Principles and Application of Immunotherapy for Cancer: Advanced Melanoma

This program is supported by educational grants from Genentech and Merck.
About These Slides

- Users are encouraged to use these slides in their own noncommercial presentations, but we ask that content and attribution not be changed. Users are asked to honor this intent.

- These slides may not be published or posted online without permission from Clinical Care Options (email permissions@clinicaloptions.com).

Disclaimer
The materials published on the Clinical Care Options Web site reflect the views of the authors of the CCO material, not those of Clinical Care Options, LLC, the CME providers, or the companies providing educational grants. The materials may discuss uses and dosages for therapeutic products that have not been approved by the United States Food and Drug Administration. A qualified healthcare professional should be consulted before using any therapeutic product discussed. Readers should verify all information and data before treating patients or using any therapies described in these materials.
Core Faculty

Jeffrey S. Weber, MD, PhD  
*Senior Member and Director*  
Comprehensive Melanoma Research Center  
H. Lee Moffitt Cancer Center  
Tampa, Florida

Peg Esper, DNP, ANP-BC, AOCN  
*Nurse Practitioner*, Medical Oncology  
Department of Hematology-Oncology  
Comprehensive Cancer Center  
University of Michigan  
Ann Arbor, Michigan
Faculty Disclosures

**Jeffrey S. Weber, MD, PhD,** has disclosed that he has served as a consultant for Bristol-Myers Squibb, Celldex, Genentech, GlaxoSmithKline, and Merck and has ownership interest in Altor, cCAM and Celldex.

**Peg Esper, DNP, ANP-BC, AOCN,** has no real or apparent conflicts of interest to report.
Agenda

- Melanoma and the Immune System
  - Defining the role of the immune system in cancer
  - Tumor escape from immune surveillance
  - Harnessing the immune system for melanoma treatment

- Current Immunotherapy for Melanoma
  - Efficacy and safety of currently approved agents
  - Managing potential adverse events associated with immunotherapy

- Novel Agents and Immunotherapy Combinations
T-Cell Response: First Signal

T-Cell Response: Accelerate or Brake?

Coactivation Signals
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Use agonistic mAbs to ↑ activation

Inhibitory Signals
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Use blocking mAbs to ↑ activation

T-Cell Stimulation

T-Cell Inhibition

**Tumor Immunology: Overview**

1. **Tumor antigen**
   - Dendritic cell
   - MHC
   - B7

2. **Lymph node**
   - Resting T cell
   - TCR
   - CD28

3. **Activated T cell**
   - T-cell clonal expansion
   - Perforin
   - Granzyme
   - Cytokines (IL-2)

Activated T cells interact with tumor cells, leading to the release of perforin and granzyme, which can induce cell death. Cytokines like IL-2 are produced to further activate the T cells and promote their proliferation.
Dampening the Immune System in Cancer

Priming Phase
- Dendritic cell
- CTLA-4
- B7
- CD28
- Cytotoxic T cell

Effector Phase
- PD-L1
- PD-1
- Exhau**stion**
- Cytotoxic T cell
- T reg
- MDSC

- Negative immune regulators
  - Inhibitory receptors
  - Suppressive cells
  - Suppressive enzymes (IDO, arginase)

Immunotherapy for Melanoma
High-Dose IL-2 Therapy: Durable Responses Seen

- High-dose IL-2 produces durable responses in 16% of pts with advanced melanoma
- Few relapses in pts responding for over 2.5 yrs (likely cured)
- FDA approval in 1998 for melanoma

Metastatic Melanoma (N = 270)

![Graph showing probability of continuing response over duration of response](image)

High-Dose IL-2 Therapy in Melanoma

- High-dose IL-2 appears to benefit pts, but:
  - Toxic
  - Complex; must be delivered as an inpatient regimen
- Use remains limited to selected pts treated at experienced centers
- Efforts to develop more tolerable regimens unsuccessful
- Efforts to better select pts who might benefit from high-dose IL-2 therapy have produced modest advances
- Proof of principle that immunotherapy can produce durable benefit in pts with cancer, but newer immunotherapies are needed
**Blocking Immunologic Checkpoints**

