Strategies to Address Immune-Related Adverse Events

Jeffrey Weber, MD, PhD
Laura and Isaac Perlmutter Cancer Center
NYU Langone Medical Center
New York, New York
Checkpoint Inhibitor Treatment and Immune-Related Adverse Events (irAEs)

- Blockade of CTLA-4 and PD-1/PD-L1 can lead to the development of irAEs
- Treatment results in loss of tolerance to self-antigens by T cells
- Preclinical melanoma tumor models utilizing CTLA-4 knockouts have demonstrated enhanced immune-mediated tumor rejection AND immune-related depigmentation, but not irAEs as seen in patients; PD-1 knockouts do develop autoimmunity
- Common irAEs in pts treated with checkpoint inhibitors include
  - Dermatitis
  - Enterocolitis
  - Hepatitis
  - Endocrinopathies
- Toxicity does not equal response, but there does appear to be a weak association with IPI, stronger association with PD-1

Checkpoint Inhibitor Treatment and irAEs: Basic Issues

• Most irAEs occur during the first 12 weeks of checkpoint inhibitor therapy, ie, during induction
• Steroids can be used to manage almost all irAEs
• Prolonged steroid tapers are required
• irAEs can wax and wane, particularly colitis
• Late irAEs can occur: one episode has been seen at month 47 during maintenance
• Each irAE has different kinetics of onset:
  – Skin first, then colitis, then hypophysitis, and finally hepatitis

Immune-Related Adverse Events With Checkpoint Protein Inhibition

- Infections and other etiologies should be ruled out or deemed unlikely as contributing to the irAE
- 4 main categories: GI, liver, endocrine, skin
- At 3 mg/kg PD-1 dose level in melanoma:
  - High-grade (grades 3/4) irAE rate is 8%-10%
- At 3 mg/kg IPI dose level in melanoma:
  - High-grade (grades 3/4) irAE rate is ~14%
- At 10 mg/kg dose level in melanoma
  - High-grade (grades 3/4) irAE rate is ~25%
Kinetics of Induction of irAEs With Ipilimumab

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.

Kinetics of Onset and Resolution of Select Treatment-Related AEs With Nivolumab Any Grade

The beginning and end of each curve represent the median time to onset and median time to resolution, respectively. Each peak reflects incidence of the AE.
Immune-Related Adverse Events With Checkpoint Inhibition

- Unique potential side effect profile first observed with ipilimumab
- While frequent, primarily low grade
- Most cases of grade 3 or 4 easily managed with steroids: suggestions/algorithms/communication
- Treatment with steroids or infliximab does not significantly compromise antitumor activity
Colitis and Enteritis With Checkpoint Inhibition

- Diarrhea is a common irAE (37% all grade and 12% grades 3/4) with IPI; less common with PD-1 blockade
- Colonoscopy or sigmoidoscopy shows diffusely erythematous, friable, and occasionally ulcerated mucosa
- Colon biopsy usually demonstrates inflammatory colitis with CD4>CD8 infiltrate in interstitium
- Most cases respond to symptomatic treatment or high-dose steroids with a long taper (over a month)
- Infliximab is used in steroid-refractory cases
- Can rarely lead to gastrointestinal perforation (1%), profound ileus, or megacolon requiring surgery
Dermatitis With Checkpoint Inhibition

- Low-grade rashes common
  - Reticular erythema
  - Papules to plaques
- Photos to document and follow
- Dermatology, biopsy
- Symptomatic treatment (eg, antihistamines)
- Topical or oral steroids if more severe symptoms
- Rare toxic epidermal necrosis
- Skin side effects with PD-1 blockade associated with response and survival

Hepatitis With Checkpoint Inhibition

• Liver function tests (LFTs) must be assessed prior to administration of each dose of ipilimumab or PD-1/PD-L1 drugs

• LFT elevations in patients may be associated with symptoms of hepatotoxicity (jaundice, right upper quadrant pain, vomiting) or may be completely asymptomatic; many patients have other nonspecific symptoms (fever, malaise)

• Often elevated LFTs are of long duration

• All subjects must meet LFT criteria before each dose of ipilimumab
  – With no liver mets <2.5 x ULN for AST, ALT
  – Liver mets; <5 x ULN for AST, ALT, <2.5 x ULN for total bilirubin
Endocrinopathies With Checkpoint Inhibition

• Relatively infrequent (6% all grades) with IPI or PD-1/PD-L1

• Symptoms:
  – headache, fatigue, weakness, memory loss, impotence, personality changes, and visual-field impairment\(^1-^3\); headache can be severe

• Observed so far:
  – panhypopituitarism, hypothyroidism, hyperthyroidism
  – pancreatitis, adrenal insufficiency

• Management\(^1-^3\)
  – discontinue ipilimumab, work-up including labs and brain MRI, temporary corticosteroid administration with a brief taper over 10-20 days
  – replace deficient hormones
  – symptoms resolve with treatment\(^1-^3\)
  – slow return of some endocrine function\(^1,^2\)

