Presenter Disclosures

• I have received consulting fees and/or speaking honoraria from the following companies:
  – Bristol Myers Squibb
  – Roche
  – Merck
  – Novartis

• I have received unrestricted educational grants or sponsorship for five multidisciplinary melanoma meetings in Victoria held between 2013-2015 from BMS, Roche, Merck, Novartis.

• Some slides were provided to me by Bristol Myers Squibb.
Overview

• Review how the immune system targets cancer.
• Review the mechanisms of action and efficacy of checkpoint inhibitors
  – CTLA4 antagonists
  – PD1 inhibitors
• Review the patterns of response to checkpoint inhibitors.
• Review the standard AE and how to manage them.
Immuno-Oncology
Helping Your Immune System Fight Cancer
810,045 Canadians were alive at the beginning of 2009 with a cancer diagnosed in the previous 10 years.

2 in 5 Canadians will develop cancer in their lifetime.

202,400 Canadians will be diagnosed with cancer in 2016.

60% The five-year survival probability, in Canada, that would be observed in the hypothetical situation where cancer is the only possible cause of death.

78,800 Canadians will die of cancer in 2016.

1 in 4 Canadians will die from cancer.

Image Taken From Canadian Cancer Statistics 2016
Long-term Survival Remains a Challenge in Some Advanced Cancers

- Five-year survival remains poor for many patients with metastatic solid tumours

- There is a need for new treatments and therapeutic modalities for patients with advanced cancers

Five-year survival (%) 2010 data

- Lung: 3.9%
- Colorectal: 12.5%
- Kidney and renal pelvis: 12.3%
- Melanoma*: 16%

Immuno-oncology (I-O) therapies are being investigated in an attempt to fill the unmet need for improving clinical outcomes in advanced cancer

Surveillance, Epidemiology and End Results (SEER) Program. [http://seer.cancer.gov](http://seer.cancer.gov) (statistics for diagnosis years 2003 through 2009, with all patients followed through 2010); 2. Rosenberg SA. Sci Transl Med. 2012;4(127ps8):1-5. * including current immunotherapies. Rate was less than 5% prior to the introduction of immuno-oncology (Korn, JCO. 2008 Feb 1; 26(4)
Evolution of Cancer Therapy: Treatment Modalities

Surgery 1846

Chemotherapy 1946

Immunology 2010

Radiation Therapy 1901

Immunotherapy Interferon-α 1995 Interleukin-2 1998

Targeted Therapy 1997

Sipuleucel-T 2010 Ipilimumab 2011
Immuno-oncology (I-O) Is an Emerging Therapeutic Modality

- Traditional therapies for advanced cancer targets the tumour and include\(^1,2\)
  - Surgery, radiation and cytotoxic/targeted therapy
- Immunotherapy harnesses the body’s own immune system to fight diseases\(^3\)
- Immuno-oncology (I-O) uses immunotherapy to treat cancer.\(^1,2\)

The Immune System is Comprised of Two “Arms”: Innate and Adaptive

- Immediate
- First line of immune defense
- Not antigen-specific response

Innate Immunity

- External threats: viruses, parasites, protozoa, fungi, bacteria, toxins
- Internal threats: cancer

Adaptive Immunity

- Slow response
- Antigen-specific response
- Memory

Activating T Cells Against Cancer

**Step 1**
- Tumor cell
- Antigens
- Tumor apoptosis

**Step 2**
- Dendritic cell

**Step 3**
- Initiating and propagating anticancer immunity
  - Oncogenesis leads to the expression of mutated antigens that can be captured by dendritic cells
  - Dendritic cells can present antigens to T cells, priming and activating T cells to attack the cancer cells

**Step 4**
- Accessing the tumor
  - Activated T cells travel to the tumor and infiltrate the tumor microenvironment

**Step 5**
- Cancer cell recognition and initiation of cytotoxicity
  - Activated T cells can recognize and kill target cancer cells
  - Dying cancer cells release additional cancer antigens, perpetuating the cancer immunity cycle

**Step 6**
- Tumor cell

**Step 7**
- Tumor apoptosis
Adaptive Immune Response

Immune Escape in Cancer

Many tumours escape the immune response by creating an immunosuppressive microenvironment that prevents an effective antitumour response\(^1,2\)

Recruitment of immunosuppressive cells

- Tregs
- MDSCs

Ineffective presentation of tumour antigens to the immune system

- Downregulation of MHC Expression
- Suppression of APC

Tumour Cells

T-cell checkpoint dysregulation

- CTLA-4
- PD-1
- B7-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Release of immunosuppressive factors

Factors/enzymes directly or indirectly suppress immune response

Tumour Microenvironment

The mechanisms tumours use to escape the immune system provide a range of potential therapeutic targets for cancer

APC=antigen-presenting cell; MDSC=myeloid-derived suppressor cell; MHC=major histocompatibility complex; Treg=regulatory T cell.

CD8+ T-cell Exhaustion Due to Chronic Antigen Simulation: Model Based on Viral Infections

Naïve CD8+ T cell + Antigen + costimulation → Effector CD8+ T cell

Acute infection
Antigen cleared

Highly polyfunctional memory CD8+ T cell

High cytotoxic capacity and proliferative potential
Low apoptosis

Chronic infection
Antigen persists

CD8+ T-cell Exhaustion

Inflammation

PD-1
LAG-3
CD244 (2B4)
CD160 (and so on)

Cytotoxic capacity
Proliferative Potential
Apoptosis

T-Cell Checkpoint Regulation is an Evolving Approach to Cancer Therapy

- T-cell responses are regulated through a complex balance of inhibitory ("checkpoint") and activating signals
- Tumours can dysregulate these pathways, and consequently the immune response
- Targeting these pathways is an evolving approach to cancer therapy

Immuno-oncology: Blocking CTLA-4 and PD-1 Pathways with Monoclonal Antibodies

CTLA-4 pathway blockade

PD-1 pathway blockade

CTLA-4=cytotoxic T-lymphocyte antigen-4; PD-1=programmed cell death 1; PD-L1/2=PD ligand 1/2; TCR=T cell receptor.

Proof of Concept – Efficacy of Checkpoint Blockade: CTLA-4 and PD-1 Inhibition
Novel Immune Therapy: Targeting the Natural T-cell Braking System from CTLA-4

**T-cell activation**

- Antigen presentation and ligation of B7/CD28 co-activators results in T-cell activation.

**T-cell inhibition**

- In the activated T cell, CTLA-4 competes with CD28 and acts as the brakes on T-cell activation by binding to B7.

**T-cell activation and proliferation**

- By inhibiting CTLA-4, ipilimumab releases the natural braking system and restores T-cell activation, allowing T-cell proliferation to continue.