**Primming:**

T-Cell Activation in the Lymph Node

- Dendritic cell
- CD28
- B7
- CTLA-4
- Ipilimumab
- Tremelimumab

**Effector Phase:**

Peripheral Tissues

- Tumor
- PD-L1
- MPDL3280A
- MEDI4736
- MSB0010718C
- PD-L1
- Nivolumab
- Pembrolizumab
- Pidilizumab

Ipilimumab, gp100, or Both: OS in Advanced Melanoma

Median OS, Mos
Ipi + gp100 (n = 403) 10.0
Ipi alone (n = 137) 10.1
Gp100 alone (n = 136) 6.4

HR P
0.68 < .001
0.66 .003
Comparison vs gp100 alone

1-yr OS:
Ipi + gp100 44%
Ipi alone: 46%
Gp100 alone: 25%

2-yr OS, %
Ipi + gp100 22%
Ipi alone: 24%
Gp100 alone: 14%

Analysis From Phase II and Phase III Trials of Ipilimumab Show OS Plateau at 3 Years

Median OS: 11.4 mos (95% CI: 10.7-12.1)

3-yr OS rate: 22% (95% CI: 20% to 24%)

Pts at Risk, n
Ipilimumab  1861   839   370   254   192   170   120   26   15   5   0

## Ipilimumab, gp100, or Both in Advanced Melanoma (MDX010-20): irAEs

<table>
<thead>
<tr>
<th>irAE, %</th>
<th>All Grades (Grade 3/4)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ipi + gp100 (n = 380)</td>
<td>Ipi + Placebo (n = 131)</td>
<td>gp100 + placebo (n = 132)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>58 (9.7/0.5)</td>
<td>61 (12.2/2.3)</td>
<td>32 (3.0/0)</td>
<td></td>
</tr>
<tr>
<td>Dermatologic</td>
<td>40 (2.1/0.3)</td>
<td>44 (1.5/0)</td>
<td>17 (0/0)</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>32 (5.3/0.5)</td>
<td>29 (7.6/0)</td>
<td>14 (0.8/0)</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>4 (1.1/0)</td>
<td>8 (2.3/1.5)</td>
<td>2 (0/0)</td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>2 (1.1/0)</td>
<td>4 (0/0)</td>
<td>5 (2.3/0)</td>
<td></td>
</tr>
</tbody>
</table>

Kinetics of Appearance of irAEs with Ipilimumab

- Rash, pruritus
- Liver toxicity
- Diarrhea, colitis
- Hypophysitis

Ipilimumab: Key to Optimal Patient Management

- First Dose: baseline assessment; review medical history, check standard of care lab values including LFTs, TFTs
- Subsequent doses: before each infusion or as needed, check lab values including AST, ALT, total bilirubin, and thyroid function
- Conduct thorough assessment of immune-mediated symptoms
- Educate on importance of detecting and prompt reporting of symptoms
  - Discuss key points about immune-mediated adverse events and importance of prompt medical intervention
  - Confirm patient’s ability to verbalize important symptoms
  - Emphasize that symptoms may be intermittent and can occur wks to mos after treatment is complete
# Ipilimumab: Managing Immune-Related Adverse Events

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI tract</td>
<td>Diarrhea</td>
<td>Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (&gt; 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory pts.</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dark, bloody stools</td>
<td></td>
</tr>
<tr>
<td>Skin</td>
<td>Rash (± itching)</td>
<td>Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids.</td>
</tr>
<tr>
<td></td>
<td>Blistering/peeling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral sores</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>Jaundice</td>
<td>Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST &gt; 2.5 x but ≤ 5 x ULN; permanently discontinue if AST/ALT &gt; 5 x ULN or bilirubin &gt; 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory pts.</td>
</tr>
<tr>
<td></td>
<td>Nausea/vomiting</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Numbness/tingling</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensory changes</td>
<td></td>
</tr>
<tr>
<td>Endocrine</td>
<td>Headaches</td>
<td>Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the pt.</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Behavior/mood changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Menstruation changes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dizziness/light-headedness</td>
<td></td>
</tr>
<tr>
<td>Eyes</td>
<td>Vision problems</td>
<td>Monitor for redness suggesting uveitis; treat with topical steroidal eye drops.</td>
</tr>
<tr>
<td></td>
<td>Irritation</td>
<td></td>
</tr>
</tbody>
</table>
# Ipilimumab: Managing Immune-Related Adverse Events

