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

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Faculty Disclosure

Emily Borders, PharmD, M.S., BCOP, has no relevant financial relationships to disclose.
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

• Discuss strategies for monitoring and treating immune-related toxicities
Inside the brutally selective, hugely expensive, lifesaving trials of immunotherapy.

By Alice Park
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

Evidence of Immune Surveillance

Figure 14-10 Immunobiology, 6/e. (© Garland Science 2005)
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

Immune Checkpoints

Immunogenicity of Tumors

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

Recent Immunotherapy Approvals

- Dinutuximab for neuroblastoma (March 2015)
- Ramucirumab for colorectal cancer (April 2015)
- Ipilimumab + nivolumab for melanoma (September 2015)
- Pembrolizumab for NSCLC (October 2015)
- Nivolumab for NSCLC (November 2015)
- Talimogene for melanoma (May 2016)
- Daratumumab for myeloma (August 2016)
- Necitumumab for NSCLC (October 2016)
- Elotuzumab for myeloma (November 2015)
- Atezolizumab for urothelial cancer (August 2016)
- Pembrolizumab for head & neck cancer (October 2016)
- Pembrolizumab and Atezolizumab for NSCLC (October 2016)
Recent Immunotherapy Approvals

Nivolumab for head & neck Cancer
November 2016

Nivolumab for urothelial Cancer
February 2017

Avelumab for Merkel cell Cancer
March 2017

Pembrolizumab for Lymphoma

Pembrolizumab for MSI-H or dMMR solid tumors and urothelial cancer
May 2017

Avelumab for urothelial cancer

Durvalumab for bladder cancer
August 2017

Nivolumab for MSI-H or dMMR colorectal cancer

Avelumab for urothelial cancer

MORE TO COME!!!!
Role of Immunotherapy in Melanoma
Ipilimumumab (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

**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.

Improved Survival with Ipilimumab

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

PD-1 and PD-L1 Inhibitors

INACTIVATED T-CELL

ACTIVATED T-CELL

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

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
  - Recurrent or metastatic squamous cell head and neck cancer following platinum based therapy
  - 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
  - Locally advanced or metastatic urothelial carcinoma following platinum based therapy
  - Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan


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 Dosing

• 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

• NSCLC, renal cell, urothelial, colorectal
  • 240 mg every 2 weeks

• Hodgkin lymphoma and head and neck
  • 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

ORR = objective response rate; q2w = every 2 weeks

CheckMate 066: Results

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

Ipilimumab vs Nivolumab 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

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 (200 mg/kg every 3 weeks):
  • Unresectable or metastatic melanoma, as a single agent
  • Metastatic NSCLC whose tumors have high PD-L1 expression as determined by an FDA-approved test, with no EGFR or ALK genomic tumor aberrations
  • Metastatic NSCLC whose tumors express PD-L1 as determined by an FDA-approved test, with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab
  • In combination with pemetrexed and carboplatin, as first-line treatment of patients with metastatic nonsquamous NSCLC
  • Recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) with disease progression on or after platinum-containing chemotherapy
  • Refractory or relapsed Classical Hodgkin’s lymphoma
  • Locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin or have disease progression following platinum therapy
  • Unresectable or metastatic, microsatellite instability high (MSIH) or mismatch repair deficient solid tumors with no other alternatives or progressed colorectal

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
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

**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)

Stratification
- Histology (squamous vs. nonsquamous)
- ECOG PS (0 vs. 1)
- Region of enrollment

No ALK or EGFR sensitizing mutations

- PD-L1 tumor proportion score of 50% or greater required

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 NCCN¹

• Increased in overall survival
  • Similar effect seen in squamous and nonsquamous histology