**Ipilimumab blocks CTLA-4**

B7: B7.1 (CD80) or B7.2 (CD86)

**Definitions**

- APC = antigen-presenting cell
- CTLA-4 = cytotoxic T-lymphocyte-associated antigen-4
- MHC = major histocompatibility complex
- TCR = T-cell receptor

Past Treatments for Metastatic Melanoma

**Treatment**

- Dacarbazine (DTIC)
  - In large randomized trials, Response rate (RR) of <15%
- Temozolomide
  - Similar to DTIC
- IL-2
  - RR of 15-20%
  - A minority are durable responses
  - Highly toxic treatment

**Survival**

- Median OS: 6.2 months
- One year OS: 25.5% (95% CI, 23.6% to 27.4%)

---

OS=overall survival.
1. Korn, JCO. 2008 Feb 1; 26(4)
Long-Term Survival with Ipilimumab in Melanoma

**Pooled Analysis: Phase III and Phase II Trials**
- 10 prospective trials and two retrospective, observational studies (n = 1861)
- Median OS: 11.4 months (95% CI, 10.7-12.1 months)
- 3-year survival rate: 22% (95% CI, 20% to 24%)

**Pooled Analysis: Phase III, Phase II Trials and EAP**
- 12 clinical investigations (n = 1861)
- US EAP (n = 2985)
- Median OS: 9.5 months (95% CI, 9.0-10.0 months)
- 3-year survival rate: 21% (95% CI, 20% to 22%)

PD-1 and PD-L1 Antibodies

- PD-1 – inhibitory receptor found on activated lymphocytes and monocytes and is associated with tumour immune escape
- Binds with PD-L1 on tumour cells
- Interaction between PD-1 and PD-L1 suppresses the cytotoxic T-cell response

Adapted from *N Engl Med*. 2012;366(26):2517
Nivolumab Improved Overall Survival vs. Dacarbazine in Melanoma

Patients who died, n/N
Median OS mo (95% CI)
Nivolumab 50/210 NR
Dacarbazine 96/208 10.8 (9.3–12.1)

NR = not reached.
Based on 5 August 2014 database lock.

Follow-up since randomization: 5.2–16.7 months.

Nivolumab Demonstrated 51% 1-Year Overall Survival as 2nd-line Treatment for Non-squamous NSCLC

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab (n = 292)</th>
<th>Docetaxel (n = 290)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>mOS, mo</strong></td>
<td>12.2</td>
<td>9.4</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>0.73 (96% CI: 0.59, 0.89)</td>
<td><em>P</em> = 0.0015</td>
</tr>
</tbody>
</table>

1-yr OS rate = 51%

1-yr OS rate = 39%

Number of Patients at Risk

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nivolumab</th>
<th>Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>292</td>
<td>290</td>
</tr>
<tr>
<td>3</td>
<td>232</td>
<td>244</td>
</tr>
<tr>
<td>6</td>
<td>194</td>
<td>194</td>
</tr>
<tr>
<td>9</td>
<td>169</td>
<td>150</td>
</tr>
<tr>
<td>12</td>
<td>146</td>
<td>111</td>
</tr>
<tr>
<td>15</td>
<td>123</td>
<td>88</td>
</tr>
<tr>
<td>18</td>
<td>62</td>
<td>34</td>
</tr>
<tr>
<td>21</td>
<td>32</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Symbols represent censored observations.

Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma


**Figure 1.** Kaplan–Meier Curve for Overall Survival. CI denotes confidence interval, and NE not estimable.
Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck


A. Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>No. of Deaths</th>
<th>1-Yr Overall Survival Rate % (95% CI)</th>
<th>Median Overall Survival mo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab</td>
<td>240</td>
<td>133</td>
<td>36.0 (28.5–43.4)</td>
<td>7.5 (5.5–9.1)</td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>121</td>
<td>85</td>
<td>16.6 (8.6–26.8)</td>
<td>5.1 (4.0–6.0)</td>
</tr>
</tbody>
</table>

Hazard ratio for death, 0.70 (97.73% CI, 0.51–0.96) P=0.01

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Nivolumab</th>
<th>Standard therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>No at Risk</td>
<td>240</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td>167</td>
<td>87</td>
</tr>
<tr>
<td></td>
<td>109</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>52</td>
<td>17</td>
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<td></td>
<td>24</td>
<td>5</td>
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<tr>
<td></td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
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</tbody>
</table>
Pembrolizumab Showed Improved OS (RECIST v1.1) vs. Ipilimumab at the First Interim Analysis

### Table: Overall Survival

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Median (95% CI) mo</th>
<th>Rate at 12 mo</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab 10 mg/kg Q2W NR</td>
<td>NR</td>
<td>74.1%</td>
<td>0.63 (0.47-0.83)</td>
<td>&lt;0.0005</td>
</tr>
<tr>
<td>Pembrolizumab 10 mg/kg Q3W NR</td>
<td>NR</td>
<td>68.4%</td>
<td>0.69 (0.52-0.90)</td>
<td>0.0036</td>
</tr>
<tr>
<td>Ipilimumab 3 mg/kg IV Q3W x 4 doses NR</td>
<td>NR (12.7-NR)</td>
<td>58.2%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Month</th>
<th>0</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
<th>14</th>
<th>16</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pembrolizumab</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2W</td>
<td>279</td>
<td>266</td>
<td>248</td>
<td>233</td>
<td>219</td>
<td>212</td>
<td>177</td>
<td>67</td>
<td>19</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Q3W</td>
<td>277</td>
<td>266</td>
<td>251</td>
<td>238</td>
<td>215</td>
<td>202</td>
<td>158</td>
<td>71</td>
<td>18</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Ipilimumab</td>
<td>278</td>
<td>242</td>
<td>212</td>
<td>188</td>
<td>169</td>
<td>157</td>
<td>117</td>
<td>51</td>
<td>17</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

NR= not reached

73-80% of Patients Experienced Treatment-related AEs with Pembrolizumab

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab 10 mg/kg Q2W n = 279</th>
<th>Pembrolizumab 10 mg/kg Q3W n = 277</th>
<th>Ipilimumab 3 mg/kg x 4 doses n = 278</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days on therapy, mean (range)</td>
<td>163.9 (1-336)</td>
<td>151.5 (1-332)</td>
<td>49.9 (1-92)</td>
</tr>
<tr>
<td>No of doses, median (range)</td>
<td>13 (1-20)</td>
<td>9 (1-16)</td>
<td>4a (1-4)</td>
</tr>
<tr>
<td>&gt;1 Treatment-related AE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade</td>
<td>79.5%</td>
<td>72.9%</td>
<td>73%</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>13.3%</td>
<td>10.1%</td>
<td>19.9%</td>
</tr>
<tr>
<td>Death</td>
<td>0%</td>
<td>0%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>4.0%</td>
<td>6.9%</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

a 56% of patients received all 4 ipilimumab doses
Efficacy and Safety with Nivolumab Alone or Combined with Ipilimumab vs. Ipilimumab Alone in Treatment-naïve Patients: Study Design

Unresectable or Metastatic Melanoma

• Previously untreated
• 945 patients

Randomize 1:1:1

Stratify by:
• PD-L1 expression*
• BRAF status
• AJCC M stage

N = 314

NIVO 1 mg/kg + IPI 3 mg/kg Q3W for 4 doses then NIVO 3 mg/kg Q2W

N = 316

NIVO 3 mg/kg Q2W + IPI-matched placebo

N = 315

IPI 3 mg/kg Q3W for 4 doses + NIVO-matched placebo

Treat until progression* or unacceptable toxicity

*This study was not powered to compare the combination Ipi + Nivo to Nivo alone
**Verified PD-L1 assay with 5% expression level was used for the stratification of patients; validated PD-L1 assay was used for efficacy analyses.
***Patients could have been treated beyond progression under protocol-defined circumstances.

