Cancer Immunotherapy: Exploring the Role of Novel Agents in Cancer Treatment

Patrick Medina, Pharm.D., BCOP
Professor
The University of Oklahoma College of Medicine
Stephenson Cancer Center

Faculty Disclosure

Patrick Medina, PharmD, BCOP, has served on the Advisory Board for Astra Zeneca
Learning Objectives

- Distinguish novel immunotherapy classes and individual agents based on their mechanism of action, efficacy and safety in cancer treatment

- Discuss the role of immunotherapy in cancer treatment as it relates to patient responses to therapy and challenges with treatment

The History of Immunotherapy

- Paul Erlich in the late 1800s described the term “Magic Bullet”

- The basic theory is related to the thought that tumor cells express an antigenic profile distinct from normal cells
  - Immune system is capable of recognizing these antigenic differences

- In addition, tumor cells turn off T-cells specific for tumor antigens
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

Hallmarks of Cancer

Targeting the Hallmarks of Cancer


Immune Surveillance

Evidence of Immune Surveillance

Types of Immunotherapy

- Monoclonal antibodies
  - Bevacizumab, rituximab, and many others
    - Direct tumor effects
    - Complement-dependent cytotoxicity (CDCC)
    - Antibody-dependent cellular cytotoxicity (ADCC)

- Cancer vaccines
  - BCG, Sipuleucel-T, HPV

- Non-specific immune boosters
  - Interleukin-2, interferon
  - Adoptive T-cell therapy (Chimeric antigen receptor [CAR] T-cell therapy)

- Immune checkpoint inhibitors
  - CTLA-4, PD-1, and PD-L1 monoclonal antibodies

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


Immunogenicity of Tumors

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


Recent Immunotherapy Approvals

- Dinutuximab for neuroblastoma
- Ramucirumab for colorectal cancer
- Ipilimumab + nivolumab for melanoma
- Talimogene for melanoma
- Daratumumab for myeloma
- Pembrolizumab for NSCLC
- Nivolumab for renal cell carcinoma
- Nivolumab for NSCLC
- Necitumumab for NSCLC
- Nivolumab for Hodgkin Lymphoma
- Atezolizumab for bladder cancer
- Pembrolizumab for head & neck cancer
- Pembrolizumab for NSCLC

Recent Immunotherapy Approvals

- Nivolumab for Head & Neck Cancer: November 2016
- Nivolumab for Urothelial Cancer: January 2017
- Pembrolizumab for Lymphoma: March 2017
- MORE TO COME!!!!

Role of Immunotherapy in Melanoma
Ipilimumab (Yervoy)

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

Ipilimumab

- Unresectable or metastatic melanoma
  - 3 mg/kg administered intravenously over 90 minutes every 3 weeks for a total of 4 doses
    - Unresectable or metastatic melanoma, 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


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

R A N D O M I Z E

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

Median OS ipilimumab + gp100: 10 months
Median OS gp100: 6.4 months
HR 0.68; P < .001

Median OS ipilimumab: 10.1 months
Median OS gp100: 6.4 months; HR 0.66; P = .003

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

EORTC 18071: Ipilimumab in the Adjuvant Melanoma Setting

Treatment option for:
- Resected stage IIIA with metastases > 1 mm
- Resected IIIB-C
- Resected nodal recurrence

Dose:
- 10 mg/kg every 3 weeks for 4 doses, followed by 10 mg/kg every 12 weeks for up to 3 years (or recurrence/toxicity)

Toxicity:
- 54% grade 3 or 4 (gastrointestinal, hepatic, endocrine most common)
- 1% fatal reactions
- Risk 3-fold higher than standard dose

---

Anti–PD-1: Mechanism of Action

Nivolumab (Opdivo)

- A human IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2

- FDA approved for:
  - Unresectable or metastatic melanoma, as a single agent
  - Unresectable or metastatic melanoma, in combination with ipilimumab
  - Metastatic NSCLC and progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have had disease progression on FDA-approved therapy for these aberrations prior to receiving nivolumab.
  - Advanced renal cell carcinoma patients who have received prior anti-angiogenic therapy
  - Classical Hodgkin lymphoma that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin.


