Recent Advances in Cancer Immunotherapy

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Financial Disclosure and Resolution

Under guidelines established by the Accreditation Council for Pharmacy Education (ACPE), disclosure must be made regarding financial relationships with commercial interests within the last 12 months.

Patrick Medina, PharmD, BCOP, has no relevant financial relationships or affiliations with commercial interest to disclose.
Learning Objectives

At the completion of this activity, pharmacists will be able to:

- Summarize the recently approved indications for cancer immunotherapies.
- Explain the mechanism of action, efficacy, safety, and role of cancer immunotherapies for recent indications, as well as appropriate diagnostic testing.
- Identify strategies for pharmacists to improve patient access to cancer immunotherapies and provide appropriate supportive care.

Pre-Assessment Question 1

Which of the following best describes Durvalumab’s FDA approved indication?

A. Metastatic Prostate Cancer
B. Metastatic Urothelial Cancer
C. Metastatic Breast Cancer
D. Metastatic Lung Cancer
**Pre-Assessment Question 2**

KL is a 61-year-old woman with stage IV NSCLC (PD-L1 60%, **EGFR** and **alk** mutation negative). What FDA approved options is available to treat this patient?

A. Nivolumab  
B. Atezolizumab  
C. Pembrolizumab  
D. Ipilimumab

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**Pre-Assessment Question 3**

JM is a 67-year old male diagnosed with stage IV renal cell cancer.  
- Clear cell type  
- He was originally started on sunitinib monotherapy but progressed after 4 cycles  
- The decision was made to start nivolumab 240 mg every 2 weeks. He tolerated therapy well for the first 5 doses, but prior to his 6th dose, he complains of sudden onset severe diarrhea that is graded as grade 3.
Pre-Assessment Question 3 [Cont.]

Which of the following is correct regarding the management of this adverse effect?

A. Continue therapy and start oral prednisone 1 mg/kg daily
B. Continue therapy and start mycophenolate 500 mg PO every 12 hours
C. Hold therapy and start infliximab 5 mg/kg IV every 2 weeks
D. Hold therapy and start IV methylprednisolone 2 mg/kg daily
A New Paradigm in Cancer Treatment

• Chapter 1 – Cytotoxic Chemotherapy – Nonspecifically Killed Cells
  • Normal cells were more resistant and recovered faster from toxicity than tumor cells.
  • Derived from natural products
• Chapter 2 – Targeted Antitumor Agents
  • Determine molecular drivers stimulating cancer growth and block with signaling pathway
• Chapter 3 – Immunotherapy
  • Augment the immune system’s ability to kill cancer cells

Immune Surveillance

Targeting the Hallmarks of Cancer

**Immune Checkpoints**

- Cell surface receptors
  - Bind to ligand to modulate immune responses

- CTLA-4 and PD-1 are the best characterized, but many others exist

- CTLA-4 is thought to limit T-cell activity early in the immune response

- PD-1 is thought to reduce T-cell activity later, during the course of the immune response
  - PD-1 may also be important for the suppressive function of regulatory T cells

CTLA-4 and PD-1–PD-L1 Immune Checkpoints

- Programmed death ligand 1 (PD-L1) is a negative regulator of T-cell function by binding to its receptors, programmed death 1 (PD-1) or B7-1 on activated T lymphocytes and other immune cells.
- Expression of PD-L1 in the tumor microenvironment gives the tumor a mechanism to avoid destruction by the host immune system.
- Atezolizumab, Durvalumab, and Avelumab are antibodies to PD-L1.
  - Does not effect PD-L2 interaction with PD-1.


Immunogenicity of Tumors

AML = acute monocytic leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma

### Ipilimumab

- **MOA:** Monoclonal antibody that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands
- **Indications**
  - Unresectable or metastatic melanoma
    - 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses
    - In combination with nivolumab at the same dose
  - Adjuvant melanoma
    - 10 mg/kg administered intravenously over 90 minutes every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years or until documented disease recurrence or unacceptable toxicity
    - Locally or advanced or metastatic urothelial cancer, and adult and pediatric patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer
    - 1 mg/kg administered as an intravenous infusion over 30 minutes on the same day, every 3 weeks for 4 doses with nivolumab


