Immunotherapy: Toxicity Management

Dr. Megan Lyle
Medical Oncologist
Liz Plummer Cancer Care Centre – Cairns Hospital
Honoraria and travel support from BMS, MSD, Novartis
Advisory board for MSD

Some slides I will be presenting have been supplied by BMS and MSD
What causes immune-related adverse events?
- Checkpoint inhibitors and rates of irAE’s
- Common irAE’s
- Management approach
Immune-related adverse events

- Caused by the immune system being **too** active and attacking normal body tissues
  - “Auto-immunity”
- Most are temporary and **reversible** with treatment
Checkpoint Blockade

Dendritic cell

MHC

TCR

CD28

B7

CTLA-4

---

anti-CTLA-4

T cell

MHC

TCR

B7

CD28

CTLA-4

---

anti-CTLA-4

Activation
(cytokines, lysis, proliferation, migration to tumor)

CTLA-4 Blockade (ipilimumab)

PD-1 Blockade (nivolumab)

Tumor cell

PD-1

PD-L1

PD-1

PD-L2

anti-PD-1

anti-PD-1

Tumor Microenvironment
The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.


Skin
- Macropapular rash¹
- Pruritus¹,²

Hepatic
- Autoimmune hepatitis¹,³
- ALT/AST increases¹,²

Renal
- Nephritis¹
- Renal failure⁵

Endocrine
- Hypophysitis¹,³
- Thyroiditis¹,³
- Type 1 diabetes⁴

Respiratory
- Pneumonitis¹,³

Gastrointestinal
- Colitis/diarrhea¹,²

Neuromuscular
- Peripheral sensory neuropathy¹

Skin
- Macropapular rash¹
- Pruritus¹,²

*The AEs described here represent some but not all irAEs that may occur with immune checkpoint inhibitor therapies.*

Treatment-Related AEs With Incidence ≥10% at IA1

- Pembrolizumab Q2W
- Pembrolizumab Q3W
- Ipilimumab

*Incidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.
AEs of Special Interest at IA1

Pembrolizumab Q2W
Pembrolizumab Q3W
Ipilimumab

*Incidence not adjusted for duration of exposure.
Analysis cut-off date: September 3, 2014.
CheckMate 067: Adverse event profile in treatment-naïve, advanced melanoma\textsuperscript{1,2}\textsuperscript{†}

\textsuperscript{†}OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)\textsuperscript{2}

Treatment-related adverse events reported in ≥15% of patients with advanced melanoma\textsuperscript{1,2}

<table>
<thead>
<tr>
<th>Treatment-related adverse event</th>
<th>Iplimumab monotherapy (n=311)</th>
<th>Nivolumab monotherapy (n=313)</th>
<th>Nivolumab + Ipilimumab Combination Regimen (n=313)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade (%)</td>
<td>Grade 3 or 4 (%)</td>
<td>Any grade (%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>86</td>
<td>27</td>
<td>82</td>
</tr>
<tr>
<td>Rash</td>
<td>33</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Fatigue</td>
<td>28</td>
<td>2</td>
<td>34</td>
</tr>
<tr>
<td>Pruritus</td>
<td>35</td>
<td>&lt;1</td>
<td>19</td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td>&lt;1</td>
<td>13</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>7</td>
<td>&lt;1</td>
<td>6</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>13</td>
<td>&lt;1</td>
<td>11</td>
</tr>
<tr>
<td>Elevated alanine aminotransferase</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Elevated aspartate aminotransferase</td>
<td>4</td>
<td>&lt;1</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7</td>
<td>&lt;1</td>
<td>6</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4</td>
<td>0</td>
<td>9</td>
</tr>
</tbody>
</table>

**Discontinuation due to a treatment-related adverse event**

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>29</td>
</tr>
</tbody>
</table>

- No treatment-related deaths were reported with nivolumab + ipilimumab vs. one each for the other groups\textsuperscript{1†}

Adapted from Larkin J et al.\textsuperscript{1} Phase III study of nivolumab (1 mg/kg, q3w) plus ipilimumab (3 mg/kg, q3w) for four doses followed by nivolumab monotherapy (3 mg/kg, q2w) or nivolumab (3 mg/kg, q2w) vs. ipilimumab monotherapy (3 mg/kg, q3w, 4 doses) in 945 treatment-naïve advanced (unresectable stage III or metastatic stage IV) melanoma patients. Study was not designed for statistical analysis between nivolumab + ipilimumab combination regimen vs. nivolumab monotherapy. Patients in the safety population received ≥1 dose of study drug.\textsuperscript{1,2}

Adverse events were graded according to the NCI-CTCAE, v4.0.

