory after 2-3 days |

GI Toxicity Discussion for Case 3

- Infectious workup is initiated including stool culture, *C. difficile* assay, viral pathogen panel
- CT Abdomen/pelvis demonstrates diffuse stranding involving the transverse and descending colon
- Referral placed to gastroenterology for a colonoscopy
- *C. difficile* assay returns positive
- Patient is started on oral vancomycin, with improvement in symptoms in 3-4 days
- Additional considerations: chemotherapy-induced diarrhea, colitis
- Difficult to determine cause when patients on multiple agents

Case Presentation 4

- RC is a 56-year-old female with unresectable stage III NSCLC treated with definitive chemotherapy and radiation
- She is started on consolidation durvalumab per the PACIFIC study
- 3 months after starting durvalumab she presents with several days of dyspnea on exertion (only able to walk 10 ft)
- On exam, her oxygen saturation is 88% on room air, lung exam has coarse lower lobe breath sounds
- What work-up should be completed?

Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

**Lung Related irAEs**

- More common with PD-1 inhibitors than inhibitors of CTLA-4 or PD-L1
- Can be challenging to diagnose especially in patients with lung cancer or chronic lung disease
  - Radiographic features: organizing pneumonia, ground glass opacities, hypersensitivity, interstitial
- Associated with:
  - Treatment in the first-line setting
  - Any type of lung inflammation
    - Chemotherapy, radiation, smoking history, or underlying lung disease
- Can be severe, require hospitalization and may be fatal in some cases, especially in more frail patients


---

**Pneumonitis (highlights)**

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
</table>
| **G1**: Asymptomatic, confined to one lung lobe or < 25% of lung parenchyma | • Hold ICPI with radiographic evidence of pneumonitis progression  
• May resume ICPI with radiographic evidence of improvement or resolution. If no improvement, treat as a grade 2.  
• Monitor weekly |
| **G2**: Symptomatic, involves more than one lung lobe or 25-50% of lung parenchyma, medical intervention indicated | • Hold ICPI until resolution to ≤ grade 1  
• Prednisone 1-2 mg/kg/day with taper by 5-10 mg/week over 4-6 weeks  
• Consider empiric antibiotics  
• Monitor every 3 days, if no improvement after 48-72 hours of prednisone, treat as grade 3. |
| **G3**: Severe symptoms, hospitalization required, involves all lung lobes or >50% of lung parenchyma, oxygen indicated | • Permanently discontinue ICPI  
• Empiric antibiotics and methylprednisolone IV 1-2 mg/kg/day, if no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1g twice a day or IVIG for 5 days or cyclophosphamide. Steroids should be tapered over 4-6 weeks  
• Pulmonary and infectious disease consults if necessary  
• Hospitalize for further management |
| **G4**: Life threatening respiratory compromise, urgent intervention (intubation) required | |


©2020 American Society of Health-System Pharmacists, Inc. All rights reserved.
Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

Pneumonitis Presentation for Case 4

- Patient undergoes a non-contrast chest CT with new nodular opacities in the lower lobes
- Infectious work-up including viral swab, induced sputum culture are negative
- She is referred to interventional pulmonary for a bronchoscopy with bronchoalveolar lavage (BAL) and biopsy
  - BAL: negative for infection
  - Biopsy: organizing pneumonia, no malignant cells
- Initiated therapy with prednisone with significant improvement in 3-4 days

Image courtesy of Dr. Saeed Soltany Hosn, Radiopaedia.org, rID: 21385

Immune Checkpoint Inhibitor Endocrine Toxicity

- Can present in a variety of ways:
  - Asymptomatic with routine lab changes
  - Fatigue
  - Headaches (mild to severe)
  - Polyuria/polydipsia
  - Shortness of breath
  - Palpitations

Endocrine irAEs

- Most common manifestations
  - Hypothyroidism or hyperthyroidism
    - More common with PD-1/PD-L1 inhibitors than CTLA-4 inhibitors
  - Hypopituitarism
  - Type 1 diabetes mellitus
  - Hypophysitis: inflammation of the pituitary gland
    - Associated with fatigue, weakness, headaches, visual changes, and nausea
    - Less common with PD-1 inhibitors than CTLA-4 inhibitors


Comparison of Endocrine irAEs

- Meta-analysis of 38 randomized clinical trials with a total of 7551 patients
  - PD-1 inhibitor monotherapy
  - PD-L1 inhibitor monotherapy
  - CTLA-4 inhibitor monotherapy (ipilimumab)
  - Combination PD-1 and CTLA-4 inhibitors

- Results
  - Combination therapy had the highest rate of hypothyroidism (OR 3.81, p<0.001) and hyperthyroidism (OR 4.27, p=0.001) compared with ipilimumab alone
  - PD-1 inhibitor-treated patients had a higher risk of developing hypothyroidism (OR 1.89, p<0.03) compared with ipilimumab
  - Risk of hyperthyroidism (not hypothyroidism) was higher with PD-1 inhibitors compared with PD-L1 inhibitors (OR 5.36, p=0.002)
  - Hypophysitis was more common with ipilimumab than PD-1 inhibitors.