### Nivolumab

- **MOA:** PD-1 Monoclonal Antibody
- **Indications**
  - Unresectable or metastatic melanoma or adjuvant melanoma
    - 240 mg every 2 weeks or 480 every 4 weeks
    - In combination with ipilimumab: dose is 1 mg/kg, followed by ipilimumab on the same day, every 3 weeks for 4 doses, then 240 mg every 2 weeks or 480 every 4 weeks
  - 2nd-Line or after progression for metastatic NSCLC or SCLC, advanced renal cell carcinoma, recurrent or metastatic squamous cell carcinoma of the head and neck, locally advanced or metastatic urothelial cancer, and adult and pediatric patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer, hepatocellular cancer.
    - 240 mg every 2 weeks or 480 every 4 weeks
  - Classical Hodgkin lymphoma (after progression)
    - 240 mg every 2 weeks or 480 every 4 weeks

Pembrolizumab

• MOA-PD-1 Monoclonal Antibody
• Indications
  • Unresectable or metastatic melanoma, 1st and 2nd line metastatic NSCLC (alone or
    with chemotherapy), recurrent or metastatic HNSCC, refractory classical Hodgkin
    lymphoma, locally or advanced urothelial carcinoma (including first line if cisplatin
    ineligible), microsatellite instability-high cancers, gastric, cervical, hepatocellular,
    merkel cell
  • 3rd line Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
    • 200 mg every 3 weeks for adults
  • PD-L1 testing required for single agent NSCLC, urothelial, gastric and cervical
    • Tumor Proportion Score (TPS) ≥50% for 1st line lung, Tumor Proportion Score (TPS)
      ≥1% for 2nd line lung, PD-L1 [Combined Positive Score (CPS) ≥10] for bladder and
      PD-L1 [Combined Positive Score (CPS) ≥1] for lung

NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell carcinoma; PD-1i = programmed death 1 inhibitor

Atezolizumab

• MOA-Monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1
  and B7.1 receptors
• Indications
  • 1st line (non-squamous) and recurrent metastatic NSCLC, locally advanced or
    metastatic urothelial carcinoma (including for cisplatin ineligible patients)
    • 1200 mg every 3 weeks
    • In combination with bevacizumab, paclitaxel, and carboplatin, for the first-line
      treatment, of patients with metastatic non-squamous NSCLC with no EGFR or
      ALK genomic tumor aberrations.
  • PD-L1 testing required for 1st line urothelial cisplatin ineligible (if not eligible for any
    platinum than not needed)
    • PD-L1 (PD-L1 stained tumor-infiltrating immune cells [IC] covering ≥ 5% of the
      tumor area), as determined by an FDA-approved test

**Durvalumab**

- MOA: Monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors
- Indications
  - Locally advanced or metastatic urothelial carcinoma
    - 10 mg/kg every 2 weeks
  - Unresectable, Stage III non-small cell lung cancer (NSCLC) whose disease has not progressed following concurrent platinum-based chemotherapy and radiation therapy
    - Same dose


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**Avelumab**

- MOA: Monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors
- Indications
  - Metastatic Merkel cell carcinoma (MCC) and locally advanced or metastatic urothelial carcinoma (UC) who have disease progression after platinum therapy
    - 800 mg every 2 weeks

Role of Immunotherapy in Melanoma

Ipilimumab (Yervoy)

• Mechanism of action
  • Human monoclonal antibody against CTLA-4
• FDA approved for treatment of melanoma

Improved Survival with Ipilimumab in Patients with Metastatic Melanoma

- Randomized, double-blind phase III study
- Patients with unresectable stage III or IV melanoma
- Previously treated
- ECOG performance status of 0 or 1
- HLA-A*0201 positive

**Randomize**

- Ipilimumab 3 mg/kg q3w x 4 + gp100 (n = 403)
- Ipilimumab 3 mg/kg q3w x 4 (n = 137)
- gp100 alone (n = 136)

**Primary Endpoint:** OS
**Secondary Endpoints:**
- Best overall response rate
- Duration of response
- Progression-free survival

ECOG = Eastern Cooperative Oncology Group; gp100 = glycoprotein 100; OS = overall survival; q3w = every 3 weeks.