\textsuperscript{†}One death in the nivolumab group was due to neutropenia and one death in the ipilimumab group was due to cardiac arrest.

CheckMate 067: Time to resolution of immune-related adverse reactions (irARs)\(^1\)–\(^3\)†

†OPDIVO, in combination with YERVOY (ipilimumab) is only indicated for the treatment of patients with metastatic (Stage IV) melanoma with M1c disease or elevated lactic dehydrogenase (LDH)\(^3\)

Resolution to baseline of grade 3 or 4 immune-related adverse reactions\(^3\)†

<table>
<thead>
<tr>
<th>Immune-related adverse reaction (irAR) organ category</th>
<th>Nivolumab + Ipilimumab Combination Regimen (n=313)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients with resolution of irARs, n (%)</td>
</tr>
<tr>
<td>Skin</td>
<td>12 (86)</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>41 (98)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>5 (46)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>38 (100)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>2 (100)</td>
</tr>
<tr>
<td>Renal</td>
<td>3 (100)</td>
</tr>
</tbody>
</table>

• With the exception of endocrinopathies, the majority of grade 3 or 4 immune-related adverse reactions resolved with the use of immunomodulatory agents according to established guidelines\(^1\)–\(^3\)

Adapted from Larkin J et al. (ECC 2015)\(^1\) Phase III study of nivolumab (1 mg/kg; q3w) plus ipilimumab (3 mg/kg; q3w) for four doses followed by nivolumab monotherapy (3 mg/kg; q2w) or nivolumab (3 mg/kg; q2w) vs. ipilimumab monotherapy (3 mg/kg; q3w; 4 doses) in 945 treatment-naïve advanced (unresectable stage III or metastatic stage IV) melanoma patients. Study was not designed for statistical analysis between nivolumab + ipilimumab combination regimen vs. nivolumab monotherapy.\(^1\)–\(^3\)

‡Includes events reported between the first dose and 30 days after last dose of study therapy. NE=not evaluable.

References: 1. Larkin J et al. Efficacy and safety in key patient subgroups of nivolumab alone or combined with ipilimumab vs. ipilimumab alone in treatment-naïve patients with advanced melanoma. Presented at European Cancer Congress 2015; September 25–29, 2015; Vienna, Austria (abstract).
Ref: Champiat et al, Annals Oncol 2016
Skin toxicity

- Rash, pruritus and vitiligo are common
- Rarely – Steven Johnson syndrome
- Usually manageable with topical steroids, anti-histamine, moisturiser
- Occasionally may require a short course of oral prednisone
- Usually immunotherapy can continue un-interrupted
Diarrhoea/colitis

- Increased frequency of bowel motions +/- other symptoms e.g. fever, PR bleeding, abdominal pain
- Risk of bowel perforation is very low (<1%)
- Exclude other causes, e.g. infection (stool culture)
- May require colonoscopy and biopsy to confirm diagnosis
- Mild cases: symptomatic management
- Moderate/severe: corticosteroids
- Steroid refractory: infliximab
- Watch out for rebound symptoms with steroid wean
• Often asymptomatic abnormality on routine blood tests
• May present with RUQ pain, jaundice, nausea, anorexia
• Exclude other causes, e.g. disease progression, viral hepatitis
• Treatment is with corticosteroids
• Steroid refractory: mycophenolate
**Thyroid dysfunction**

- Often asymptomatic and detected on routine screening
- Symptoms of hypo- or hyper-thyroidism
- Thyroiditis will often manifest as transient hyperthyroidism followed by development of permanent hypothyroidism
- Treatment rarely required for hyperthyroidism (e.g. carbimazole)
- Hypothyroidism is treated with thyroxine
- Usually immunotherapy can continue un-interrupted
Hypopituitarism