Neurologic irAEs With Checkpoint Inhibition

• Relatively infrequent (<1% all grades) with IPI or PD-1

• Symptoms:
  – Numbness, tingling, foot drop, and localized muscle weakness, or generalized ascending motor and diaphragmatic weakness

• Observed so far:
  – Myasthenia gravis (MG)-like syndrome; Guillain-Barré syndrome
  – Peripheral neuropathy
  – Encephalitis

• Management: get a neurologic consult!
  – for grade 2 or more, discontinue antibodies, work-up including labs and brain MRI, high-dose corticosteroid administration with a prolonged taper, neurology consultation, EMG if appropriate
  – Hospitalize if MG-like syndrome
  – Consider rapidly moving to IVIG and infliximab if grades 3-4 and without resolution of symptoms within 24-48 hours

EMG, electromyography; IVIG, intravenous immunoglobulin
Management of Pneumonitis With PD-1 Antibodies

• Relatively rare: 0.5% to 1.5% of patients at grades 2-3
• Very uncommon with PD-L1 antibodies
• We routinely check pulse oximetry in all PD-1/PD-1/IPI patients
• Get a chest X-ray in anyone on PD-1 ab with SOB, chronic cough, increased sputum, and have a low threshold for obtaining a CT of the chest
• High dose steroids with at least 45-60 day tapers with starting doses of at least 1-2 mg/kg are required
• CT findings will lag behind the patient’s symptoms
• Steroids may need to be re-tapered if symptoms return
• Use infliximab at 5 mg/kg if without relief in one week

ab, antibody; SOB, shortness of breath
Other irAEs With Checkpoint Inhibition

• Pancreatitis
  – Amylase/lipase elevation, abdominal pain low, and out of proportion to elevation of lab tests

• Uveitis
  – Redness, change in vision; ophtho evaluation
  – Topical corticosteroid eye drops

• Nephritis (rare)
  – CT scans show stranding = inflammation
  – Consider steroids if Cr > 2.0

• Arthritis
  – Late manifestation with chronic PD-1/PD-L1
  – Often exacerbation of pre-existing arthritis

CT, computed tomography; Cr, creatinine
PD-1 Antibody-Induced irAEs

- Similar spectrum of adverse events as with IPI, but rate of grades 3-4 irAEs only about 5-6%
- Pneumonitis that is symptomatic is more common with PD-1 antibodies at 1-2%
- Grades 3-4 colitis are rare, at 1%
- Thyroiditis is more common, but hypophysitis is present at about the same rate at 1-2%
- Colitis, when present, has the same, often prolonged course as with ipilimumab
- Chronic arthritis can occur with prolonged PD-1
Difference Between IPI and NIVO/PEMBRO irAEs

- The spectrum of side effects is similar
- Thyroiditis is slightly more common with PD-1 antibodies
- Hypophysitis is similar in frequency
- Infusion reactions are also slightly more common
- Pneumonitis is more common with PD-1 antibodies
- Colitis is much less common, 1% at grades 3-4 for PD-1 antibodies vs 7% with IPI alone
- The rare toxicities are similar in incidence
- Chronic arthritis is seen with PD-1 antibodies, rare with IPI
- PD-1 antibodies are much less toxic than IPI
- IPI + NIVO: more rapid onset, longer duration, slower resolution, more hepatitis, more multiple irAEs are seen
## Treatment-Related Select AEs Reported in ≥10% of Patients: IPI + NIVO vs IPI vs NIVO

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI n = 313</th>
<th>NIVO n = 313</th>
<th>IPI n = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
<td>Any Grade</td>
</tr>
<tr>
<td>Skin</td>
<td>59.1</td>
<td>5.8</td>
<td>41.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>33.2</td>
<td>1.9</td>
<td>18.8</td>
</tr>
<tr>
<td>Rash</td>
<td>28.4</td>
<td>2.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Rash maculopapular</td>
<td>11.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>46.3</td>
<td>14.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Colitis</td>
<td>44.1</td>
<td>9.3</td>
<td>19.2</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in alanine aminotransferase</td>
<td>30.0</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Increase in aspartate aminotransferase</td>
<td>17.6</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>30.0</td>
<td>4.8</td>
<td>14.4</td>
</tr>
</tbody>
</table>

With immune modulatory agents, resolution rates for the majority of grade 3–4 select AEs were: 85%-100% for NIVO + IPI, 50%-100% for NIVO, and 83%-100% for IPI.

- As observed in prior studies, most endocrine events did not resolve.

Grade ≥2 Treatment-Related Select AEs Across Organ Categories With the NIVO + IPI Regimen (CheckMate 067)

- A higher proportion of patients who received the combination experienced at least two grade 2–4 AEs across organ categories during treatment.