FDA = US Food and Drug Administration; IgG4 = immunoglobulin G4; NSCLC = non-small cell lung cancer; PD-1 = programmed death receptor 1; PD-L1 = programmed death ligand 1; PD-L2 = programmed death ligand 2.


Nivolumab

- Unresectable or metastatic melanoma
  - 240 mg every 2 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

- Metastatic NSCLC
  - 240 mg every 2 weeks

- Advanced renal cell carcinoma
  - 240 mg every 2 weeks

- Classical Hodgkin lymphoma
  - 3 mg/kg every 2 weeks
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%
Ipilimumab vs Nivolumab vs the Combination in Metastatic Melanoma


Nivo = nivolumab.

Pembrolizumab (Keytruda)

• A humanized IgG4 monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2

• FDA approved for:
  • Unresectable or metastatic melanoma, as a single agent
  • Metastatic NSCLC patients whose tumors express PD-L1 as determined by an FDA-approved test and who have disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have had disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab.
  • Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy.
  • The dose is 2 mg/kg every 3 weeks for NSCLC and melanoma.
  • The dose is 200 mg every 3 weeks for HNSCC.

NSCLC = non-small cell lung cancer; HNSCC = head and neck squamous cell carcinoma; PD-1i = programmed death 1 inhibitor
Ipilimumab vs Pembrolizumab in Metastatic Melanoma (KEYNOTE-006)

One-year OS
Pembro q2w = 74%
Pembro q3w = 68%
Ipilimumab = 58%
HR = 0.63, \( P = .0005 \)
HR = 0.69, \( P = .0036 \)


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)

Nivolumab vs Docetaxel in NSCLC

- Primary endpoint
  - OS
- Secondary endpoints
  - ORR
  - PFS

Previously treated
PS 0–1
Stage IIIb/IV
Squamous NSCLC

1:1

Nivolumab 3 mg/kg IV q2w
n = 135

Docetaxel 75 mg/m² IV q3w
n = 137

OS = overall survival; ORR = objective response rate; PFS = progression free survival

Nivolumab in NSCLC

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 Csőszi, 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*


Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer (Keynote-024)

N=305, phase II portion

- PD-L1 tumor proportion score of 50% or greater required
- Histology (squamous vs. nonsquamous)
- ECOG PS (0 vs. 1)
- Region of enrollment

Randomize

ARM A: Investigator Choice
Chemotherapy for 4-6 cycles (n=151)
- Treat to specified cycles or progression, toxicity or patient withdrawal
- Patients in the chemotherapy arm could cross-over to pembrolizumab until disease progression
- Tumor evaluated every 9 weeks according to RECIST Criteria

ARM B: Pembrolizumab 200 mg every 3 weeks for 35 cycles (n=154)
- No ALK or EGFR sensitizing mutations

Results

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

Practice Changing/Implications?

- Therapy is now FDA approved
- Category 1 listing by NCCN\(^1\)
- Increased in PFS and OS
  - Similar effect seen in squamous and nonsquamous histology
- Toxicity manageable and distinct from chemotherapy
- Biomarker testing
  - What is the effect in patients with lower PD-L1 proportion scores?
  - CheckMate 026 with nivolumab did not demonstrate a PFS benefit\(^2\)
- Cost
  - AWP approximately $112,000 (with a median of 10.5 cycles given)

---
Nivolumab and pembrolizumab dosing

<table>
<thead>
<tr>
<th>NIVOLUMAB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Head and neck cancer</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>3 mg/kg</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 mg/kg in combination with ipilimumab 240mg flat dose as single agent</td>
</tr>
<tr>
<td>NSCLC</td>
<td>240mg flat dose</td>
</tr>
<tr>
<td>RCC</td>
<td>240mg flat dose</td>
</tr>
<tr>
<td>Urothelial carcinoma</td>
<td>240mg flat dose</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PEMBROLIZUMAB</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>2 mg/kg</td>
</tr>
<tr>
<td>NSCLC</td>
<td>200mg flat dose</td>
</tr>
<tr>
<td>Head and neck cancer</td>
<td>200mg flat dose</td>
</tr>
</tbody>
</table>