Ipilimumab vs Nivolumab vs the Combination in Metastatic Melanoma

**Intention-to-Treat Population**

<table>
<thead>
<tr>
<th>Months</th>
<th>Nivolumab</th>
<th>Nivolumab plus ipilimumab</th>
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**Median PFS**

- Nivo = 6.9 months
- Ipi = 2.9 months
- Ipi plus Nivo = 11.5 months

**HR 0.42, P < 0.001**


Nivo = nivolumab; PFS = progression-free survival.
Ipilimumab vs Pembrolizumab in Metastatic Melanoma (Keynote-006)

![Survival Graph](image)

**One-year OS**
Pembro q2w = 74%
Pembro q3w = 68%
Ipilimumab = 58%

HR = 0.63, \(P = .0005\)
HR = 0.69, \(P = .0036\)


PD-1 and PD-L1 Inhibitors

**INACTIVATED T-CELL**

**ACTIVATED T-CELL**

PD-1: pembrolizumab, nivolumab
PD-L1: atezolizumab, avelumab, durvalumab

Nivolumab for First-line Treatment of Metastatic Melanoma (CheckMate 066)

- Patients with unresectable stage III or IV melanoma
- No BRAF mutation
- No prior treatment
- ECOG performance status of 0 or 1

Randomize

Nivolumab 3 mg/kg q2w \((n = 210)\)

Dacarbazine 1000 mg/m² q3w \((n = 208)\)

Primary Endpoint: OS
Secondary Endpoints: PFS, ORR, PD-L1 expression

CheckMate 066: Results

OS rate at 1 year
Nivolumab: 72.9%
Dacarbazine: 42.1%

Patients Surviving (%)

Patients Who Died

No. at Risk

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No. at Risk

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<th>Nivolumab</th>
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</thead>
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<td>Months</td>
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<tr>
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<td>44</td>
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<tr>
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</table>

OS rate at 1 year
Nivolumab: 72.9%
Dacarbazine: 42.1%
Ipilimumab (Ipi) vs Nivolumab (Nivo) vs the Combination in Metastatic Melanoma

Median PFS:
- Ipi = 2.9 mo
- Nivo = 6.9 mo
- Ipi plus Nivo = 11.5 mo; HR = 0.42, P < .001

A New Standard for First-line Metastatic Melanoma

- Dacarbazine approved 1975 (no placebo-controlled trials)
- Ipilimumab >dacarbazine
- Nivolumab >dacarbazine
- Pembrolizumab >ipilimumab
- Nivolumab >ipilimumab
- Nivolumab and ipilimumab >ipilimumab
- PD-1i +/- CTLA-4 inhibitor is best

CTLA-4 = cytotoxic T-lymphocyte-associated protein 4; PD-1i = programmed death 1 inhibitor.
Role of Immunotherapy in Non-Small Cell Lung Cancer (NSCLC)

Checkpoint Inhibitors for NSCLC

- PD-L1 + pembrolizumab
- Targeted therapy or chemotherapy
- Non-Squamous Pembrolizumab + Chemotherapy

Advanced NSCLC

After failing chemotherapy
- Nivolumab or
- Pembrolizumab or
- Atezolizumab

Essentially all lung cancer patients will get immunotherapy in the first or second line setting (except EGFR or ALK + patients)

NSCLC = non-small cell lung cancer.
KEYNOTE-024

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csősz, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O’Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators

### Results

**Overall Survival**

Additional results:
- Median PFS 10.3 months with pembrolizumab and 6.0 months with chemotherapy [HR 0.5 (95% CI 0.37–0.68); P<0.001]
- Response rate 44.8% with pembrolizumab and 27.8% with chemotherapy
- Time to response did not differ between groups


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### Trial Design and Treatment

**Randomized, open-label, phase II trial in the US and Taiwan**

First Line Tx:
- Non-squamous, non-small cell, advanced stage lung cancer
- Stratified for PD-L1 TPS (<1%)

Outcomes: ORR, PFS, OS

- Carboplatin/Pemetrexed/ Pembrolizumab
  - Q21d X 4 cycles
  - Maintenance:* Pembrolizumab N=60

- Carboplatin/Pemetrexed
  - Q21d X 4 cycles
  - Maintenance:* N=63

*Investigators could determine to can continue pemetrexed as maintenance after combination therapy – maximum duration of pembrolizumab = 24 mo.
Results

Patients on Chemotherapy offered pembrolizumab monotherapy upon progression

Lancet Oncol 2016; 17: 1497–508

Practice Changing/Implications?

- Therapy is now FDA approved for first-line with or without chemotherapy
- Category 1 listing by NCCN
- Increased in overall survival
  - Similar effect seen in squamous and nonsquamous histology
- Toxicity manageable and distinct from chemotherapy


Investigator-Assessed Progression-free Survival in the ABCP Group and the BCP Group.

A. Kaplan-Meier Estimates of Progression-Free Survival

B. Hazard Ratios for Disease Progression or Death in Molecular Subgroups

Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.

