Managing Side Effects of Immune Checkpoint Blockade

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Disclosures

Research support: Bristol-Myers Squibb

Honorarium: Merck, Bristol-Myers Squibb

Advisory Board: Amgen, Caladrius
Immunotherapy = T cell kills a cancer cell

cancer cell

cytotoxic T cell
FDA Approved Immune Checkpoint Blocking Antibodies

Ipilimumab (Melanoma)

Pembrolizumab (Melanoma and NSCLC)

Nivolumab (Melanoma and NSCLC)
KIDNEY CANCER

IMMUNE SYSTEM
1. What are the side effects? (Immune-related AEs)

2. When do they happen?

3. What do you do about them?
### Safety Summary in Melanoma Phase 3
**Nivo, Ipi, Nivo + Ipi**

<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>Treatment-related adverse event (AE)</td>
<td>95.5</td>
<td>55.0</td>
<td>82.1</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>36.4</td>
<td>29.4</td>
<td>7.7</td>
</tr>
<tr>
<td>Treatment-related death*</td>
<td>0</td>
<td>0.3</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*One reported in the NIVO group (neutropenia) and one in the IPI group (cardiac arrest).*

67.5% of patients (81/120) who discontinued the NIVO + IPI combination due to treatment-related AEs developed a response.

Wolchok et al. ASCO 2015
## Treatment-Related Select AEs Reported in ≥10% of Patients

<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></td>
<td></td>
<td></td>
</tr>
<tr>
<td></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 maculo-papular</td>
<td>11.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46.3</td>
<td>14.7</td>
<td>19.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>44.1</td>
<td>9.3</td>
<td>19.2</td>
</tr>
<tr>
<td>Colitis</td>
<td>11.8</td>
<td>7.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.0</td>
<td>18.8</td>
<td>6.4</td>
</tr>
<tr>
<td>Increase in alanine...</td>
<td>17.6</td>
<td>8.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Increase in aspartate...</td>
<td>15.3</td>
<td>6.1</td>
<td>3.8</td>
</tr>
<tr>
<td>Endocrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30.0</td>
<td>4.8</td>
<td>14.4</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.0</td>
<td>0.3</td>
<td>8.6</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

Wolchok et al. ASCO 2015

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**Fourteenth International Kidney Cancer Symposium**

Miami, Florida, USA—November 6-7, 2015

www.kidneycancersymposium.com
Nivolumab side effects in RCC appear similar to other diseases

1. Grade 3 or 4 in 19% of patients in nivolumab vs. everolimus phase 3 study

2. Fatigue, skin, pneumonitis, strange taste, diarrhea

Motzer et al. *NEJM* 2015
### Treatment-related select AE categories

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grade 3-4</td>
<td>All Grade 3-4</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>3 (14.3)</td>
<td>8 (34.8)</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>6 (28.6)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (4.8)</td>
<td>9 (39.1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>2 (9.5)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (4.8)</td>
<td>2 (8.7)</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>2 (9.5)</td>
<td>3 (13.0)</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>8 (38.1)</td>
<td>9 (39.1)</td>
</tr>
</tbody>
</table>

- No high-grade pulmonary AEs, including pneumonitis, were observed

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Hammers et al. ASCO 2014
Main Questions

1. What are the side effects?

2. When do they happen?

3. What do you do about them?
Time to Onset of Select Treatment-related AEs for Nivolumab  
(Any Grade; N = 474)

- Median time to onset for treatment-related select AEs ranged from 5.0 weeks for skin AEs to 15.1 weeks for renal AEs.

Circles represent median; bars signify ranges.

Weber et al. ASCO 2015
Main Questions

1. What are the side effects?

2. When do they happen?

3. What do you do if they happen?
IPILIMUMAB MANAGEMENT

[PDF] YERVOY (ipilimumab)
YERVOY (ipilimumab) is indicated for the treatment of unresectable or metastatic melanoma. Immune-mediated adverse reaction management guide. This guide is...

IPILIMUMAB'S UNIQUE SIDE EFFECTS REQUIRE UNIQUE MANAGEMENT
www.onclive.com/web-exclusives/IPilimumabs...require-unique-management
The FDA recently approved the immunotherapy IPILIMUMAB (Yervoy) as a second-line treatment for patients with metastatic melanoma. Researchers at San Francisco...