<table>
<thead>
<tr>
<th>Number of Organ Categories, % (n/N)a</th>
<th>NIVO + IPI n = 313</th>
<th>NIVO n = 313</th>
<th>IPI n = 311</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>91 (29)</td>
<td>236 (75)</td>
<td>171 (55)</td>
</tr>
<tr>
<td>1</td>
<td>125 (40)</td>
<td>61 (20)</td>
<td>112 (36)</td>
</tr>
<tr>
<td>2</td>
<td>77 (25)</td>
<td>14 (5)</td>
<td>24 (8)</td>
</tr>
<tr>
<td>3</td>
<td>15 (5)</td>
<td>2 (1)</td>
<td>4 (1)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>5 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

### Safety Summary by Key Subgroups (CheckMate 067)

<table>
<thead>
<tr>
<th>Patients Reporting Event, %</th>
<th>NIVO + IPI n = 313</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any Grade</td>
<td>Grade 3–4</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>96</td>
<td>55</td>
</tr>
<tr>
<td>Aged ≥65 and &lt;75 years</td>
<td>95</td>
<td>50</td>
</tr>
<tr>
<td>Aged ≥75 and &lt;85 years</td>
<td>97</td>
<td>48</td>
</tr>
<tr>
<td>M1c disease</td>
<td>94</td>
<td>54</td>
</tr>
<tr>
<td>PD-L1 expression ≥5%</td>
<td>97</td>
<td>53</td>
</tr>
<tr>
<td>Patients with complete response</td>
<td>100</td>
<td>58</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>36</td>
<td>29</td>
</tr>
<tr>
<td>Treatment-related death(^a)</td>
<td>0</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

- Treatment-related AEs reported with IPI were consistent with prior experience

\(^a\)One death in the NIVO group was reported as neutropenia.

Checkpoint Inhibition in the Elderly

- No difference in incidence of toxicity or grade of toxicity for the use of IPI or PD-1 under or over 65.
- The overall survival for those treated with ipilimumab does not vary significantly by age.
- It appears that ipilimumab and PD-1/PD-L1 antibodies can be safely given to those at any age.
- I have personally treated a 90 year old with ipilimumab, and a 90 year old with nivolumab.
- That being said, caution should be used in using IPI or IPI/NIVO in those functionally over 80 with comorbidities, who will not tolerate the colitis or prolonged steroid taper very well.
**Immune-Related Adverse Events With Combination Immune Therapies**

- The rate of grades 3-4 irAEs is higher with IPI + NIVO at full doses of IPI at 3 mg/kg; less with pembro + IPI with IPI at 1 mg/kg

- With concurrent or sequential combination IPI + NIVO, irAEs are higher, deeper, and more long lasting than with PD-1 blockade alone

- The partner with PD-1 blockade will determine the pattern of irAEs

- The type of irAEs with PD-1/PD-L1 blockade alone or in combination is similar to IPI, but since therapy is longer, the chronic pattern and kinetics are a bit different
Toxicities With Other I-O Combinations?

- IDO + PEMBRO: fatigue, rash, arthralgia, pruritus, diarrhea, and nausea were most common. Grade 3 irAEs were observed in 18%
- IPI + PEG INTRON: fatigue, colitis
- IPI + VEMURAFENIB: hepatitis and dermatitis
- DABRAFENIB + TRAMETINIB + PEMBRO: grade 3-4 irAEs in 4/38 pts: rash, nausea/vomiting, fevers/chills
- PEMBRO + TVEC: fatigue, no grade 3-4 irAEs
- PEMBRO + IPI: 38% grade 3-4 IRAEs
- Oncolytic herpesvirus HF-10 + IPI: 3/43 grade 3-4 irAEs
- OX-40 ab + ATEZO: The majority of irAEs were grade 1; 1 related grade 3 event of pneumonitis
With an irAE, When to Call the Sub-Specialist?

- Grades 1-2 Skin  - no, manage the symptoms
- Grades 3-4 Skin  - yes, consider a biopsy
- Grades 1-2 GI  - only if scoping changes the management
- Grades 3-4 GI  - only if therapy refractory or grade 4
- Grades 1-2 Hepatic  - no
- Grades 3-4 Hepatic  - only if grade 4 or if refractory to therapy
- Grades 1-2 Endocrine  - yes, if symptomatic
- Grades 3-4 Endocrine  - yes, always
With an irAE, When to Call the Sub-Specialist?

- Grades 1-2 Pancreatic - no
- Grades 3-4 Pancreatic - only if grade 4 or symptomatic

- Grades 1-2 Pulmonary - generally no, but consider
- Grades 3-4 Pulmonary - almost always

- Grades 1-2 Neurologic - generally yes if grade 2
- Grades 3-4 Neurologic - almost always

- Grades 1-2 Renal - no
- Grades 3-4 Renal - only if refractory to therapy
Optimized Management of Immuno-Oncology Side Effects: Conclusions

• Good patient-provider communication is key
• Virtually all anti-CTLA-4/PD-1/PD-L1 side effects will be immune based and mechanism related
• Infusion reactions will be rare but treatable
• Treat immune-related side effects early, aggressively
• Use steroids for grade 3 and prolonged grade 2 irAEs, and employ intravenous methylprednisolone for 1-2 days for severe toxicity
• Treat with tapering schedules not less than 30-45 days
• If symptoms do not resolve within 3-5 days, use infliximab 5 mg/kg, may repeat every 2 weeks