![Graph showing survival rates for ABCP and BCP groups]


### Second-line Check Point Inhibitors

<table>
<thead>
<tr>
<th>Drug (study)</th>
<th>Comparisons</th>
<th>PFS</th>
<th>Overall Survival</th>
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</thead>
<tbody>
<tr>
<td>Atezolizumab (OAK)</td>
<td>Atezolizumab 1200 mg IV q3week vs Docetaxel 75 mg/m² IV q3week</td>
<td>Median 2.8 months vs 4.1 months</td>
<td>Median 13.8 months vs 9.6 months ($P = 0.0003$)</td>
</tr>
<tr>
<td>Nivolumab (CheckMate 017) Squamous Histology</td>
<td>Nivolumab 3 mg/kg IV q2week vs Docetaxel 75 mg/m² IV q3week</td>
<td>Median 3.5 months vs 2.8 months</td>
<td>Median 9.2 months vs 6.0 months ($P &lt; 0.001$)</td>
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<tr>
<td>Nivolumab (CheckMate 057) Nonsquamous</td>
<td>Nivolumab 3 mg/kg IV q2week vs Docetaxel 75 mg/m² IV q3week</td>
<td>Median 2.3 months vs 4.2 months</td>
<td>Median 12.2 months vs 9.4 months ($P = 0.002$)</td>
</tr>
<tr>
<td>Pembrolizumab (KEYNOTE-010)</td>
<td>Pembrolizumab 2 mg/kg IV q3week vs Docetaxel 75 mg/m² IV q3week</td>
<td>Median 3.9 months vs 4 months</td>
<td>Median 10.4 months vs 8.5 months ($P = 0.0008$)</td>
</tr>
</tbody>
</table>

Continuation Therapy

- Patients with metastatic nonsquamous lung cancer
  - For patients with a stable disease or better response
    - Pembrolizumab + pemetrexed or atezolizumab ± bevacizumab
- Patients with unresectable stage III disease
  - For patients with SD or better response after 2 or more cycles of chemoradiation
    - Durvalumab for 1 year


Approval for Renal Cell Cancer
Second-line Renal Cell Comparing Nivolumab to Everolimus (CheckMate 025)

NOTE: 76% of patients had tumors with less than 1% PD-L1 expression.

CheckMate025 = Study of Nivolumab vs Everolimus in Pre-Treated Advanced or Metastatic Clear-cell RCC; NE = not estimable.

Approvals for Bladder Cancer

Muscle Invasive Bladder Cancer
### PD1 or PD-L1 inhibitors for Bladder CA

<table>
<thead>
<tr>
<th>Setting</th>
<th>Drug</th>
<th>Comparator</th>
<th>Primary Outcome</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Platinum</td>
<td>Atezolizumab</td>
<td>None</td>
<td>ORR = 24%</td>
<td>OS = 14.8 mo</td>
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<td>CR = 7%</td>
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<td>Pembrolizumab</td>
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<td>ORR = 29%</td>
<td>Duration of response NA</td>
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<tr>
<td>Contraindicated</td>
<td></td>
<td></td>
<td>CR = 7%</td>
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<tr>
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<td>Nivolumab</td>
<td>None</td>
<td>ORR = 20%</td>
<td>OS = 9 mo</td>
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<td></td>
<td></td>
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<td>CR = 2%</td>
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<td>Atezolizumab</td>
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<td>Chemotherapy</td>
<td>OS</td>
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<td>ORR 21% vs 11%</td>
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<td>Avelumab</td>
<td>None</td>
<td>ORR = 13%</td>
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<td>CR = 3%</td>
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### Recurrent or Metastatic Head and Neck Cancer

- Keynote-12 – SAT led to accelerated approval
- Keynote-40 should be complete soon (RCT vs chemo)

HPV = human papillomavirus; RCT = randomized controlled trial.