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI tract</td>
<td>Diarrhea, Abdominal pain, Dark, bloody stools</td>
<td>Moderate enterocolitis: hold ipilimumab, administer antidiarrheal. Persistent diarrhea (&gt; 1 wk): systemic corticosteroids. 7+ stools/day: start methylprednisolone, permanently discontinue ipilimumab. Consider infliximab for corticosteroid-refractory pts.</td>
</tr>
<tr>
<td>Skin</td>
<td>Rash, ± itching, blistering/peeling, Oral sores</td>
<td>Moderate/nonlocalized rash: hold ipilimumab, start topical or systemic corticosteroids. Severe dermatitis: permanently discontinue ipilimumab, start corticosteroids.</td>
</tr>
<tr>
<td>Liver</td>
<td>Jaundice, Nausea/vomiting</td>
<td>Assess ALT/AST, bilirubin, and thyroid function before each dose and as necessary. Hold ipilimumab if ALT/AST &gt; 2.5 x but ≤ 5 x ULN; permanently discontinue if AST/ALT &gt; 5 x ULN or bilirubin &gt; 3 x ULN. The immunosuppressant mycophenolate can be used for hepatotoxicity in corticosteroid-refractory pts.</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Headaches, Fatigue, Behavior/mood changes, Menstruation changes, Dizziness/light-headedness</td>
<td>Moderate endocrinopathy: hold ipilimumab, start corticosteroids. Endocrine abnormalities can be difficult to detect, due to nonspecific symptoms. Consider having an endocrinologist follow the pt.</td>
</tr>
<tr>
<td>Eyes</td>
<td>Vision problems, Irritation</td>
<td>Monitor for redness suggesting uveitis; treat with topical steroidal eye drops.</td>
</tr>
</tbody>
</table>

**Principles of Managing irAEs:**
- Hold ipilimumab
- Initiate steroids therapy (1–2 mg/kg of prednisone or equivalent daily)
- Consider infliximab (if gastrointestinal toxicity) or mycophenolate (if hepatotoxicity) if steroids do not resolve symptoms

Ipilimumab in Melanoma: Current Issues

- **Dose:** 3 mg/kg or 10 mg/kg?
  - Phase III results pending in patients with metastatic melanoma\(^1\)

- **Schedule:** maintenance therapy or not?

- **Role in the adjuvant setting?**
  - EORTC 18071: ipilimumab 10 mg/kg vs placebo\(^2\)
  - E1609: ipilimumab 3 or 10 mg/kg vs IFN\(^3\)

- **In combinations?**
  - Bevacizumab, other immunotherapies (GM-CSF, IFN, IL-2, PD-1 antibodies, and T-Vec), and radiation therapy
  - High toxicity when combined with BRAF inhibitors\(^4\)

---

OS: Ipi + GM-CSF vs Ipi Alone

- Phase II trial: pts randomized to receive ipilimumab 10 mg/kg IV on day 1 ± GM-CSF 250 μg SQ on days 1 to 14 of a 21-day cycle

Stratified 1-sided log-rank $P = .014$

HR: 0.64 (90% RCI: -- to 0.90)

<table>
<thead>
<tr>
<th></th>
<th>1-yr OS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipi (n = 122)</td>
<td>52.9%</td>
<td>12.7 mos</td>
</tr>
<tr>
<td>Ipi + GM-CSF (n = 123)</td>
<td>68.9%</td>
<td>17.5 mos</td>
</tr>
</tbody>
</table>
Priming: T-Cell Activation in the Lymph Node