• Toxicity manageable and distinct from chemotherapy

¹NCCN Guidelines—NCCN v.1.2017. Available at:
## Nivolumab Data Summary

<table>
<thead>
<tr>
<th>Indication</th>
<th>Study</th>
<th>Comparator</th>
<th>Primary Objective Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Small Cell Lung</td>
<td>CHECKMATE-017 (squamous)</td>
<td>vs. docetaxel</td>
<td>OS: 9.2 mo vs 6.0 mo (p-val=0.0002)</td>
</tr>
<tr>
<td></td>
<td>CHECKMATE-057 (non-squamous)</td>
<td>vs. docetaxel</td>
<td>OS: 12.2 mo vs 9.4 mo (p-val=0.0015)</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>CHECKMATE-037 (previously treated)</td>
<td>vs. dacarbazine or carboplatin/paclitaxel</td>
<td>ORR: 32%</td>
</tr>
<tr>
<td></td>
<td>CHECKMATE-066 (untreated)</td>
<td>vs. dacarbazine</td>
<td>Not reached vs 10.8 mo (p-val &lt;0.0001)</td>
</tr>
<tr>
<td></td>
<td>CHECKMATE-067 (untreated)</td>
<td>vs. ipilimumab or nivolumab/ipilimumab</td>
<td>PFS: 11.5 mo vs 6.9 mo vs 2.9 mo (p-val &lt;0.0001)</td>
</tr>
<tr>
<td>Renal Cell</td>
<td>CHECKMATE-025</td>
<td>vs. everolimus</td>
<td>OS: 25 mo vs. 19.6 mo (p-val=0.0018)</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>CHECKMATE-141</td>
<td>vs. SOC</td>
<td>OS: 7.5 mo vs 5.1 mo (p-val=0.0101)</td>
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<tr>
<td>Hodgkin Lymphoma</td>
<td>CHECKMATE-205</td>
<td>Single arm</td>
<td>ORR: 66%</td>
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<tr>
<td></td>
<td>CHECKMATE-039</td>
<td>Dose-escalation</td>
<td></td>
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<tr>
<td>Urothelial Carcinoma</td>
<td>CHECKMATE-275</td>
<td>Single arm</td>
<td>ORR: 20%</td>
</tr>
<tr>
<td>MSI-H or dMMR Colorectal</td>
<td>CHECKMATE-142</td>
<td>Single arm</td>
<td>ORR: 32%</td>
</tr>
<tr>
<td>Indication</td>
<td>Study</td>
<td>Comparator</td>
<td>Primary Objective Results</td>
</tr>
<tr>
<td>-------------------------</td>
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<td>---------------------------------------------------</td>
<td>---------------------------------------------------------------------</td>
</tr>
<tr>
<td>Non-Small Cell Lung</td>
<td>KEYNOTE-024 (untreated)</td>
<td>vs. investigator’s choice</td>
<td>PFS: 10.3 mo vs 6.0 mo (p-val&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td>KEYNOTE-021 (combination with pemetrexed/carboplatin)</td>
<td>vs. pemetrexed/carboplatin</td>
<td>ORR: 55% vs 29% (p-val=0.0032)</td>
</tr>
<tr>
<td></td>
<td>KEYNOTE-010 (previously treated)</td>
<td>vs. docetaxel</td>
<td>OS: 14.9 vs 8.2 mo (p-val&lt;0.001)</td>
</tr>
<tr>
<td>Metastatic Melanoma</td>
<td>KEYNOTE-006 (ipilimumab naive)</td>
<td>vs. ipilimumab</td>
<td>OS: Hazard ratio 0.69 (p=0.004)</td>
</tr>
<tr>
<td></td>
<td>KEYNOTE-002 (ipilimumab refractory)</td>
<td>vs. investigator’s choice</td>
<td>PFS: 2.9 mo vs 2.7 mo (p-val &lt;0.0001)</td>
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<tr>
<td>Head and Neck</td>
<td>KEYNOTE-012</td>
<td>Dose variation</td>
<td>ORR: 16%</td>
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<tr>
<td>Hodgkin Lymphoma</td>
<td>KEYNOTE-012</td>
<td>Single arm</td>
<td>ORR: 69%</td>
</tr>
<tr>
<td>Urothelial Carcinoma</td>
<td>KEYNOTE-052, KEYNOTE-045</td>
<td>Single arm vs. Chemo</td>
<td>ORR: 29% OS: 10.3 vs 7.4 mo (p-val=0.004)</td>
</tr>
<tr>
<td>MSI-H or dMMR Colorectal</td>
<td>KEYNOTE-016, -164, -012, -028, -158</td>
<td></td>
<td>ORR: 39.6%</td>
</tr>
</tbody>
</table>
Challenges with Immunotherapy

- Testing for PD-L1?
- Pseudoprogression
- Toxicity management
- Cost
KEYNOTE-010: Prognostic or Useful to Select Therapy?

Prognostic or Useful to Select Therapy?

<table>
<thead>
<tr>
<th>Overall Survival</th>
<th>Events/patients (n)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>332/634</td>
<td>0.65 (0.52-0.81)</td>
</tr>
<tr>
<td>Female</td>
<td>189/399</td>
<td>0.63 (0.51-0.94)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>317/504</td>
<td>0.63 (0.50-0.75)</td>
</tr>
<tr>
<td>≥65</td>
<td>204/479</td>
<td>0.76 (0.57-1.02)</td>
</tr>
<tr>
<td><strong>ECOG performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>149/348</td>
<td>0.73 (0.52-1.02)</td>
</tr>
<tr>
<td>1</td>
<td>267/578</td>
<td>0.63 (0.51-0.78)</td>
</tr>
<tr>
<td><strong>PD-L1 tumour proportion score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50%</td>
<td>204/442</td>
<td>0.53 (0.40-0.70)</td>
</tr>
<tr>
<td>1-49%</td>
<td>317/591</td>
<td>0.76 (0.59-0.96)</td>
</tr>
<tr>
<td><strong>Tumour sample</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Archival</td>
<td>266/455</td>
<td>0.70 (0.54-0.89)</td>
</tr>
<tr>
<td>New</td>
<td>255/578</td>
<td>0.64 (0.50-0.83)</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous</td>
<td>128/222</td>
<td>0.74 (0.50-1.09)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>332/708</td>
<td>0.63 (0.50-0.79)</td>
</tr>
<tr>
<td><strong>EGFR status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutant</td>
<td>46/86</td>
<td>0.88 (0.45-1.70)</td>
</tr>
<tr>
<td>Wild-type</td>
<td>447/875</td>
<td>0.66 (0.55-0.82)</td>
</tr>
<tr>
<td>Overall</td>
<td>521/1033</td>
<td>0.67 (0.56-0.80)</td>
</tr>
</tbody>
</table>