Nivolumab better than standard chemotherapy (CheckMate-141)
Recurrent Hodgkin’s Lymphoma

Nivolumab

ORR = 87% CR = 17%

All patients had failed standard therapy and second line treatment with transplant or brentuximab or both


ASCT = autologous stem-cell transplantation. ORR = Objective/Overall Response Rate CR = Complete Response Rate

Pembrolizumab

ORR = 69%, CR = 22%

MSI-H/dMMR across multiple solid tumors

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<th>Objective response rate</th>
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<tr>
<td></td>
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<tr>
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<td>Non-CRC</td>
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<td>3 (38%)</td>
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<td>Thyroid cancer</td>
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<td>Retropertitoneal adenocarcinoma</td>
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</tbody>
</table>

ORR = 40%, CR = 7% - Summary from 5 trials – All patients had 1+ prior regimens

Keytruda Prescribing Information 5-2017
## irRECIST

<table>
<thead>
<tr>
<th>RECIST</th>
<th>Unidimensional Measurement</th>
<th>irRECIST</th>
<th>Bidimensional Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>Disappearance of all lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>$\geq 30%$ decrease in tumor burden compared with baseline†</td>
<td>$\geq 50%$ decrease in tumor burden compared with baseline†</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>Not PR, CR, or PD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>$\geq 20%$ + 5-mm absolute increase in tumor burden compared with nadir</td>
<td>$\geq 25%$ increase in tumor burden compared with baseline, nadir, or reset baseline†</td>
<td>New lesions added to tumor burden†</td>
</tr>
</tbody>
</table>

† Confirmation Required – next scan $\geq 4$ weeks later

CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease


## PD-L1 Testing

- Do we really need to test for PD-L1 expression?
  - Clear that high expressers respond better
- Each drug has a different methodology for testing
- Currently we use testing per FDA labeling
  - Required for pembrolizumab and atezolizumab
Immunotherapy Introduces a New Era of Toxicity Management

Clinical Spectrum of irAEs

**irAEs Associated with Immune-checkpoint Blockade**

<table>
<thead>
<tr>
<th>Immune-mediated adverse reaction</th>
<th>Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colitis</td>
<td>Diarrhea, abdominal pain, blood in stool</td>
<td>Antidiarrheals followed by systemic corticosteroids if persistent; infliximab if refractory</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Dyspnea, cough</td>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>ALT/AST, bilirubin elevation</td>
<td>Systemic corticosteroids; mycophenolate mofetil if refractory</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Pruritic/macular/papular rash, Stevens-Johnson syndrome (rare), toxic epidermal necrolysis (rare)</td>
<td>Topical betamethasone or oral antihistamines; systemic corticosteroids if refractory</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Sensory/motor neuropathy, Guillain-Barre syndrome (rare), myasthenia gravis (rare)</td>
<td>Systemic corticosteroids</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>Hypo- or hyperthyroid, hypopituitarism, adrenal insufficiency, hypogonadism, Cushing’s syndrome (rare)</td>
<td>Systemic corticosteroids with appropriate hormone replacement (potentially long-term)</td>
</tr>
<tr>
<td>Other irAEs</td>
<td>Arthritis, nephritis, meningitis, pericarditis, uveitis, iritis, anemia, neutropenia</td>
<td>Organ system specific</td>
</tr>
</tbody>
</table>


**Kinetics of Appearance of Ipilimumab Immune-Related Adverse Events**

![Graph showing the kinetics of appearance of ipilimumab immune-related adverse events](image)

Immune-Mediated Endocrinopathies

- Hypophysitis
- Thyroid disorders
- Adrenal insufficiency
- Type 1 diabetes mellitus


Immunotherapy Toxicity Management

- Prevent
  - Identify risk factors
  - Inform patients and their health care team

- Anticipate
  - Baseline check-up
  - On and off treatment follow-up
  - Know the kinetics of adverse effects

- Monitor
  - Resolution
  - Relapse
  - Immunosuppression adverse effects

- Detect
  - Baseline values = reference values
  - Always ask patient

- Treat
  - Immunotherapy suspension
  - Steroids
  - Refer to specialist
  - Other immunosuppressive/hormonal drugs

Effect on Therapy

- Clinical response has been associated with the occurrence of irAEs
- Patients presenting with ipilimumab-related hypophysitis have been reported to have a median survival time of 19.4 months compared with a median survival time of 8.8 months for those not presenting with hypophysitis ($P < 0.05$)
  - All patients had anterior hypopituitarism (none had diabetes insipidus)
  - Hypopituitarism was persistent in most individuals (76%)
- Cutaneous toxicity (in particular, vitiligo) may also correlate to response
  - Meta-analysis of 27 studies in patients with melanoma treated with various immunotherapeutic agents; vitiligo was significantly associated with both progression-free survival (HR, 0.51; 95% CI, 0.32-0.82; $P < 0.005$) and overall survival (HR, 0.25; 95% CI, 0.10-0.61; $P < 0.003$).


ICER Evaluation

What is a fair price for PD-1 immunotherapies based on their value to patients and the health care system?