Dendritic cell

CD28

B7

CTLA-4

Cytotoxic T cell

Ipilimumab

Tremelimumab

Effector Phase: Peripheral Tissues

Tumor

Interferons

PD-L1

MPDL3280A

MEDI4736

MSB0010718C

Nivolumab

Pembrolizumab

Pidilizumab

Phase I (KEYNOTE-001): Pembrolizumab Leads to Frequent and Durable Responses

- ORR is 37%; 81% with response continue to receive treatment

Phase I (KEYNOTE-001): Pembrolizumab Leads to Frequent and Durable Responses

- ORR is 37%; 81% with response continue to receive treatment


Pembrolizumab received FDA approval 9/4/14
Phase I: Nivolumab Leads to Frequent and Durable Responses

- ORR is 31%; 58% with response ongoing at time of analysis

Phase I: Nivolumab Leads to Frequent and Durable Responses

- ORR is 31%; 58% with response ongoing at time of analysis

Nivolumab received FDA approval 12/21/14

**KEYNOTE-001: Pembrolizumab AE Profile**

<table>
<thead>
<tr>
<th>Grade 3/4 AEs in ≥ 1 Pt, %</th>
<th>Pembro 2 mg/kg (n = 89)</th>
<th>Pembro 10 mg/kg (n = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Amylase increase</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Confusion</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Muscular weakness</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral motor neuropathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

# Nivolumab AE Profile

<table>
<thead>
<tr>
<th>Grade 3/4 AEs, %</th>
<th>Nivolumab (N = 107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>22.4</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>2.8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.9</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.9</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.9</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>0.9</td>
</tr>
<tr>
<td>Blood thyroid-stimulating hormone increased</td>
<td>0.9</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>0.9</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>0.9</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.9</td>
</tr>
</tbody>
</table>

KEYNOTE-002: Phase II Trial of Pembro vs Chemotherapy in Ipi-Refractory Pts

Pts with advanced melanoma who progressed on or after ipilimumab (and BRAF, if BRAF V600+)

- Pembrolizumab 2 mg/kg IV q2w (n = 268)
- Pembrolizumab 10 mg/kg IV q2w (n = 268)
- Investigator’s choice of chemotherapy* (n = 102)

Pts with PD confirmed by independent central review could cross over to pembrolizumab treatment after the first 3-mo assessment

*Carboplatin + paclitaxel, paclitaxel alone, dacarbazine, or temozolomide.

- Primary endpoint: PFS, OS
- Secondary endpoints: ORR, DoR

KEYNOTE-002: Pembrolizumab vs Chemotherapy in Ipi-Refractory Melanoma

An international, randomized phase II study in pts with advanced melanoma with PD within 24 wks after ≥ 2 Ipi doses

<table>
<thead>
<tr>
<th>Arm</th>
<th>ORR, %</th>
<th>Median PFS, Mos (95% CI)</th>
<th>Mean PFS, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembro 2 mg/kg q3w</td>
<td>21</td>
<td>2.9 (2.8-3.8)</td>
<td>5.4</td>
</tr>
<tr>
<td>Pembro 10 mg/kg q3w</td>
<td>25</td>
<td>2.9 (2.8-4.7)</td>
<td>5.8</td>
</tr>
<tr>
<td>Chemo</td>
<td>4</td>
<td>2.7 (2.5-2.8)</td>
<td>3.6</td>
</tr>
</tbody>
</table>

PFS HR (95% CI) PFS value
0.57 (0.45-0.73) < .0001
0.50 (0.39-0.64) < .0001

Checkmate-037: Phase III Trial of Nivolumab vs Chemotherapy in IPI-Refractory Pts

Stratified by PD-L1 expression (+ vs - or indeterminate)*; BRAF wt vs V600 mutant; best overall response prior to anti-CTLA-4 (clinical benefit vs no clinical benefit)

Nivolumab
3 mg/kg IV q2w
(n = 268)

Investigator’s choice of chemotherapy (ICC):
- Dacarbazine 1000 mg/m² q3w
- Carboplatin AUC 6 IV + Paclitaxel 175 mg/m² q3w
(n = 102)

Treat until
- Progression
OR
- Unacceptable toxicity

Pts receiving nivolumab may be treated beyond initial progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug

Pts with advanced melanoma who progressed on or after ipilimumab (and BRAF, if BRAF V600+)

*Positive: ≥ 5% tumor cell surface staining cutoff by immunohistochemistry.