PFS (Intent-to-Treat) was Improved with Nivo + Ipi vs. Either Alone

<table>
<thead>
<tr>
<th></th>
<th>NIVO + IPI</th>
<th>NIVO</th>
<th>IPI</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N = 314)</td>
<td>(N = 316)</td>
<td>(N = 315)</td>
<td></td>
</tr>
<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>
<td>--</td>
</tr>
</tbody>
</table>

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

## Safety Summary

<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.

Potential Clinical Response Patterns With I-O Therapeutic Approaches
Example of Evolution of Response to CTLA-4 Inhibitor

Week 12: Initial increase in total tumour burden (mWHO PD)

Week 96: Durable & ongoing response without signs of irAEs

Week 16: Responding


irAE: immune-related adverse event
mWHO: modified World Health Organization (criteria)
PD: progressive disease
Immune Response Criteria for Tumour Immunotherapy?
Pseudo-progression: Inflammation Causes Swelling, May Appear as Tumour Growth or New Lesions Upon Imaging

Considerations when evaluating true progression vs. pseudo-progression

<table>
<thead>
<tr>
<th></th>
<th>May indicate progression</th>
<th>May indicate pseudo-progression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Performance status</strong></td>
<td><em>Deterioration of performance</em></td>
<td><em>Remains stable or improves</em></td>
</tr>
<tr>
<td><strong>Systemic symptoms</strong></td>
<td><em>Worsen</em></td>
<td><em>May or may not improve</em></td>
</tr>
<tr>
<td><strong>Symptoms of tumour enlargement</strong></td>
<td><em>Present</em></td>
<td><em>May or may not be present</em></td>
</tr>
<tr>
<td><strong>Tumour burden</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td><em>Increase</em></td>
<td><em>Increase followed by response</em></td>
</tr>
<tr>
<td>New lesions</td>
<td><em>Appear and increase in size</em></td>
<td><em>Appear then remain stable and/or subsequently respond</em></td>
</tr>
<tr>
<td><strong>Biopsy may reveal</strong></td>
<td><em>Evidence of tumour growth</em></td>
<td><em>Evidence of T-cell infiltration</em></td>
</tr>
</tbody>
</table>

Key Principles of Managing Immune Mediate Adverse Events (irAE)
Systemic Oncology Therapies

**CHEMOTHERAPY**
Target: rapidly dividing tumour and normal cells
Adverse events: diverse due to non-specific nature of therapy

**TARGETED THERAPIES**
Target: specific molecules involved in tumour growth and progression
Adverse events: reflect targeted nature

**I-O THERAPIES**
Target: immune system
Adverse events: unique events can occur as a result of immune-system activity

Different spectrum of adverse events with each type of therapy

Although adverse events may have different etiologies, some adverse events with I-O may present like those with other therapies

Require different management strategies

I-O Therapy May Induce Inflammation in Certain Organ Systems

I-O therapy–associated AEs target certain organ systems

<table>
<thead>
<tr>
<th>Skin$^{1-6}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine system$^{2,4,7-10}$</td>
</tr>
<tr>
<td>Liver$^{2,6,11-12}$</td>
</tr>
<tr>
<td>Gastrointestinal tract$^{2,6,9,13}$</td>
</tr>
<tr>
<td>Nervous system$^{6,10,14,15}$</td>
</tr>
<tr>
<td>Eyes$^{1,4,16-18}$</td>
</tr>
<tr>
<td>Respiratory system$^{1,5,6,10,15,19}$</td>
</tr>
<tr>
<td>Hematopoietic cells$^{6,9,12,20-22}$</td>
</tr>
</tbody>
</table>

# Organ Specific Immune-related Adverse Events

## GI

| Incidence * | • All grades: 10-25%  
| • Grades 3-4: 1-5% |
|---|---|
| Symptoms | • Diarrhea  
| | • Stomach pain  
| | • Nausea/vomiting/pain  
| | • Blood in stool  
| | • Constipation  
| | • Abdominal cramping |
| Assessment | • Number of BM/day  
| | • Presence of watery diarrhea  
| | • Blood or mucus in stool |
| Management | • Most cases respond to symptomatic treatment or high-dose steroids with a long taper (over a month)  
| | • Infliximab is used in steroid-refractory cases  
| | • Consider GI consultation in patients with moderate to severe symptoms  
| | • In patients symptomatic for enterocolitis, rule out infectious etiologies and consider endoscopic evaluation for persistent or severe symptoms |

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)*

If not vigilant, may result in more serious immune-related adverse events
### Infliximab for the Management of I/O-Associated Colitis

| **Dosing** | 5 mg/kg IV induction regimen at 0, 2 and 6 weeks followed by 5 mg/kg IV every 8 weeks thereafter as required |
| **Contraindications** | • Severe infections (e.g., sepsis, abscesses, tuberculosis and opportunistic infections)  
• Moderate or severe (NYHA Class III/IV) congestive heart failure |
| **Most common adverse events** | • Infections  
• Allergic reactions  
• Infusion-related reactions |
| **Considerations for co-administration with other agents** | • Do not administer concurrently with another biologic (e.g., abatacept, rituximab, tocilizumab)  
• Live vaccines should not be given concurrently (acetaminophen and antihistamines may be used to manage reactions).  
• Monitor the effects/concentration of drugs with a narrow therapeutic index metabolized through CYP450 |

Adapted from Janssen Inc. Remicade Product Monograph, Date of Authorization: July 22, 2015.
## Incidence*

- **All grades:** 7-25%
- **Grades 3-4:** $<1\%$

Most cases are grade 1-2

## Symptoms / Assessment

- **Itchiness**
- **Redness**
- **Presence of rash or pruritus**
- **Peeling**
- **Skin excoriations**

## Management

Most cases are grade 1/2 and treatable with:

- **Symptomatic therapy** (e.g., antihistamines), and
- **Topical therapy** (e.g., moisturizing creams and topical steroids)
- **Generally reversible**
- **Important to evaluate and identify alternative etiologies not attributable to I-O therapy** (e.g., viral/bacterial infection)
- **Do not administer I-O therapy if moderate-to-severe rash is present**