Atezolizumab

- Mechanism: Atezolizumab is a humanized monoclonal antibody that binds to PD-L1 and blocks its interactions with both PD-1 and B7.1 receptors. This releases the PD-L1/PD-1 mediated inhibition of the immune response, including activation of the anti-tumor immune response without inducing antibody dependent cellular cytotoxicity.
- Indications
  - Metastatic NSCLC after platinum-containing therapy
  - Locally advanced or metastatic urothelial carcinoma after platinum-containing therapy or who have disease progression within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy
PD-1 and PD-L1 blockade

- 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 is a humanized IgG1 antibody to PD-L1
  - Does not affect PD-L2 interaction with PD-1

Challenges with Immunotherapy

- Testing for PD-L1?
- Pseudoprogression
- Toxicity management
- Cost
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

KEYNOTE-010: Prognostic or Useful to Select Therapy?

Prognostic or Useful to Select Therapy?

<table>
<thead>
<tr>
<th>Sex</th>
<th>Patients (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>189/399</td>
<td>0.69 (0.51–0.94)</td>
</tr>
<tr>
<td>Female</td>
<td>322/634</td>
<td>0.65 (0.52–0.81)</td>
</tr>
</tbody>
</table>

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group.


Nivolumab in PD-L1–Negative Patients

CI = confidence interval; ECOG = Eastern Cooperative Oncology Group.

The Challenges: Pseudoproggression

Patterns of Response to Ipilimumab Observed in Advanced Melanoma

SPD = sum of the product of perpendicular diameters

### Immune-Related Response Criteria (irRC)

<table>
<thead>
<tr>
<th></th>
<th>WHO</th>
<th>irRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong></td>
<td>Disappearance of all lesions not less than 4 weeks apart</td>
<td>Disappearance of all lesions not less than 4 weeks apart</td>
</tr>
<tr>
<td><strong>PR</strong></td>
<td>≥ 50% decrease in SPD of all index lesions compared with baseline in 2 observations</td>
<td>≥ 50% decrease in SPD of all index lesions compared with baseline in 2 observations</td>
</tr>
<tr>
<td><strong>SD</strong></td>
<td>Not PR, CR, or PD</td>
<td>Not PR, CR, or PD</td>
</tr>
<tr>
<td><strong>PD</strong></td>
<td>At least 25% increase in SPD compared with nadir and/or unequivocal progression of non-index lesions and/or appearance of new lesions (at any single time point)</td>
<td>At least 25% increase in tumor burden compared with nadir in 2 consecutive observations at least 4 weeks apart</td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td>Always represent PD</td>
<td>Incorporated into tumor burden if possible</td>
</tr>
</tbody>
</table>

PD = progressive disease; SD = stable disease; SPD = sum of the product of perpendicular diameters; WHO = World Health Organization.


---

### Immunotherapy Introduces a New Era of Toxicity Management

Immune-related adverse events (irAEs)
Ipilimumab: Safety

- The most common adverse reactions (≥ 5%) in patients who received 10 mg/kg were:
  - Rash (50%)
  - Diarrhea (49%)
  - Fatigue (46%)
  - Pruritus (45%)
  - Headache (33%)
  - Weight loss (32%)
  - Nausea (25%)
  - Pyrexia (18%)
  - Colitis (16%)
  - Decreased appetite (14%)
  - Vomiting (13%)
  - Insomnia (10%)

- The most common adverse reactions (≥ 5%) in patients who received 3 mg/kg were:
  - Fatigue (41%)
  - Diarrhea (32%)
  - Pruritus (31%)
  - Rash (29%)
  - Colitis (8%)