[PDF] RISK EVALUATION AND MITIGATION STRATEGY (REMS)
www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafety...

Fourteenth International Kidney Cancer Symposium
Miami, Florida, USA—November 6-7, 2015
Management Algorithms

**Determine Severity of Enterocolitis**

- **Moderate**
  - 4 to 6 stools/day over baseline
  - Abdominal pain
  - Blood or mucus in stool

- **Severe or Life Threatening**
  - ≥ 7 stools/day over baseline
  - Peritoneal signs consistent with bowel perforation
  - Nausea
  - Fever

**Management**

- Withhold YERVYO
  - Administer antidiarrheal treatment while etiology is investigated

- Permanently Discontinue YERVYO
  - Rule out bowel perforation; if bowel perforation is present, do not administer corticosteroids
  - Consider endoscopic evaluation
  - Administer systemic corticosteroids of 1 to 2 mg/kg/day of prednisone or equivalent

**Follow Up**

- **Symptoms Resolved**
  - Resume YERVYO if symptoms have improved to mild severity or resolution

- **Symptoms Ongoing >1 week**
  - Start systemic corticosteroids (eg, 0.5 mg/kg/day of prednisone or equivalent)
  - Continue steroids until improvement to mild severity or resolution; taper steroids as medically appropriate
  - Resume YERVYO if symptoms have improved to at least mild severity, and steroid dose is 2.5 mg prednisone equivalent or less
  - **IF SYMPTOMS WORSEN TO SEVERE, SEE BELOW**

- **Symptoms Resolved**
  - Continue steroids until improvement to mild and taper steroids over 1 month

- **Symptoms Ongoing**
  - Patient should be continually evaluated for evidence of gastrointestinal perforation or peritonitis
  - Consider repeat endoscopy
  - Consider alternative immunosuppressive therapy
Mild checkpoint inhibitor rash

Can be treated with topical corticosteroids
More severe checkpoint inhibitor rash

Sanlorenzo M et al. JAMA Dermatology 2015
Rash Management

1. Topical corticosteroid cream (triamcinolone)

2. Benadryl or hydroxyzine for pruritus

3. Oral steroids, often several weeks are required
Diarrhea and Colitis

Slangen et al., *World J Gastrointest Pharmacol Ther*, 2013
Diarrhea/Colitis Management

1. Stools < 4X baseline: imodium, budesonide

2. Stools < 7X baseline: 1mg/kg of prednisone

3. Stools > 7X baseline or refractory to oral steroids:
   1. Hospitalize for IV solumedrol 1-2mg/kg
   2. Consider infliximab 5mg/kg if no improvement after approximately 3 days
   3. Consider colonoscopy and CT scan

**Taper steroids slowly over at least 3-4 weeks**

***Do not use infliximab if autoimmune hepatitis is also occurring***
Hypophysitis Endocrinopathy

Weber et al. JCO 2012, reprinted from Blansfield J Immunother 2005
Endocrinopathy Management

1. Replace the missing hormones—usually permanently
   1. Levothyroxine
   2. Hydrocortisone (typically 20mg morning and 10mg evening)

2. Controversial whether higher doses of steroids during acute hypophysitis can prevent long-term pituitary dysfunction

3. Be aware of possibility of adrenal crisis with stressful situations (surgery/infection)
Two doses of ipilimumab and four of nivolumab
Pneumonitis Management

1. Radiographic changes: monitor

2. Mild symptoms: 2mg/kg of prednisone, consider hospitalization

3. Severe symptoms or hypoxia: 2-4mg/kg of solumedrol, bronchoscopy, infliximab
Summary and Future Questions

- Side effects are different, and in most cases of PD-1, better than chemotherapy.

- Most patients completely recover with immunosuppression, and immunosuppression does not appear to affect therapeutic efficacy.

- Consider opportunistic infections.

- More study needed in patients with underlying autoimmune diseases.
Sweet’s Syndrome

Pintova et al. *Melanoma Res* 2013
Kinetics of Onset and Resolution of Select Nivolumab Treatment-related AEs (Any Grade)

- Select AEs generally resolved within several weeks, apart from endocrinopathies, as some events were not considered resolved due to the continuing need for hormone replacement therapy.

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.