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)*

---

If not vigilant, may result in more serious immune-related adverse events
Skin/Dermatologic Adverse Events of I-O Therapy

Example of ipilimumab-associated rash in a patient with advanced melanoma

Reticular erythematous rash

Immune-related maculopapular rash in a patient receiving ipilimumab

Perivascular lymphocyte infiltrate extending into epidermis. Magnification: x125

Ipilimumab-stimulated melanocyte immune recognition

CD4+ T cells apposed to dying melanocytes. Magnification: x250

CD8+ T cells apposed to dying melanocytes. Magnification: x250
### Organ Specific Immune-related Adverse Events

#### Incidence*
- All grades: 6.4-7.1%
- Grades 3-4: 1.6-2.6%

#### Symptoms
- Jaundice
- Tiredness
- Nausea, vomiting
- Abdominal pain

#### Assessment
- Liver function tests before each dose of I-O agents

#### Management
- Delay I-O therapy if grade 2, discontinue if grade 3-4
- Increase frequency of monitoring
- Consider IV steroids if grade 3-4
- Add prophylactic antibiotics for opportunistic infections
- Consult gastroenterologist

---

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events.

---

ALT: alanine aminotransferase
AST: aspartate aminotransferase
irAE: immune-related adverse event
LFT: liver function test
## Organ Specific Immune-related Adverse Events

| Incidence* | • All grades: 10.9-14.4%  
| • Grades 3-4: 0.6-2.3% |
|---|---|
| **Symptoms** | • Headaches  
| • Visual changes  
| • Fever  
| • Fatigue/weakness  
| • Mental status changes, confusion  
| • Hypotension  
| • Abdominal pain and/or unusual bowel habits |
| **Assessment** | • Monitor patients for signs and symptoms of hypophysitis, adrenal insufficiency (including adrenal crisis), and hyper- or hypothyroidism |
| **Management** | • Delay I-O therapy if grade 2, discontinue if grade 3-4  
| • Consider IV steroids if grade 3-4  
| • Monitor thyroid function tests and clinical chemistries at the start of treatment, before each dose, and as clinically indicated based on symptoms. |

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events
Organ Specific Immune-related Adverse Events

**Incidence***
- Grades 3-4: 0-0.4%

**Symptoms**
- Sensory or motor neuropathy
- Muscle weakness
- Fatigue
- Difficulty waking up

**Assessment**
- Monitor signs and symptoms indicative of motor or sensory neuropathy such as:
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

**Management**
- Consider IV steroids

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)

If not vigilant, may result in more serious immune-related adverse events
### Organ Specific Immune-related Adverse Events

#### Incidence*
- All grades: 2%
- Grades 3-4: <1%

#### Risk factors
- No underlying factor identified to date
- No apparent relationship to tumor type

#### Symptoms
- Cough, SOB/Dyspnea (rest or exertion), fever
- Asymptomatic radiographic changes

#### Assessment
- Pulse oximetry (rest and exertion)
- CXR and/or CT

#### Management
- Delay I-O therapy dosing
- Corticosteroids
- If not improving in 48 hrs or worsening, add immunosuppressants (e.g., infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil)

*If not vigilant, may result in more serious immune-related adverse events

---

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)
**Organ Specific Immune-related Adverse Events**

| Incidence* | • <1% of subjects treated with nivolumab or pembrolizumab monotherapy have experienced a related SAE of acute renal failure  
• Case reports of renal dysfunction associated with ipilimumab have also been reported |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>• Most commonly present with elevations in serum creatinine</td>
</tr>
<tr>
<td>Management</td>
<td>• Steroids generally lead to clinical improvement/resolution</td>
</tr>
<tr>
<td>Renal biopsy</td>
<td>• May help distinguish inflammatory versus non-inflammatory etiologies</td>
</tr>
</tbody>
</table>

*I-O monotherapy (pembrolizumab, ipilimumab, nivolumab)  
SAE= serious adverse event  
If not vigilant, may result in more serious immune-related adverse events
Kinetics of irAEs: Example for Nivolumab

Time to onset of select treatment-related AEs (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

- Skin (n = 155; 33%): 5.0 (0.1–57.0)
- Gastrointestinal (n = 66; 14%): 7.3 (0.1–37.6)
- Hepatic (n = 19; 4%): 7.7 (2.0–38.9)
- Pulmonary (n = 9; 2%): 8.9 (3.6–22.1)
- Endocrine (n = 36; 8%): 10.4 (3.6–46.9)
- Renal (n = 8; 2%): 15.1 (3.9–26.4)

Circles represent median; bars signify ranges. The kinetics of AEs presented on the slide are for melanoma but may not reflect the kinetics of AEs in other tumor types.
Stepwise Approach to Using I-O Agents in Clinic

- **Medical History**
  - Specific questions on organ function which may be affected by immune related adverse reactions, for example:
    - Shortness of breath on exertion?
    - Rash?
    - Bowel function?
    - Previous history of autoimmune disease?
- **Physical examination**
  - Vital signs (with oximetry when clinically indicated), physical exam, weight, other significant findings
- **Laboratory investigations**
  - CBC, biochemistry, renal function, LFT, TSH, other endocrine function evaluation when appropriate
Stepwise Approach to Using I-O Agents in Clinic

1. Patient education*
2. Multidisciplinary team (nurse, pharmacist, emergency, etc.)
3. Involve specialists
   - Gastroenterologist
   - Endocrinologist
   - Dermatologist
   - Pulmonologist
   - Ophthalmologist
   - Etc.

*Patient tools are available
Stepwise Approach to Using I-O Agents in Clinic

- Initiate treatment according to prescribing Product Monograph
- Careful ongoing clinical assessment is necessary for early identification of irAEs
- irAEs can be severe or life-threatening if not identified early
- irAEs can occur any time
- Keep in mind that toxicity does not equal response
- Early recognition is key
- Consider all symptoms and signs as potential irAE
- Refer to organ-specific algorithms for the management of irAEs
The majority of immune-related AEs are manageable and reversible with drug interruption ± corticosteroid. **Steroid taper is generally required over at least one month.**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Management</th>
<th>Continue the drug?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (gr 1)</td>
<td>Monitor closely</td>
<td>Continue (except for pneumonitis consider delay)</td>
</tr>
</tbody>
</table>
| Moderate (gr 2) | Symptomatic management  
Monitor closely  
Oral corticosteroids | Delay the dose  
Resume IO drug when AEs resolve to grade ≤ 1 or baseline |
| High (gr 3-4) | Administer high dose IV Corticosteroids  
Symptomatic management  
Monitor closely  
Involve specialist consultant* | Discontinue I-O Drug permanently (Delay in some situations) |

* In the event of grade 3 or 4 toxicity for practitioners in non-tertiary centres, consult with an oncologist or consider transfer to a tertiary centre.
I-O research and development will continue to inform future strategies, including new targets and rationale for drug combinations and sequencing.