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost/QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atolizumab</td>
<td>$219,179/QALY</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>$415,950/QALY</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>$236,492/QALY</td>
</tr>
</tbody>
</table>

Note: These cost-effectiveness ratios are not directly comparable since the populations of patients (based on PD-L1 level) and the tests used to measure PD-L1 are different.


ICER’s value-based price benchmark is comprised of two components: a range associated with the prices needed to achieve long-term cost-effectiveness between $900,000-$1,500,000 per QALY and the price at which the potential short-term budget impact could be so substantial that policymakers should consider whether special coverage, pricing, or payment mechanisms are needed to assure sustainable access to high-value care for all patients.
ICER Evaluation

A LOOK AT NON-SMALL CELL LUNG CANCER TREATMENTS

What is a fair price for tyrosine kinase inhibitors (TKIs) based on their value to patients and the health care system?

Long-Term Cost-Effectiveness at List Price

$110,840 to $147,244/QALY

- Computer modeling of long-term clinical benefits and costs estimated gains in both quality of life and survival.
- Despite cost offsets associated with oral administration and lower rates of side effects, TKIs were associated with higher costs than platinum chemotherapy due primarily to higher drug costs.

The incremental cost-effectiveness ratio was measured by calculating the cost per additional quality-adjusted life year (QALY). Cost-effectiveness estimates were similar across the TKIs, ranging from $110,840 to $147,244 per QALY gained. The cost per QALY range that is generally accepted as “reasonable” value in the US is $50,000-$150,000, so the TKIs at list prices would represent reasonable value in the long-term.

ICER’s Value-Based Price Benchmark

Because we did not find adequate evidence to distinguish among the TKIs, we did not calculate a separate value-based price benchmark for each of the drugs.

To achieve a cost-effectiveness threshold of $100,000/QALY, TKIs would need to be discounted approximately 21%.

To meet a cost-effectiveness threshold of $150,000/QALY, each drug’s list price could be increased.

The average of these increases would represent an approximately 18% rise in price.

Conclusions

- Immunotherapies are indicated for a variety of solid and hematologic tumors as first and second line agents
- Immunotherapies lack the traditional profile of chemotherapy-related adverse effects
- However, a rare, but serious group of IRAEs has emerged
  - Though adverse effects are can be permanent, once under control, treatment is typically able to resume with no adverse effect on outcomes
  - Prompt management is the key to successful outcomes
Post-Assessment Question 1

Which of the following best describes Durvalumab’s FDA approved indication?

A. Metastatic Prostate Cancer
B. Metastatic Urothelial Cancer
C. Metastatic Breast Cancer
D. Metastatic Lung Cancer

Post-Assessment Question 2

KL is a 61-year-old woman with stage IV NSCLC (PD-L1 60%, EGFR and \( \text{alk} \) mutation negative). What FDA approved options is available to treat this patient?

A. Nivolumab
B. Atezolizumab
C. Pembrolizumab
D. Ipilimumab
Post-Assessment Question 3

JM is a 67-year old male diagnosed with stage IV renal cell cancer.

- Clear cell type
- He was originally started on sunitinib monotherapy but progressed after 4 cycles
- The decision was made to start nivolumab 240 mg every 2 weeks. He tolerated therapy well for the first 5 doses, but prior to his 6th dose, he complains of sudden onset severe diarrhea that is graded as grade 3.

Post-Assessment Question 3 [Cont.]

Which of the following is correct regarding the management of this adverse effect?

A. Continue therapy and start oral prednisone 1 mg/kg daily
B. Continue therapy and start mycophenolate 500 mg PO every 12 hours
C. Hold therapy and start infliximab 5 mg/kg IV every 2 weeks
D. Hold therapy and start IV methylprednisolone 2 mg/kg daily
Additional Resources

- ASCO (special article on irAE management)
  - ascopubs.org/doi/full/10.1200/JCO.2017.77.6385
- Institute for Clinical Immuno-Oncology
  - accc-iclio.org
- American Cancer Society
  - cancer.org/treatment/treatmentsandsideeffects/treatmenttypes/immunotherapy/index
- Research Cancer Immunotherapy
  - www.researchcancerimmunotherapy.com
- National Cancer Institute
  - cancer.gov/research/areas/treatment/immunotherapy-using-immune-system

Recent Advances in Cancer Immunotherapy

Patrick Medina, Pharm.D., BCOP
Director of Pharmacy, Stephenson Cancer Center