Weber et al. ASCO 2015
Nivolumab and nivolumab + ipilimumab improve PFS compared to ipilimumab

<table>
<thead>
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<th>NIVO + IPI (N=314)</th>
<th>NIVO (N=316)</th>
<th>IPI (N=315)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, months (95% CI)</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>HR (99.5% CI) vs. IPI</td>
<td>0.42 (0.31–0.57)*</td>
<td>0.57 (0.43–0.76)*</td>
<td>--</td>
</tr>
<tr>
<td>HR (95% CI) vs. NIVO</td>
<td>0.74 (0.60–0.92)**</td>
<td>--</td>
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</tr>
</tbody>
</table>

*Stratified log-rank P<0.00001 vs. IPI
**Exploratory endpoint

Wolchok et al. ASCO 2015
### Treatment-related AEs (≥10% of patients)

<table>
<thead>
<tr>
<th>Event</th>
<th>N3 + I1 (n=21)</th>
<th>N1 + I3 (n=23)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Total patients with an event, n (%)</td>
<td>16 (76.2)</td>
<td>6 (28.6)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (52.4)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (38.1)</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>6 (28.6)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (28.6)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>4 (19.0)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (19.0)</td>
<td>0</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>4 (19.0)</td>
<td>0</td>
</tr>
<tr>
<td>Chills</td>
<td>3 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>3 (14.3)</td>
<td>0</td>
</tr>
<tr>
<td>Lipase increased</td>
<td>3 (14.3)</td>
<td>3 (14.3)</td>
</tr>
<tr>
<td>Amylase increased</td>
<td>1 (4.8)</td>
<td>1 (4.8)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>1 (4.8)</td>
<td>0</td>
</tr>
<tr>
<td>AST increased</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Hammers et al. ASCO 2014
Time to Onset of Grade 3/4 Treatment-related Select AEs
Patients receiving nivolumab + ipilimumab or ipilimumab alone

Most grade 3/4 treatment-related select AEs occurred during the combination phase.

Circles represent median; bars signify ranges.

Hodi et al. ASCO 2015
More severe checkpoint inhibitor rash

Sometimes requires systemic steroids (Prednisone 1mg/kg)
## Immunosuppression to treat AEs does not reduce efficacy

### Nivolumab in melanoma

<table>
<thead>
<tr>
<th></th>
<th>NIVO monotherapy with IM N = 139</th>
<th>NIVO monotherapy without IM N = 437</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ORR, n (%), [95% CI]</strong></td>
<td>40 (28.8) [21.4–37.1]</td>
<td>141 (32.3) [27.9–36.9]</td>
</tr>
<tr>
<td><strong>BOR, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>7 (5.0)</td>
<td>22 (5.0)</td>
</tr>
<tr>
<td>PR</td>
<td>33 (23.7)</td>
<td>119 (27.2)</td>
</tr>
<tr>
<td>SD</td>
<td>31 (22.3)</td>
<td>102 (23.3)</td>
</tr>
<tr>
<td>PD</td>
<td>63 (45.3)</td>
<td>173 (39.6)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>5 (3.6)</td>
<td>21 (4.8)</td>
</tr>
<tr>
<td><strong>Median duration of response, mo (95% CI)</strong></td>
<td>NR (9.3–NR)</td>
<td>22.0 (22.0–NR)</td>
</tr>
<tr>
<td><strong>Median time to response, mo (range)</strong></td>
<td>2.1 (1.2–8.8)</td>
<td>2.1 (1.4–9.2)</td>
</tr>
</tbody>
</table>

Weber et al. ASCO 2015
Immunosuppression to treat AEs does not reduce efficacy

Ipilimumab in melanoma

Horvat et al. *J Clin Oncol* 2015
Possibility of Opportunistic Infection

- Ipilimumab diarrhea treated with prednisone and infliximab, subsequent *Aspergillus fumigatus* infection treated with voriconazole
- Consider prophylaxis for PCP (Bactrim, atovaquone) in patients on 20mg of prednisone for at least 4 weeks (Category 2B from NCCN)

Kyi and Postow *JITC* 2014
Safety in Patients with Existing Autoimmune Diseases?

1. Knowledge is limited since patients with autoimmunity not included in clinical trials

2. Anecdotal observations suggest it may be safe

Kyi and Postow *JITC* 2014
Douglas Johnson et al. *ASCO* 2015
Ways to keeping the T cells “active”