I-O Therapies have the Potential to be Used as Monotherapy or Part of Combination Regimens

Re-challenging with Immune Checkpoint Inhibitors after irAEs:

- irAEs can be re-challenged with immune checkpoint inhibitors once ≤ grade 1
- irAEs should NOT be re-challenged in grade 3-4 with the exception of some situations (e.g., skin, perhaps diarrhea)
Key Considerations on Management of Immune-related Events

- Result from enhanced or excessive immune activity
- Early diagnosis and appropriate management is essential
- Health care team and patient education for early recognition
- Multidisciplinary team approach is required for optimal management
- Can be severe or life-threatening, may involve various organs
- Delayed irAE may occur
- Unless an alternate etiology has been identified, consider all symptoms and signs as potential irAE
- Systemic high-dose corticosteroids* may be required for severe events

*with or without additional immunosuppressive therapy

Bristol-Myers Squibb. YERVOY (ipilimumab) Immune-related Adverse Reactions (IrAR) Management Guide and online Tool at https://www.yervoy.co.uk/

For Healthcare Professionals

Click here if you would like to find out more information about OPDIVO

Adverse Drug Events Reporting

Adverse reactions to Bristol-Myers Squibb’s products can be reported to Bristol-Myers Squibb at 1-866-463-6267.

www.opdivo.ca
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Process ➔ Or Cancel
OPDIVO®, indicated for the treatment of:

- patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor
- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO
- adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy and have been issued marketing authorization without conditions.

OPDIVO, indicated for the treatment of:

- unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults

For further information for OPDIVO please refer to Health Canada’s Notice of Compliance with conditions – drug products web site.

Product Monograph
Download now

Patient Assistance Program Form
Download now

Patient Alert Card
Download now

Healthcare Professional Adverse Reaction Management Guide
Download now

Consult the Product Monograph at http://www.bmscanada.ca/sites/prod/en PM pdf/OPDIVO_EN_PM.pdf for contraindications, warnings, precautions, adverse reactions, interactions, dosing, and conditions of clinical use. The Product Monograph is also available through our medical department. Call us at 1-800-463-6267.
OPDIVO® (nivolumab) Immune-Mediated Adverse Reaction Management Guide

OPDIVO®, indicated for the treatment of
- patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

has been issued marketing authorization with conditions, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for OPDIVO please refer to Health Canada’s Notice of Compliance with conditions - drug products web site.

OPDIVO®, indicated for the treatment of
- unresectable or metastatic BRAF V600 wild-type melanoma in previously untreated adults
- adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumour aberrations should have disease progression on a therapy for these aberrations prior to receiving OPDIVO
- adult patients with advanced or metastatic renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy

have been issued marketing authorization without conditions.

Important safety information This guide is intended to provide information about the management of the important identified risks of prescribing OPDIVO for melanoma, NSCLC and RCC including immune-mediated endocrinopathies, gastrointestinal, hepatic, pulmonary, renal, rash, neurological and other adverse reactions, as well as infusion reactions.

All patients receiving treatment with OPDIVO must be given a Patient Alert Card to educate them about the symptoms of immune-mediated adverse reactions and the need to report them to their treating doctor immediately. Treating doctors should also advise their patients to keep the Patient Alert Card with them at all times and show it to any healthcare professional who may treat them.

For more information, please refer to OPDIVO Product Monograph available at Bristol-Myers Squibb Canada website at: http://www.bmscanada.ca
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<th>Page</th>
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<td>Recognize and Manage Adverse Reactions Associated With Therapy</td>
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<td>Immune-Mediated Endocrinopathies</td>
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<td>Immune-Mediated Gastrointestinal Adverse Reactions</td>
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<td>Immune-Mediated Hepatic Adverse Reactions</td>
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<td>Immune-Mediated Pulmonary Adverse Reactions</td>
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<td>Immune-Mediated Renal Adverse Reactions</td>
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<td>Immune-Mediated Skin Adverse Reactions</td>
<td>20</td>
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<td>Immune-Mediated Neurological Adverse Reactions</td>
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<td>Other Immune-Mediated Adverse Reactions</td>
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<td>Infusion Reactions</td>
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<td>Appendix</td>
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What is OPDIVO?

OPDIVO® (nivolumab) is a medicine that helps the immune system to attack and destroy cancer cells.

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T-cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumours. Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Common adverse reactions

**Melanoma**
- In patients who received 3 mg/kg OPDIVO monotherapy in studies CA209066 and CA209037, the most frequently reported adverse reactions (occurring at ≥15%) were fatigue, nausea, diarrhea, pruritus and rash.1,2

**NSCLC**
- In patients who received 3 mg/kg OPDIVO monotherapy in studies CA209017 and CA209057, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, nausea, rash and decreased appetite.4,5
- In patients who received 3 mg/kg OPDIVO monotherapy in study CA209063, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, decreased appetite, nausea, diarrhea and rash.6

**RCC**
- In patients who received 3 mg/kg OPDIVO monotherapy in study CA209025, the most frequently reported adverse drug reactions (occurring in ≥10%) were fatigue, nausea, diarrhea, rash, pruritus and decreased appetite.7
Recognize and Manage Adverse Reactions Associated With Therapy

**OPDIVO** (nivolumab) is associated with immune-mediated adverse reactions.

- Early identification of adverse reactions and intervention are an important part of the safe use of OPDIVO.
- Patients should be monitored continuously as an adverse reaction with OPDIVO may occur at any time during OPDIVO therapy. Adverse reactions are sometimes delayed and may develop weeks or months after the last dose of OPDIVO.

If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1-month duration should be initiated upon improvement.

- Rapid tapering may lead to worsening of the adverse reaction.
- Non-corticosteroid immunosuppressive medications should be added if there is worsening or no improvement despite corticosteroid use.
- Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications.

**Do not resume OPDIVO while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive medications.**

**Permanently discontinue treatment with OPDIVO for:**

- Any Grade 4 immune-mediated adverse reactions;
- Grade 3 or 4 infusion reaction;
- Grade 3 hypophysitis, Grade 3 adrenal insufficiency, Grade 3 pneumonitis, Grade 3 serum creatinine elevation, Grade 3 aspartate aminotransferase (AST), alanine aminotransferase (ALT) or total bilirubin elevations;
- Any Grade 3 immune-mediated adverse reactions that persist despite treatment modifications;
- Any Grade 3 immune-mediated adverse reactions that recur;
- Any Grade 2 or 3 immune-mediated adverse reactions that persist despite treatment modifications;
- Any immune-mediated encephalitis;
- Inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.
Immune-Mediated Endocrinopathies