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

Nivolumab in PD-L1–Negative Patients

HR = hazard ratio.

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
  - Nivolumab: not required
  - Pembrolizumab – Test in Lung Only:
    - 1st line single agent: ≥ 50%
    - 1st line combination with carboplatin and pemetrexed: Not required
    - 2nd line or greater: ≥ 1%
The Challenges: Pseudoprogression
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><strong>At least 25% increase in tumor burden compared with nadir in 2 consecutive observations at least 4 weeks apart</strong></td>
</tr>
<tr>
<td><strong>New lesions</strong></td>
<td>Always represent PD</td>
<td><strong>Incorporated into tumor burden if possible</strong></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)
<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

Kinetics of Appearance of Ipilimumab Immune-Related Adverse Events

Nivolumab Toxicity Over Time

Overall 17% had grade 3 to 4 toxicities.

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

# Tumor Immunotherapy: Tips

<table>
<thead>
<tr>
<th>Counseling</th>
<th>Monitoring</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| • Diarrhea  
• Shortness of breath, chest pain, cough  
• Weight gain/loss, muscle aches, abdominal pain  
• Headaches, weakness, vision changes  
• Decreased urine output  
• Skin changes | • Liver function tests, serum creatinine, thyroid function  
• Signs/symptoms of immune-mediated adverse reaction (pneumonitis, colitis, etc.) | • In general: Corticosteroid until improvement to grade 1 or less and then taper over 1 month |
Dermatitis*

Baseline: Emollients ± skin moisturizers

**Signs/symptoms:**
- Rash < 30% of the body surface
- Dry skin
- Pruritus (localized)
- Vitiligo

**Grade 1**
- Moisturizers
- Topical steroids
- Monitor
- Continue therapy

**Grade 2**
- Topical steroids
- Antihistamines
- Persistent symptoms > 1-2 weeks
  - Start oral prednisone 1 mg/kg/day
- Dermatology consult
- Restart when grade 1 or less

**Grade 3 or 4**
- Systemic steroids (taper over 4 weeks after symptoms resolve)
- May need hospitalization
- Dermatology consult
- Discontinue therapy (may consider restarting if grade 3 and resolution of symptoms)

*Please consult current package insert for individual products

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Enterocolitis/ Pneumonitis/ Neuropathies*

- Grade 1: Monitor and continue therapy

- Grade 2: Monitor and continue therapy when ≤ grade 1
  - Symptoms persist, start prednisone 1mg/kg/day with a 4 week taper and continue therapy when ≤ grade 1
    - If symptoms persist or relapse on taper start IV steroids

- Grade 3/4
  - IV methylprednisolone 2 mg/kg and discontinue therapy (GI consult and hospitalization recommended)
  - Consider infliximab 5 mg/kg IV every 2 weeks if symptoms persist

*Please consult current package insert for individual products

Hepatitis*

- **Grade 1** - AST or ALT <1-2.5 X the upper limit of normal (ULN), or total bilirubin 1-1.5 X the ULN
  - Monitor and continue therapy

- **Grade 2** - AST or ALT >2.5-5 X the ULN, or total bilirubin >1.5-3 X the ULN
  - Monitor and continue therapy when ≤ grade 1
  - Symptoms persist, start prednisone 1mg/kg/day with a 4 week taper and continue therapy when ≤ grade 1
    - If symptoms persist or relapse on taper start IV steroids

- **Grade 3/4** - AST or ALT >5 X the ULN, or total bilirubin >3 times the ULN
  - IV methylprednisolone 2 mg/kg and discontinue (consider hepatology consult and hospitalization recommended)
  - Consider if symptoms persist mycophenolate 500 mg PO every 12 hours

*Please consult current package insert for individual products

Patient ID Card

Name, Family name:
Immunotherapy drug(s):
I am currently receiving an immunotherapy, which may increase the risk of occurrence of autoimmune diseases and in particular:

- 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 (inflammation of the hormone-producing organs)
- 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.

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

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