Targeting T Cells With Nivolumab Leads to Higher Response Rate vs Chemotherapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>CR + PR, n</th>
<th>ORR,* % (95% CI)</th>
<th>Best Overall Response,* %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CR</td>
</tr>
<tr>
<td>Central review†</td>
<td></td>
<td></td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>120</td>
<td>38 (4 CR)</td>
<td>32 (24-41)</td>
<td>3</td>
</tr>
<tr>
<td>ICC</td>
<td>47</td>
<td>5 (0 CR)</td>
<td>11 (4-23)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Confirmed response.
†Independent radiology review committee based on RECIST 1.1.
# Nivolumab vs Pembrolizumab in Ipilimumab-Refractory Patients

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Nivolumab (Checkmate-037)</th>
<th>Pembrolizumab (KEYNOTE-002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (IPI-R)</td>
<td>120 (preliminary subset)</td>
<td>180</td>
</tr>
<tr>
<td>FDA Approved Schedule</td>
<td>3 mg/kg IV every 2 weeks</td>
<td>2 mg/kg IV every 3 weeks</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>32 (24-41)</td>
<td>21 (15-28)</td>
</tr>
<tr>
<td>Grades 3-4 drug related toxicities, %</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

Phase III CA209-066 First-line Nivolumab vs Chemotherapy Trial: Study Design

**Stratified by PD-L1 status,†**

- Unresectable, treatment-naive stage III or IV melanoma; *BRAF* wild-type; ECOG PS 0-1; 18 yrs of age or older (N = 418)

**Double-blind**

- **Nivolumab 3 mg/kg IV q2w + Placebo IV q3w**
  (n = 210; 206 treated)

- **Placebo IV q2w + Dacarbazine 1000 mg/m² IV q3w**
  (n = 208; 205 treated)

Treat until progression* or unacceptable toxicity

**Primary endpoint:**
- OS

**Secondary endpoints:**
- PFS
- ORR
- PD-L1 correlates

†PD-L1 positive: ≥ 5% tumor cell surface staining.

*Pts may be treated beyond initial RECIST v1.1–defined progression if considered by the investigator to be experiencing clinical benefit and tolerating study drug.

OS: First-line Nivolumab vs Chemotherapy

- Objective response rate: 40% with nivolumab vs 13.9% with chemo (P <.001)
- Significantly better OS with nivolumab vs dacarbazine

KEYNOTE-006: Analysis of Pembro vs Ipi

Trial Design

- A multicenter, randomized, controlled phase III study
- Unresectable stage III or IV melanoma; ≤1 prior therapy, excluding checkpoint inhibitors; ECOG PS 0-1; 18 yrs of age or older (estimated N = 645)

Stratified by ECOG PS (0 vs 1), line of therapy (first vs second), PD-L1 status (positive vs negative)

- **Pembrolizumab** 10 mg IV every 2 weeks for up to 2 yrs
- **Pembrolizumab** 10 mg IV every 3 weeks for up to 2 yrs
- **Ipilimumab** 3 mg/kg IV once every 3 weeks for 4 doses

- Primary endpoint: PFS, OS
- Secondary endpoint: ORR, DoR, Safety

KEYNOTE-006: Survival Efficacy at First Interim Analysis of Pembro vs Ipi

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Median PFS (95% CI), mo</th>
<th>Rate at 6 mo, %</th>
<th>HR (95% CI)</th>
<th>Rate at 12 mo, %</th>
<th>HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab Q2W</td>
<td>5.5 (3.4-6.9)</td>
<td>47.3</td>
<td>0.58 (0.46-0.72)</td>
<td>&lt;.00001</td>
<td>NR (NR-NR)</td>
<td>74.1</td>
</tr>
<tr>
<td>Pembrolizumab Q3W</td>
<td>4.1 (2.9-6.9)</td>
<td>46.4</td>
<td>0.58 (0.47-0.72)</td>
<td>&lt;.00001</td>
<td>NR (NR-NR)</td>
<td>68.4</td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>2.8 (2.8-2.9)</td>
<td>26.5</td>
<td>—</td>
<td>—</td>
<td>NR (12.7-NR)</td>
<td>58.2</td>
</tr>
</tbody>
</table>