Data for the following immune-mediated adverse reactions are based on patients who received nivolumab 3 mg/kg monotherapy in clinical studies across tumour types (melanoma, NSCLC and RCC), and includes the melanoma indication based on studies CA209066, CA209037, CA209067, CA209017, CA209057, CA209063 and CA209025, approved with conditions. Although the rates of immune-mediated adverse reactions were generally similar across tumour types, hepatic and renal adverse reactions occurred most commonly in RCC (11.3% and 6.9%, respectively); gastrointestinal and skin adverse reactions occurred most commonly in melanoma (17.7% and 38.4%, respectively); and pulmonary reactions, specifically pneumonitis occurred most commonly in RCC and NSCLC (3.9% and 3.6%, respectively). 1,9

- Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, diabetes mellitus and diabetic ketoacidosis, have been observed with OPDIVO (nivolumab) treatment.
- Monitor patients for signs and symptoms of endocrinopathies (see below).
- In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 8.6% (149/1728). The majority of cases were Grade 1 or 2 in severity reported in 3.6% (62/1728) and 4.9% (85/1728) of patients, respectively. Grade 3 thyroid disorders were reported in 0.1% (2/1728) of patients. Hypophysitis (one Grade 1; one Grade 2; and three Grade 3), adrenal insufficiency (one Grade 1; five Grade 2; and four Grade 3), diabetes mellitus (one Grade 2) and diabetic ketoacidosis (two Grade 3) were reported. No Grade 4 or 5 cases were reported in these studies.

Endocrinopathies

Signs and symptoms
- Fatigue
- Weight change
- Headache
- Mental status change
- Abdominal pain
- Increased frequency of bowel movements
- Hypotension
- Visual disturbances
- Thirst
- Need to urinate more often
- Increased appetite with a loss of weight
- Feeling weak, sleepy, irritable or forgetful
- Dizziness or fainting
- Other non-specific symptoms
  If signs or symptoms are present, complete endocrine function evaluation.

Unresectable or Metastatic Melanoma, Metastatic NSCLC and Metastatic RCC (monotherapy):

<table>
<thead>
<tr>
<th>Median time to onset:</th>
<th>Median time to resolution:</th>
<th>Cases resolved:</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.8 months (range: 0.4-14.0)</td>
<td>66.6 weeks (range: 0.4-96.1+)</td>
<td>74 patients (45.0%)</td>
</tr>
</tbody>
</table>
Managing Immune-Mediated Endocrinopathies

Monitor patients for signs and symptoms of endocrinopathy such as fatigue, weight change or headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function.

**Symptomatic Hypothyroidism and Symptomatic Hyperthyroidism:**

<table>
<thead>
<tr>
<th>Nivolumab (treatment) modification</th>
<th>For Symptomatic Hypothyroidism</th>
<th>For Symptomatic Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withhold OPDIVO until symptoms resolve</td>
<td>Grade 2 (moderate) Grade 3 (severe)</td>
<td>Grade 2 (moderate) Grade 3 (severe)</td>
</tr>
<tr>
<td>Permanently discontinue OPDIVO</td>
<td>Grade 4 (for life-threatening situations)</td>
<td>Grade 4 (for life-threatening situations)</td>
</tr>
<tr>
<td>Hormone replacement</td>
<td>Initiate thyroid hormone replacement</td>
<td>Initiate anti-thyroid therapy</td>
</tr>
<tr>
<td>Steroids</td>
<td></td>
<td>Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents for severe symptoms</td>
</tr>
</tbody>
</table>

**Monitoring**

Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized

**Follow-up**

<table>
<thead>
<tr>
<th>Grade 2 or 3</th>
</tr>
</thead>
</table>

Upon improvement, treatment may be resumed after corticosteroid taper, if needed
APPENDIX: Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 GRADING DEFINITIONS

<table>
<thead>
<tr>
<th>Grade</th>
<th>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</th>
<th>Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL.*</th>
<th>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.**</th>
<th>Life-threatening consequences; urgent intervention indicated.</th>
<th>Death related to AE.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Adrenal insufficiency: Moderate symptoms; medical intervention indicated</td>
<td>Severe symptoms; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Hyperglycemia: Fasting glucose value &gt;160-250 mg/dL; Fasting glucose value &gt;8.9-13.9 mmol/L</td>
<td>&gt;250-500 mg/dL; &gt;13.9-278 mmol/L; hospitalization indicated</td>
<td>&gt;500 mg/dL; &gt;278 mmol/L; life-threatening consequences</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hypothyroidism: Symptomatic; thyroid replacement indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Hyperthyroidism: Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Gastrointestinal Disorders: Colitis: Abdominal pain; mucus or blood in stool</td>
<td>Severe abdominal pain; change in bowel habits; medical intervention indicated; peritoneal signs</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 6</td>
<td>Diarrhea: Increase of 4-5 stools per day over baseline; moderate increase in ostomy output compared to baseline</td>
<td>Increase of ≥7 stools per day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td>Grade 7</td>
<td>Hepatic Disorders: Alanine aminotransferase (ALT) increased: &gt;3.0-5.0 x ULN</td>
<td>&gt;5.0-20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
</tr>
<tr>
<td>Grade 8</td>
<td>Aspartate aminotransferase (AST) increased: &gt;3.0-5.0 x ULN</td>
<td>&gt;5.0-20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
<td>&gt;20.0 x ULN</td>
</tr>
<tr>
<td>Grade 9</td>
<td>Blood bilirubin (TBIL) increased: &gt;1.5-3.0 x ULN</td>
<td>&gt;3.0-10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
<td>&gt;10.0 x ULN</td>
</tr>
<tr>
<td>Pulmonary Disorders</td>
<td>Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>Symptomatic; medical intervention indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; oxygen indicated</td>
<td>Life-threatening respiratory compromise; urgent intervention indicated (e.g., tracheotomy or intubation)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Renal Disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>2</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>&gt;1.5-3.0 x baseline; &gt;1.5-3.0 x ULN</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Skin Disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>2</td>
</tr>
<tr>
<td>Rash acriform</td>
<td>Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL</td>
</tr>
<tr>
<td>Rash maculo-papular</td>
<td>Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
</tr>
<tr>
<td>Toxic epidermal necrolysis</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological Disorders</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>2</td>
</tr>
<tr>
<td>Encephalitis infection</td>
<td>-</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
</tr>
</tbody>
</table>

**Activities of Daily Living (ADL)**

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*
KEYTRUDA is a prescription medicine used to treat a kind of skin cancer called melanoma. It may be used when your melanoma has spread or cannot be removed by surgery (advanced melanoma). It also is used to treat a kind of lung cancer called non–small cell lung cancer (NSCLC). KEYTRUDA may be used when your lung cancer

- has spread (advanced NSCLC) and,
- tests positive for "PD-L1" and,
  - you have not received chemotherapy to treat your advanced NSCLC and your tumor does not have an abnormal "EGFR" or "ALK" gene or
  - you have received chemotherapy that contains platinum to treat your advanced NSCLC, and it did not work or is no longer working and
  - if your tumor has an abnormal "EGFR" or "ALK" gene, you have also received an EGFR or ALK inhibitor medicine and it did not work or is no longer working.