OR= Odds ratio

Hypothyroidism (Highlights)

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>G1</strong>: TSH &lt; 10 mIU/L and asymptomatic</td>
<td>• Continue ICPI with monitoring of TSH and free T4</td>
</tr>
<tr>
<td><strong>G2</strong>: Moderate symptoms, TSH persistently &gt; 10 mIU/L</td>
<td>• May hold ICPI until symptoms resolve to baseline</td>
</tr>
<tr>
<td></td>
<td>• Consider endocrine consult</td>
</tr>
<tr>
<td></td>
<td>• Thyroid supplementation in symptomatic patients with TSH levels &gt; 10 mIU/L, monitor every 6-8 weeks while titrating</td>
</tr>
<tr>
<td><strong>G3-4</strong>: Severe symptoms, life threatening consequences</td>
<td>• Hold ICPI until symptoms resolve to baseline with appropriate supplementation</td>
</tr>
<tr>
<td></td>
<td>• Endocrine consultation</td>
</tr>
<tr>
<td></td>
<td>• May admit for IV therapy if bradycardia and/or hyperthermia</td>
</tr>
<tr>
<td></td>
<td>• All of the above from G2</td>
</tr>
</tbody>
</table>

TSH: Thyroid stimulating hormone


Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- **Skin toxicities**
  - Rash
  - Bullous dermatoses
  - Severe cutaneous adverse reactions
- **Gastrointestinal toxicities**
  - Colitis
  - Hepatitis
- **Lung toxicities**
  - Pneumonitis
- **Endocrine toxicities**
  - Primary hypothyroidism
  - Hyperthyroidism
  - Primary adrenal insufficiency
  - Hypophysitis
  - Diabetes mellitus

Management of Immune-Related Adverse Events in Patients Treated with Immune Checkpoint Inhibitors

- Musculoskeletal toxicities
- Renal toxicities
- Nervous system toxicities
- Hematologic toxicities
- Cardiovascular toxicities
  - Myocarditis, arrhythmias, heart failure, vasculitis
  - Venous thromboembolism
- Ocular toxicities


Case Presentation 5

- SK is a 71-year-old male with glioblastoma who underwent resection
- He enrolls on a clinical trial of PD-1 blockade with post-operative chemotherapy and radiation
- 2 weeks after starting treatment he presents to clinic with new onset eyelid drooping, double vision, and difficulty swallowing
- He is admitted for further workup
Case Presentation 5 (continued)

- Repeat brain MRI is stable
- Laboratory studies are unremarkable, including negative acetylcholine receptor antibody titers
- Neurology is consulted and performs electromyography (EMG) studies which are consistent with myasthenia gravis (MG)
- Patient is treated with pyridostigmine and plasmapheresis with improvement in symptoms

** steroids can acutely worsen MG, get neurology involved early!

Immune Checkpoint Inhibitor irAE Summary

- Importance of patient education
- High level of suspicion for new side effects being treatment related
- Dose adjustments are not recommended after restarting therapy following toxicity

<table>
<thead>
<tr>
<th>Grading (CTCAE)</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 1</strong></td>
<td>Continue ICPI therapy with close monitoring</td>
</tr>
<tr>
<td></td>
<td>Exceptions: neurologic, hematologic, and cardiac toxicities</td>
</tr>
<tr>
<td><strong>Grade 2</strong></td>
<td>Hold ICPI for most toxicities, resume when resolved to ≤ G1</td>
</tr>
<tr>
<td></td>
<td>Prednisone 0.5-1 mg/kg/day or equivalent may be administered</td>
</tr>
<tr>
<td><strong>Grade 3</strong></td>
<td>Hold ICPI for G3 toxicities</td>
</tr>
<tr>
<td></td>
<td>Start prednisone 1-2 mg/kg/day or methylprednisolone IV 1-2 mg/kg/day with taper over ≥ 4-6 weeks</td>
</tr>
<tr>
<td></td>
<td>If no improvement after 48-72 hours, then consider infliximab</td>
</tr>
<tr>
<td><strong>Grade 4</strong></td>
<td>Generally warrant permanent ICPI discontinuation (except for endocrine therapy controlled by hormonal replacement)</td>
</tr>
</tbody>
</table>

Practice Essentials for Using Immune Checkpoint Inhibitors to Treat Lung Cancer and Melanoma