Checkmate-067: Nivo + Ipi vs Nivo vs Ipi for First-line Treatment of Melanoma

- A randomized, double-blind phase III study

  | Stratified by tumor PD-L1 status (positive vs negative/indeterminate), BRAF mutation status (V600 mutation–positive vs wild-type), and AJCC metastasis stage (M0, M1a, or M1b vs. M1c)

Unresectable, treatment-naive stage III or IV melanoma; ECOG PS 0-1; 18 yrs of age or older (N = 945)

- Primary endpoint: OS, PFS
- Secondary endpoint: ORR, OS by PD-L1, Safety

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

<table>
<thead>
<tr>
<th></th>
<th>Nivo + Ipi (n = 314)</th>
<th>Nivo (n = 316)</th>
<th>Ipi (n = 315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>11.5 (8.9-16.7)</td>
<td>6.9 (4.3-9.5)</td>
<td>2.9 (2.8-3.4)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (99.5% CI)</td>
<td>0.42 (0.31-0.57)*</td>
<td>0.57 (0.43-0.76)*</td>
<td>—</td>
</tr>
<tr>
<td>vs Ipi</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR (95% CI) vs Nivo</td>
<td>0.74 (0.60-0.92)†</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Stratified log-rank P < .00001 vs Ipi.
†Exploratory endpoint. Study not powered to detect a statistical difference between Nivo + Ipi and Nivo.

CheckMate 067: Improved PFS with Nivo + Ipi or Nivo Alone vs Ipi Alone

Nivolumab was FDA approved in combination with ipilimumab in patients with \textit{BRAF V600} wild-type metastatic melanoma based on data from the phase II CheckMate-069 on 9/30/2015

CheckMate 067: Nivo + Ipi Provides Most Benefit for PD-L1^{lo}, Similar to Nivo for PD-L1^{hi}

*Per validated PD-L1 immunohistochemical assay based on PD-L1 staining of tumor cells in a section of at least 100 evaluable tumor cells.

## CheckMate 067: Treatment-Related AEs Associated With Nivo and Ipi

<table>
<thead>
<tr>
<th>Select Treatment-Related AEs, %</th>
<th>Nivo + Ipi (n = 313)</th>
<th>Nivo (n = 313)</th>
<th>Ipi (n = 311)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Any select AE</td>
<td>88</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>Skin</td>
<td>59</td>
<td>6</td>
<td>42</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33</td>
<td>2</td>
<td>19</td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>3</td>
<td>22</td>
</tr>
<tr>
<td>Maculopapular rash</td>
<td>12</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>46</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Colitis</td>
<td>12</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Hepatic</td>
<td>30</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>ALT increase</td>
<td>18</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>AST increase</td>
<td>15</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Endocrine</td>
<td>30</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15</td>
<td>&lt; 1</td>
<td>9</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>7</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

PD-1/PD-L1 Inhibition: Managing Treatment-Related Adverse Events

**Any grade 1 AE**
- Isolated hypothyroidism
  - Initiate steroids or replacement therapy for hypothyroidism
  - **Continue PD-1 tx** and monitor

**Grade 2 pneumonitis, nephritis, colitis, hepatitis**
- Symptomatic hypophysitis
  - Any grade 3 AE
  - **Hold PD-1 tx** and administer steroids; After improvement to ≤ grade 1, taper steroids over at least 1 mo
  - **Resume if**: AE remains at grade 0/1 after steroid taper
  - **Discontinue if**: No improvement to ≤ grade 1 within 12 wks

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.
PD-1/PD-L1 Inhibition: Managing Treatment-Related Adverse Events

Grade 3/4 pneumonitis
Grade 3/4 nephritis
Grade 3/4 infusion-related reaction
Any life-threatening or grade 4 AE
Any severe or grade 3 recurrent AE

Hepatitis associated with
- AST/ALT > 5 x ULN
- AST/ALT ≥ 50% ↑ from baseline lasting ≥ 1 wk*
- Total bilirubin > 3 x ULN

*In pts with liver metastasis who begin treatment with grade 2 elevation of AST/ALT.