<table>
<thead>
<tr>
<th>Immune-Mediated Adverse Reactions (n = 131)</th>
<th>Grade 3–5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any immune reaction</td>
<td>15</td>
</tr>
<tr>
<td>Enterocolitis</td>
<td>7</td>
</tr>
<tr>
<td>Hypo/hyperthyroidism</td>
<td>4</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>2</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>1</td>
</tr>
<tr>
<td>Nephritis</td>
<td>1</td>
</tr>
</tbody>
</table>
PD-1 Blockade with Nivolumab: Toxicities

- Early respiratory symptoms can be fatal pneumonitis
- Renal insufficiency can also occur rarely
- Endocrinopathies and enterocolitis are more characteristic of ipilimumab but may occur in patients receiving a PD-1–blocking drug


Anti-PD-1–Related Adverse Event, n (%)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any select event</td>
<td>54 (58)</td>
<td>5 (5)</td>
</tr>
<tr>
<td>Skin</td>
<td>36 (38)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>18 (19)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Endocrinopathies</td>
<td>13 (14)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>7 (7)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>6 (6)</td>
<td>—</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>4 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Renal</td>
<td>2 (2)</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>


Nivolumab Toxicity Over Time

- Early respiratory symptoms can be fatal pneumonitis
- Renal insufficiency can also occur rarely
- Endocrinopathies and enterocolitis are more characteristic of ipilimumab but may occur in patients receiving a PD-1–blocking drug


Overall 17% had grade 3 to 4 toxicities.

GI = gastrointestinal; Inf. = infusion; P-Y = person-year.

## 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>

*Please consult current package insert for individual products


---

## Pharmacy Management of Immunotherapy Toxicity

**Prevent**
- Know the immune-toxicity spectrum
- Identify high-risk patients
- Informed patients and their healthcare providers

**Monitor**
- Recognize treatment-related toxicities
- Monitor for symptoms

**Anticipate**
- Baseline check-up
- On-treatment follow-up
- Off-treatment follow-up

**Treat**
- Symptomatic treatment
- Patient information
- Discuss:
  - Immune-related toxicity?
  - Symptom control?
  - Reconsider immunotherapy?
  - Other immunosuppressive drugs?

**Detect**
- Baseline values = reference values
- Always consider dosedose interconnectivity

Champiat S. Ann Oncol. 2016;27:559-574. For educational purposes only.
**Tumor Immunotherapy: Tips**

### Counseling
- Diarrhea
- Shortness of breath, chest pain, cough
- Weight gain/loss, muscle aches, abdominal pain
- Headaches, weakness, vision changes
- Decreased urine output
- Skin changes

### Monitoring
- Liver function tests, serum creatinine, thyroid function
- Signs/symptoms of immune-mediated adverse reaction (pneumonitis, colitis, etc.)

### Treatment
- Corticosteroid until improvement to grade 1 or less and then taper over 1 month

---

**Patient ID Card**

Name, Family name:

Immunotherapy drug(s):

- Pneumonitis (inflammation of the lungs)
- Colitis (inflammation of the gut)
- Hepatitis (inflammation of the liver)
- Nephritis (inflammation of the kidneys)
- Endocrinopathy: hypophysitis, thyroid dysfunction, diabetes, adrenal insufficiency
- Cutaneous rash (inflammation of the skin)

As well as other immune-related adverse events: neurological, hematological, ophthalmological...

The management of these dysimmune adverse events is specific and sometimes urgent. It absolutely requires coordination with the health care team that has prescribed the treatment:

Prescriber ID and contact information (reported on the back of this card)

---

Barriers to Care: Cost

- Ipilimumab $158,282
- Nivolumab $103,220
- Pembrolizumab $14,500/month at lower dose (up to 1 million per year if higher doses used)
- Combination of ipilimumab + nivolumab $295,566
  - Patient with a 20% co-pay = $60,000 out of their own pocket
- All companies have patient support programs that should be routinely used.