- Often detected on routine screening
- May be symptomatic, e.g. fatigue/lethargy, hypotension, headaches, visual disturbance
- MRI may be helpful
- Requires assessment of full endocrine panel and then replacement of deficient hormones (lifelong)
- Immunotherapy can usually continue un-interrupted (unless adrenal crisis)
Pneumonitis

- Rare (1-2%)
- May present with cough, dyspnoea, hypoxia, or asymptomatic imaging findings
- Exclude other causes, e.g. atypical infection, disease progression
- Treatment is with corticosteroids
What we **don’t** need to worry about

- Febrile neutropenia
- Infusion reactions
  - Very uncommon (<1%)
- Cytotoxic precautions
Ref: Champiat et al, Annals Oncol 2016
A Team Approach: Communication is KEY

Medical Oncologist
Pharmacist
Carer / Family
Oncology Nurse
General Practitioner
Other specialists

Patient
Consult the Oncologist or Oncology Nurse

**Lung**
- Shortness of breath
- Chest pain
- Coughing

**Liver**
- Nausea or vomiting
- Feeling less hungry
- Pain on the right side of your stomach
- Your skin looks yellow
- The whites of your eyes look yellow
- Dark urine
- You bleed or bruise more easily than normal

**Hormone gland**
(eg thyroid, pituitary and adrenal glands)
- Rapid heart beat
- Weight loss/gain
- Increased sweating
- Hair loss
- Feeling cold
- Constipation
- Your voice gets deeper
- Muscle aches
- Dizziness or fainting
- Headaches that will not go away or unusual headache

**Intestine**
- Diarrhoea or more bowel movements than usual
- Stools that are black, tarry, sticky, or have blood or mucous
- Severe stomach pain or tenderness

**Other**
- Feeling tired
- Rash or itching
- Needing to urinate more often
- Feeling more hungry or thirsty
- Changes in eyesight
- Fever
Patient education

Monitoring and **early recognition** is very important

Symptoms of irAE’s can be **subtle** and non-specific

Depending on severity, immunotherapy treatment may need to be withheld or permanently discontinued
  - Does not apply to endocrinopathies

Follow specific management algorithms
Immune-Related Adverse Event management:

<table>
<thead>
<tr>
<th>Adverse eventa</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade 1 (mild)</td>
<td>Supportive care</td>
<td>Continue treatment with KEYTRUDA and monitor</td>
</tr>
<tr>
<td>Grade 2 (moderate):</td>
<td>Withhold treatment and administer corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Pneumonitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Hypophysitis†</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Nephritis</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 (moderate or severe) colitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3 (severe) hyperthyroidism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic hypophysitis†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis associated with</td>
<td>Permanently discontinue KEYTRUDA when</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ AST/ALT &gt;3 to 5 x ULN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Total bilirubin &gt;1.5 to 3 x ULN</td>
<td></td>
</tr>
<tr>
<td>Hepatitis associated with</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ AST/ALT &gt;5x ULN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ AST/ALT increases ≥50% relative to baseline and lasts ≥1 week in patients with liver metastasis who began treatment with moderate (Grade 2) elevation of AST/ALT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Total bilirubin &gt;3 x ULN</td>
<td></td>
</tr>
<tr>
<td>Grade 3 or 4 (severe or life-threatening):</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Pneumonitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Nephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Infusion-related reaction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>■ Hypophysitis†</td>
<td></td>
</tr>
<tr>
<td>Any Grade 4 (life-threatening) adverse event</td>
<td>May be managed with replacement therapy, without KEYTRUDA treatment interruption and without corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Isolated hypothyroidism</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Grades are defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAEv4.0)*

ALT = alanine aminotransferase, AST = aspartate aminotransferase, ULN = upper limit of normal

† Pituitary gland inflammation

KEYTRUDA Approved Product Information. September 2015

Continue monitoring for adverse events during and after KEYTRUDA treatment. Treatment related adverse events can also occur after the last dose of KEYTRUDA.
Supportive care
- e.g. anti-diarrhoeal agents

**Corticosteroids** are main treatment
- e.g. oral prednisone or IV methylprednisolone
- Need to be weaned slowly (4-6 weeks minimum)

May require admission to hospital

May require stronger immunosuppressive medications
- e.g. Infliximab for colitis, mycophenolate for liver toxicity
Questions?