It also is used to treat a kind of cancer called head and neck squamous cell cancer (HNSCC). KEYTRUDA may be used when your HNSCC has returned or spread (advanced HNSCC) and you have received chemotherapy that contains platinum to treat your advanced HNSCC, and it did not work or is no longer working.
KEYTRUDA is indicated for the treatment of patients with unresectable or metastatic melanoma.

SELECTED SAFETY INFORMATION

- KEYTRUDA can cause immune-mediated pneumonitis, including fatal cases. Pneumonitis occurred in 94 (3.4%) of 2799 patients receiving KEYTRUDA, including Grade 1 (0.8%), 2 (1.3%), 3 (0.9%), 4 (0.3%), and 5 (0.1%) pneumonitis, and occurred more frequently in patients with a history of prior thoracic radiation (6.9%) compared to those without (2.9%). Monitor patients for signs and symptoms of pneumonitis. Evaluate suspected pneumonitis with radiographic imaging. Administer corticosteroids for Grade 2 or greater pneumonitis. Withhold KEYTRUDA for Grade 2; permanently discontinue KEYTRUDA for Grade 3 or 4 or recurrent Grade 2 pneumonitis.
Our Key Products

PART III: CONSUMER INFORMATION

YEROY™
(ipilimumab)

DOWNLOAD THE PRODUCT MONOGRAPH

This leaflet is part III of a three-part “Product Monograph” published when YEROY™ (ipilimumab) was approved for sale in Canada and is designed specifically for Consumers.

This leaflet is a summary and will not tell you everything about YEROY. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

YEROY™ (ipilimumab) is a prescription medicine used to treat melanoma (a kind of skin cancer) that has spread or cannot be removed by surgery. It is for the treatment of melanoma in adults.

It is not known if YEROY is safe and effective in children less than 18 years of age.

What it does:

YEROY helps your immune system attack and destroy cancer cells by your immune cells.
CASES
Case 1: Melanoma
Skin – anti-CTLA-4

- 57-year-old woman presented with a mole on left upper back
- Surgical pathology - T2b, N1a - 2.5mm, clark IV, 8 mitosis/mm
- 1 of 3 sentinel lymph node positive
- Healthy otherwise
- CT showed several small pulmonary nodules, suspicious for metastatic disease
Case 1: Melanoma
Skin – anti-CTLA-4

Treatment

Ipilimumab
3mg/kg
Case 1: Melanoma
Skin – anti-CTLA-4

2 weeks post cycle 1

Diffuse maculopapular skin rash >30% BSA (grade 3)
## Grading the Rash

<table>
<thead>
<tr>
<th>Skin Disorders</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rash acneiform</strong></td>
<td>Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADL</td>
<td>Papules and/or pustules covering &gt;30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self-care ADL; associated with local superinfection with oral antibiotics indicated</td>
<td>Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life-threatening consequences</td>
</tr>
<tr>
<td><strong>Rash maculo-papular</strong></td>
<td>Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL</td>
<td>Macules/papules covering &gt;30% BSA with or without associated symptoms; limiting self-care ADL</td>
<td>-</td>
</tr>
<tr>
<td><strong>Toxic epidermal necrolysis</strong></td>
<td>-</td>
<td>-</td>
<td>Skin sloughing covering ≥30% BSA with associated symptoms (e.g., erythema, purpura or epidermal detachment)</td>
</tr>
</tbody>
</table>
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

### Skin Adverse Event Management Algorithm

**Grade of Rash (NCI CTCAE v4)**

**Grade 1-2**
- Covering ≤ 30% BSA*

  - Symptomatic therapy (e.g. antihistamines, topical steroids)
  - Continue I-O therapy

  - If improves to Grade 1:
    - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
    - Resume I-O therapy

  - Delay or discontinue I-O therapy
  - Consider skin biopsy
  - Dermatology consult
  - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent

**Grade 3-4**
- Covering >30% BSA; Life threatening consequences*

  - Delay or discontinue I-O therapy
  - Consider skin biopsy
  - Dermatology consult
  - 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent

  - If worsens:
    - Treat as Grade 3-4

  - If improves to Grade 1:
    - Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections
    - Resume I-O therapy

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* Refer to NCI CTCAE v4 for term-specific grading criteria.
Case 1: Melanoma
Skin – anti-CTLA-4

Management

August 2013

Prednisone
50 mg daily tapering dose

Cycle #2 omitted
Cycle #3 ipilimumab: prednisone at 10 mg being tapered, Grade 1 skin rash
Case 1: Melanoma
Skin – anti-CTLA-4

Sept 2013

Received Cycle #4 ipilimumab
Off prednisone treatment
No further skin issues
Case 2: Melanoma
Endo – anti-PD-1

- 54-year-old male
- Metastatic melanoma to lungs
- Asymptomatic from lung metastases, ECOG 0
- PMHx: atrial fibrillation 1 year ago
- Medications: ASA 81 mg po OD
  Randomized to pembrolizumab q2w on a clinical trial
Case 2: Melanoma
Endo – anti-PD-1

Thyroid function at start of PD1 was normal
TSH = 2.42 (0.5-5.0)
Free T4 = 15 (10-22)
T3 = 1.3 (1.2-3.2)
Tolerated PD1 well, exception grade 1 fatigue
February 24, 2014

4th treatment visit
Informed that he was discharged from ER in community for atrial fibrillation which required cardioversion
Started on β-blocker

TSH < 0.02 (0.5-5.0)
T4 = 22 (10-22)
T3 = 2.4 (1.2-3.2)
<table>
<thead>
<tr>
<th>Endocrine Disorders</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenal insufficiency</strong></td>
<td>Moderate symptoms; medical intervention indicated</td>
<td>Severe symptoms; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td><strong>Hyperglycemia</strong></td>
<td>Fasting glucose value &gt;160-250 mg/dL; Fasting glucose value &gt;8.9-13.9 mmol/L</td>
<td>&gt;250-500 mg/dL; &gt;13.9-27.8 mmol/L; hospitalization indicated</td>
<td>&gt;500 mg/dL; &gt;27.8 mmol/L; life-threatening consequences</td>
</tr>
<tr>
<td><strong>Hypothyroidism</strong></td>
<td>Symptomatic; thyroid replacement indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
<tr>
<td><strong>Hyperthyroidism</strong></td>
<td>Symptomatic; thyroid suppression therapy indicated; limiting instrumental ADL</td>
<td>Severe symptoms; limiting self-care ADL; hospitalization indicated</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>
Managing Immune-Mediated Endocrinopathies

Monitor patients for signs and symptoms of endocrinopathy such as fatigue, weight change or headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease, changes in blood glucose levels and thyroid function.