Initiate steroid therapy
Permanently discontinue PD-1 tx

Pembrolizumab adverse reaction management guide. Nivolumab adverse reaction management guide.
Patient Education on Novel Therapies

- Patient education should include information on:
  - Adverse reaction profiles that differs from standard chemotherapy
  - Early recognition of irAEs essential for effective treatment
  - irAEs are infrequent, treatable and respond well to steroids
  - Who and when to call for adverse reactions

- Evaluate pt and caregiver for continued educational needs related to the therapy and disease process

- Reinforce teaching points at every point of contact, office and treatment visits, and phone contact
Future Directions
## ORR by PD-L1 Expression in Pts With Solid Tumors

<table>
<thead>
<tr>
<th>Rx Antibody</th>
<th>Tumor type</th>
<th>N</th>
<th>PD-L1 + RR, n/N (%)</th>
<th>PD-L1 - RR, n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab[1]</td>
<td>Solid tumors</td>
<td>42</td>
<td>9/25 (36)</td>
<td>0/17 (0)</td>
</tr>
<tr>
<td>Nivolumab[2]</td>
<td>Solid tumors</td>
<td>38</td>
<td>7/16 (44)</td>
<td>3/18 (17)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>9/23 (39)</td>
<td>5/21 (24)</td>
</tr>
<tr>
<td>Pembrolizumab[5]</td>
<td>Melanoma</td>
<td>125</td>
<td>41/83 (49)</td>
<td>4/30 (13)</td>
</tr>
<tr>
<td>Ipi/Nivo[7]</td>
<td>Melanoma</td>
<td>56</td>
<td>8/14 (57)</td>
<td>17/42 (40)</td>
</tr>
</tbody>
</table>

OS Appears to Favor PD-L1+ Tumors Treated With Pembrolizumab*

*Based on tumor PD-L1 expression by IHC

Nivo Improved OS vs Dacarbazine Regardless of PD-L1 status

Issues With PD-L1 as a Biomarker

- PD-L1 negativity an unreliable biomarker in certain settings
  - Assays are technically difficult, imperfect; results may differ depending on the antibody/assay (tumor vs immune cells)
  - Expression cut-off, tumor heterogeneity, and inducible gene = sampling error (false negative)
  - Archived tissue different than recent biopsy
- May be more useful in determining which tumors rather than which pts to treat
- PD-L1 expression may be less relevant for combination therapies
- PD-L1 expression may be constitutive (no immune infiltrate)
A Roadmap of Immunotherapy-Tumor Interactions

1. Release of cancer cell antigens
   - Chemotherapy
   - Radiation therapy
   - Targeted therapy

2. Cancer antigen presentation
   - Vaccines
   - IFN-α
   - GM-CSF
   - Anti-CD40 (agonist)
   - TLR agonists

3. Priming and activation
   - Anti-CTLA4
   - Anti-CD137 (agonist)
   - Anti-OX40 (agonist)
   - Anti-CD27 (agonist)
   - IL-2
   - IL-12

4. Trafficking of T cells to tumors

5. Infiltration of T cells into tumors
   - Anti-VEGF

6. Recognition of cancer cells by T cells
   - CARs

7. Killing of cancer cells
   - Anti-PD-L1
   - Anti-PD-1
   - IDO inhibitors

Conclusions

- Immunotherapy for melanoma induces responses of long duration and results in prolonged OS
- Novel patterns of response with checkpoint protein inhibition require new types of response criteria that accommodate progression followed by regression
- Immune-related adverse events are a unique spectrum of adverse events with checkpoint protein inhibition that require learning new ways to manage toxicity
- The best is yet to come!
Thank You!
Go Online for More CCO Coverage of Cancer Immunotherapy!

**Capsule Summaries** of all the key data from recent conferences

**Additional CME-certified activities** on cancer immunotherapy with expert faculty commentary and discussion

clinicaloptions.com/oncology