Prolonged Immunosuppression Concerns

- Some patients may require longer steroid tapers of > 4 weeks and even 6-8 weeks or longer, especially for pneumonitis and hepatitis
- Prophylaxis considerations:
  - Herpes zoster prophylaxis may be considered in general
  - For patients with a higher risk of gastritis, proton pump inhibitors or H2 receptor blockers can be considered
  - Patients receiving prednisone 20 mg or equivalent daily for > 4 weeks may require *Pneumocystis jiroveci* pneumonia prophylaxis (PJP)
  - Patients receiving prednisone 20 mg or equivalent daily for > 6-8 weeks may require antifungal prophylaxis
- Vitamin D and calcium should be used to prevent osteoporosis
- Inactivated or killed vaccines may be used during immunotherapy but live vaccines should be avoided due to current lack of supporting data


Key Takeaways

**Key Takeaway #1**
- Immune checkpoint inhibitor therapy approvals by FDA continue to increase, as single agent or combination therapies for a variety of cancer types

**Key Takeaway #2**
- Although some biomarkers, such as PD-L1 expression and MSI, are closely associated with response to immune checkpoint inhibitors in selected solid tumors, better predictors of response are needed and probably will reflect various cancer- and drug-specific factors

**Key Takeaway #3**
- Immune checkpoint inhibitors are associated with immune-related adverse effects that can involve any system of the body but most commonly involve the skin, GI tract, liver, lungs, and endocrine system. Excellent guidelines are available to help guide management

**Key Takeaway #4**
- Clear and comprehensive patient education is essential for early side effect management and maintaining patient quality of life
Which of these practice changes will you consider making?

- Discuss with patients the place in therapy of immune checkpoint inhibitors to treat melanoma and lung cancer.
- Discuss with other practitioners the place in therapy and mechanism of action of immune checkpoint inhibitors.
- Collaborate with clinicians in my practice to select companion diagnostic tests and review patient characteristics when selecting immune checkpoint inhibitors to treat patients.
- Develop a plan to recognize and manage immune related adverse events associated with immune checkpoint inhibitor use.
- Educate patients and/or their caregivers on the potential adverse effects of immune checkpoint inhibitor use.
About the Faculty

Christine M. Walko, Pharm.D., BCOP, FCCP, Activity Chair
Associate Member, Department of Individualized Cancer Management
Moffitt Cancer Center
Tampa, Florida

Christine M. Walko, Pharm.D., BCOP, FCCP, is a Personalized Medicine Specialist at the DeBartolo Family Personalized Medicine Institute at the H. Lee Moffitt Cancer Center and is also Associate Professor at the University of South Florida Morsani College of Medicine in Tampa, Florida. She is also the Chair of the Clinical Genomics Action Committee (CGAC) and attending on the Personalized Medicine Clinical Service at H. Lee Moffitt Cancer Center. Dr. Walko received her Doctor of Pharmacy from Duquesne University in Pittsburgh. She completed a pharmacy practice residency at Virginia Commonwealth University Health System/Medical College of Virginia Hospitals in Richmond, Virginia. She also completed a Hematology/Oncology specialty residency at the University of North Carolina (UNC) Hospitals and Clinics and a Hematology/Oncology fellowship at the University of North Carolina School of Pharmacy in Chapel Hill, North Carolina. She is a board certified oncology pharmacist.

She has researched and published extensively in oncology therapy and has presented nationally and internationally on oncology and pharmacogenomics and other topics related to treating patients with cancer.

Shetal Patel, M.D., Ph.D.
Assistant Professor of Medicine
Division of Hematology/Oncology
UNC School of Medicine
Chapel Hill, North Carolina

Shetal A. Patel, M.D., Ph.D., is an Assistant Professor of Medicine, Division of Hematology/Oncology at the University of North Carolina (UNC) School of Medicine in Chapel Hill, North Carolina. Dr. Patel specializes in seeing patients with thoracic and head/neck cancer.

Dr. Patel obtained her M.D. and Ph.D. at the University of Pennsylvania, studying cancer biology for her graduate work. She then completed residency training in Internal Medicine at Brigham and Women’s Hospital prior to returning to the University of Pennsylvania for a fellowship in Medical Oncology. She has particular interests in translational research related to immune and targeted therapies, by designing novel treatment trials based on preclinical studies. Dr. Patel is a member of the American Society of Clinical Oncology (ASCO), American Association of Cancer Research and the International Association for the Study of Lung Cancer. Dr. Patel also serves as a Molecular Tumor Board member for the ASCO Targeted Agent Profiling and Utilization Registry.

ADDITIONAL ACTIVITIES ON IMMUNOTHERAPY
■ Ask the Experts Webinar coming in early 2020
■ Podcasts coming in Spring 2020

www.ashpadvantage.com/immunotherapy

ACCREDITATION

The American Society of Health-System Pharmacists (ASHP) is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

ACPE #0204-0000-19-420-H01-P
1.5 contact hours, application-based

The American Society of Health-System Pharmacists is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

ASHP designates this enduring material for a maximum of 1.5 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

©2020 American Society of Health-System Pharmacists, Inc. All rights reserved.