**Symptomatic Hypothyroidism and Symptomatic Hyperthyroidism:**

<table>
<thead>
<tr>
<th>Nivolumab (treatment) modification</th>
<th>For Symptomatic Hypothyroidism</th>
<th>For Symptomatic Hyperthyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withhold OPDIVO until symptoms resolve</td>
<td>Grade 2 (moderate) Grade 3 (severe)</td>
<td>Grade 2 (moderate) Grade 3 (severe)</td>
</tr>
<tr>
<td>Permanently discontinue OPDIVO</td>
<td>Grade 4 (for life-threatening situations)</td>
<td>Grade 4 (for life-threatening situations)</td>
</tr>
</tbody>
</table>

**Hormone replacement**
- Initiate thyroid hormone replacement
- Initiate anti-thyroid therapy

**Steroids**
- Consider initiating corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone IV or oral equivalents for severe symptoms

**Monitoring**
- Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilized

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**Follow-up**

**Grade 2 or 3**
- Upon improvement, treatment may be resumed after corticosteroid taper, if needed
Referred to endocrinology and started on methimazole
Case 2: Melanoma
Endo – anti-PD-1

Follow-up
Continued on pembrolizumab and remained asymptomatic from melanoma

#9 cycle visit
Asymptomatic from his thyroid
TSH now 135 (0.5-5.0), T4 = 2 (10-22)
T3= 0.4 (1.2-3.2)
Endocrine consulted, methimazole stopped and started levothyroxine sodium, β-blocker held

October 2014
• TSH, T3 and T4 normal
• Continues follow-up with endocrinologist
• Melanoma responding to pembrolizumab, remains asymptomatic from melanoma
Case 3: Melanoma

- 78-year-old male
- T4bN2a acral lenitiginous melanoma right toe 2008. BRAF WT.
- In transit mets to leg 2011 treated with limb perfusion and later surgery
- Relapse to base of tongue and cervical nodes
- Coughing up blood but ECOG 1.
- PMHx: HTN, acid reflux
- Medications: HCTZ, perinopril, tamsulosin, ranitidine.
- Started nivolumab by Access to Hope program
Case 3: Melanoma
Renal – anti-PD-1

Mar 21, 2016

First dose of nivolumab

- Hgb 134, Cr 111. All other labs normal.
- Tolerated PD1 well, exception mild headache x 1 day

May 2, 2016

- 5th treatment visit
- He had mild diarrhea 1-2 loose stool daily.
- Lost 6 lbs.
- 4/10 chest pain x 1 week.
- Just had CT – no pneumonitis.
- ECG normal.
- Troponin 30.
- ECHO negative for pericarditis
- Cr 114.
- Cancelled treatment to work up.
Case 3: Melanoma
Renal – anti-PD-1

May 16, 2016

- 5th treatment visit
- Mild flu-like symptoms but not unwell.
- Cr 338, BUN 16
- Admitted to hospital for presumed nephritis.
Grading Toxicity

<table>
<thead>
<tr>
<th>Renal Disorders</th>
<th>Grade</th>
<th>Grade</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>&gt;1.5-3.0 x baseline; &gt;1.5-3.0 x ULN</td>
<td>&gt;3.0 baseline; &gt;3.0-6.0 x ULN</td>
<td>&gt;6.0 x ULN</td>
</tr>
</tbody>
</table>
Managing Immune-Mediated Renal Adverse Reactions

Monitor patients for signs and symptoms of nephrotoxicity, including asymptomatic increase in serum creatinine and rule out disease-related etiologies.

<table>
<thead>
<tr>
<th>Grade of serum creatinine elevation (NCI-CTCAE v4)</th>
<th>Grade 2 serum creatinine elevation</th>
<th>Grade 3 or 4 serum creatinine elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPDIVO treatment and monitoring</strong></td>
<td>Withhold OPDIVO until creatinine returns to baseline and management with corticosteroids is complete</td>
<td>Permanently discontinue OPDIVO</td>
</tr>
<tr>
<td><strong>Steroids</strong></td>
<td>Initiate corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents</td>
<td>Initiate corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents</td>
</tr>
</tbody>
</table>

NCI-CTCAE v4 - National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0

Follow-up

**Grade 2 or 3 serum creatinine elevation**

- **Upon improvement** resume OPDIVO after corticosteroid taper
- **If worsening or no improvement** occurs despite initiation of corticosteroids, increase dose to 1 to 2 mg/kg/day methylprednisolone equivalents and permanently discontinue OPDIVO
Case 3: Melanoma
Renal – anti-PD-1

May 16, 2016

- 5th treatment visit
- Mild flu like symptoms but not unwell.
- Cr 338, BUN 16
- Admitted to hospital for presumed nephritis.
- Troponin was 61 (likely related to renal dysfunction)

- Started on prednisone 1 mg/kg
- Nephrology consulted
- Renal biopsy shows nephritis.
- May 19 Cr 286
- May 20 Cr 239
- Discharged on May 20th on prednisone 100 mg po daily + septra prophylaxis.
Case 3: Melanoma
Renal – anti-PD-1

May 25, 2016
- May 25 Cr 174.
- Seen in ER May 25\textsuperscript{th} with blood in stool.
- Colonoscopy.
- Found to be a diverticular bleed.
- Seen May 30\textsuperscript{th} in clinic.
  - Cr was 154
- June 13\textsuperscript{th} Cr 123, started steroid taper.

July 26, 2016
- Down to 5 mg po bid prednisone.
- Cr 103.
- No longer coughing up blood.
- Leg edema due to prednisone.
- Did not restart therapy.

Aug 25, 2017
- CT shows progression in the liver.
- PDI resumed but switched to pembrolizumab as it was covered at BCCA.
Case 3: Melanoma
Renal – anti-PD-1

Nov 9 2016

- Developed unrelated leg infection (maybe osteomyelitis) after picking a callus.
- Pembrolizumab held.

Nov 30, 2016

- Cr 169
- CRP14
- On antibiotics.

Dec 19, 2016

- ALT 385, AST 286 (normal in Nov).
- CRP 106
- Bad rash on new antibiotic.
- Stopped antibiotic.
- Had not had anti-PDI since mid October.
Case 3: Melanoma
Renal – anti-PD-1

Dec 29, 2016
- ALT 529 AST 526
- CRP 41
- LDH 531
- Cr 151
- Started on high dose steroids 100 mg po daily prednisone for presumed autoimmune hepatitis, maybe initiated by antibiotic reaction.
- Labs 3x weekly.
- Liver lesions were stable on CT

Jan 11, 2017
- ALT 60, AST 28
- Cr 122
- On steroid taper.
- No more PDI.
- Will observe for now as clinically stable.
• Immuno-oncology is a new corner stone of cancer therapy and is resulting in significant benefit in many cancers.

• Immunoncology agents have a new spectrum of adverse events, predominantly autoimmune in nature.

• Most of the immune-associated AEs are manageable with early recognition and treatment

• Optimal management of irAEs should involve multidisciplinary care team

• Remain vigilant throughout and after treatment
  – Educate and encourage patients to monitor for and report symptoms of immune-associated AEs

• Follow management guidelines for immune-associated AEs to give patients the best chance of therapeutic success