Immunotherapy and the ‘itis’ es

March 18, 2021

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Medical Oncologist at BC Cancer Abbotsford Centre
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Objectives

1) Introduce immunotherapy and mechanism of action
2) Review adverse event profile of immunotherapy
3) Provide resources for immunotherapy management
Cancer and the Immune System

• Cancer cells are able to avoid detection and destruction by the immune system through multiple mechanisms

• Cancer cells may...
  • Reduce the expression of tumor antigens on their surface, making it harder for the immune system to detect them
  • Express proteins on their surface that inhibit immune cell activation
  • Induce cells in the microenvironment to release substances that suppress immune responses
  • Secrete substances themselves that downregulate the immune system
Immunotherapy

A Paradigm Shift

The number of publications on cancer immunotherapy in the given year

Source: Razvi E and Oosta G. GEN. March 2016
Metastatic Melanoma – 2019 updates

CHECKMATE 067 - 5Y OVERALL SURVIVAL DATA

Nivo+Ipi – NR
Nivo – 36.9m
Ipi – 19.9m

Immunotherapy

Immune Checkpoint Inhibitors

- **CTLA-4 inhibitor**
  - Ipilimumab
  - Tremelimumab

- **PD-1 and PD-L1 inhibitors**
  - PD-1: Nivolumab, pembrolizumab
  - PD-L1: Atezolizumab, duravulmab, avelumab

They’re everywhere....
Current approved indications

Currently at the BC Cancer

• **Stage IV Melanoma:**
  - Ipilimumab + Nivolumab (USMAVIPNI)
  - Pembrolizumab (SMAVPEM, SMAVPEM6)
  - Nivolumab (SMAVNIV, SMAVNIV4)
  - Ipilimumab (SMAVIPI, SMAVIPI)
  - Avelumab for Merkel Cell (SMMCCAVE)
  - Cemiplimab for SCC (USMAVCEM)

• **Stage IV RCC:**
  - Ipilimumab + Nivolumab (UGUAVIPNI)
  - Nivolumab (GUAVNIV or GUAVNIV4)
  - Pembrolizumab (UGUAVPEM or UGUAVPEM6)
  - Pembrolizumab + Axitinib (GUAVPEMAX)

• **Stage IV H&N:**
  - Nivolumab (UHNAVNIV or UHNAVNIV4)

• **Stage IIIB/C/IV NSCLC:**
  - Pembrolizumab (ULUAVPMBF, ULUAVPMBF6)
  - Pembrolizumab, Paclitaxel + Carboplatin (ULUAVPCPMB)
  - Pembrolizumab, Platinum + Gemcitabine (ULUAVPGPMB)
  - Pembrolizumab, Platinum + Pemetrexed (ULUAVPPPMB)
  - Pembrolizumab (ULUAVPMB, ULUAVPMB6, LUAVPMBM, ULAVPMBM6)
  - Pembrolizumab + Pemetrexed (LUAVPMBM)
  - Nivolumab (ULUAVNIV, ULUAVNIV4)
  - Durvalumab (ULULADUR, ULULADUR4)

• **Hodgkin Lymphoma (Relapsed/Refractory):**
  - Pembrolizumab (LYPEM, LYPEM6)
  - Nivolumab (LYNIV, LYNIV4)

• **PLUS ... several clinical trials looking at immunotherapy combined with other agents**
Checkpoint inhibitor toxicity

- Checkpoint inhibitors have a unique spectrum of toxicity due to their mechanism of action
- Chemotherapy interferes with cell cycle function and affects rapidly dividing cells, thereby affecting cancer cells but also impacting other cells in the body with a high turnover rate
  - i.e. Hair → alopecia, Bone marrow → febrile neutropenia, Gut mucosa → stomatitis, N/V, diarrhea
- Checkpoint inhibitors ‘turn on’ the immune system and adverse events related to immune system over-activity and autoimmunity
  - Any ‘itis’ you can think of!!
Tolerability of oncology therapies

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

Immunotherapy
- **Target**: immune system
- **Adverse Events**: unique events can occur as a result of immune-system activity

Different spectrum of adverse events but with potentially similar presentations
Immune-related Adverse Events (irAEs)

Just add “itis”

Some of the things we have seen so far...

- Rash
- Psoriasis
- Vitiligo
- Ophthalmopathy
- Hypo/hyperthyroidism
- Hypophysitis
- Diabetic ketoacidosis
- New onset of T1DM
- Arthritis/myositis
- Encephalitis

- Myasthenia gravis
- Febrile illness NYD
- Pneumonitis
- Sarcoidosis x 2
- Hepatitis (requiring MMF)
- Erosive esophagitis/gastritis
- Colitis (requiring infliximab)
- Protein-losing enteropathy

*Psychosis - unclear etiology on combination immunotherapy*
POLL – How familiar are you with immunotherapy?

1. Very familiar
2. Somewhat familiar
3. Neutral
4. Somewhat unfamiliar
5. Not familiar at all
POLL – Have you managed/seen any patients on immunotherapy?

1. Yes – more than 10
2. Yes – 1-10
3. Unsure
4. No
Case 1 – Ms. AS

- **ID** – 74 year old woman with metastatic melanoma
- **PMHx** – none

**History of Presenting Illness:**

- **1991** – Cutaneous R shoulder melanoma treated with excision
- Well until screening mammogram in 2014 showed mass in L breast that was biopsied & found to be melanoma
- **July 2014** - PET showed involvement of R arm, cardiophrenic LNs, multiple abdominal LNs, sacrum & R tibial plateau
- **Options** - Dacarbazine chemotherapy vs BRAF inhibitor if BRAF mutation identified. Ipilimumab available after progression on dacarbazine.
Case 1 – Ms. AS

- BUT BRAF mutation neg so started dacarbazine **Sept 2014**
- 1 cycle of dacarbazine complicated by neutropenia so switched to ipilimumab **Oct 2014**
- 3 cycles that were well tolerated but then diarrhea (6-8x per day) **Dec 2014**
  - Started on prednisone 75mg x 10 days (1mg/kg) then dropped to 50mg daily x 2 weeks however worsening with decrease in steroids requiring admission **Jan 2015**
  - Had flex sig showing mild inflammation & hydrocortisone 100mg IV initiated (no need for infliximab as per GI)
  - Stepped down to oral steroids and fully recovered by **Feb 2015**
Gastrointestinal irAE

• Important because more grade 3/4 toxicity and may lead to admission
• Terminology of AE:
  • Diarrhea – frequent & watery bowel movements
  • Colitis – inflammation of the colon
  • Enteritis – inflammation of the small bowel
  • Enterocolitis – inflammation of the small & large bowel
  • Hepatitis – inflammation of the liver
• Any ‘itis’ → esophagitis, gastritis, enteritis, colitis, pancreatitis, hepatitis
• GI irAEs can wax and wane (especially in colitis/hepatitis)
• Prompt identification and management essential!

# Frequency and Timing

## Frequency and Onset of Immune-Mediated Adverse Reactions

### OPDIVO (N=1994)

<table>
<thead>
<tr>
<th>Condition</th>
<th>All Grades n (%)</th>
<th>Median Time to Onset (months range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumonitis*</td>
<td>61 (3.1%)</td>
<td>3.5 (1 day to 22.3 months)</td>
</tr>
<tr>
<td>Colitis</td>
<td>58 (2.9%)</td>
<td>5.3 (2 days to 20.9 months)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>35 (1.8%)</td>
<td>3.3 (6 days to 9 months)</td>
</tr>
<tr>
<td><strong>Endocrinopathies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>12 (0.6%)</td>
<td>4.9 (1 months to 11 months)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>20 (1%)</td>
<td>4.3 (15 days to 21 months)</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>171 (9%)</td>
<td>2.9 (1 day to 16.6 months)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (2.7%)</td>
<td>1.5 (1 day to 14.2 months)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17 (0.9%)</td>
<td>4.4 (15 days to 22 months)</td>
</tr>
<tr>
<td>Nephritis/Renal Dysfunction</td>
<td>23 (1.2%)</td>
<td>4.6 (23 days to 12.3 months)</td>
</tr>
<tr>
<td>Skin*</td>
<td>171 (9%)</td>
<td>2.8 (&lt;1 day to 25.8 months)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>3 (0.2%)</td>
<td>-</td>
</tr>
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### OPDIVO + YERVIO (N=407)

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<th>Condition</th>
<th>All Grades n (%)</th>
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<td>Colitis</td>
<td>107 (26%)</td>
<td>1.6 (3 days to 15.2 months)</td>
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<td>Hepatitis</td>
<td>51 (13%)</td>
<td>2.1 (15 days to 11 months)</td>
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<tr>
<td>Hypophysitis</td>
<td>36 (9%)</td>
<td>2.7 (27 days to 5.5 months)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>21 (5%)</td>
<td>3.0 (21 days to 9.4 months)</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>89 (22%)</td>
<td>2.1 (1 day to 10.1 months)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>34 (8%)</td>
<td>23 days (3 days to 3.7 months)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>6 (1.5%)</td>
<td>2.5 (13 months to 4.4 months)</td>
</tr>
<tr>
<td>Nephritis/Renal Dysfunction</td>
<td>9 (2.2%)</td>
<td>2.7 (9 days to 7.9 months)</td>
</tr>
<tr>
<td>Skin*</td>
<td>92 (22.6%)</td>
<td>18 days (1 day to 9.7 months)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>1 (0.2%)</td>
<td>1.7</td>
</tr>
</tbody>
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*Fatal cases have been reported.*  
*Two cases of diabetic ketoacidosis occurred.*  
*Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids.*

Source: OPDIVO Adverse Reactions Management Guide. BMS.
# Immune-related Adverse Events

<table>
<thead>
<tr>
<th>AE</th>
<th>NIVO&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>NIVO + IPI&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>IPI&lt;sup&gt;a,d&lt;/sup&gt;</th>
<th>Pembro&lt;sup&gt;e,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18.8</td>
<td>0</td>
<td>33.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Rash</td>
<td>25.9</td>
<td>0.6</td>
<td>40.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>2.2</td>
<td>44.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.3</td>
<td>0.6</td>
<td>11.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>3.8</td>
<td>1.3</td>
<td>17.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>3.8</td>
<td>1.0</td>
<td>15.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.6</td>
<td>0</td>
<td>15.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.3</td>
<td>0.3</td>
<td>6.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Colitis Work Up

- **History, physical**
  - R/O other causes common in cancer patients → medication–related, disease progression, *C. difficile*, other bacterial/viral pathogens
- **Bloodwork** including CRP, LEs
- Stool culture, *C. difficile* toxin
- **Imaging** – AXR, CT
- **Colonoscopy & biopsy** if persistent ≥ grade 2 diarrhea
(A) Colonoscopic view of bowel edema and ulceration in the descending colon of patient 29, who experienced autoimmune colitis.
(B) Histopathologic analyses revealed focal active colitis (left panel) with crypt destruction, loss of goblet cells, and neutrophilic infiltrates in the crypt epithelium (right panel) (original magnification: left panel, ×20; right panel, ×60).
Diarrhea/Colitis Management

A Gi Adverse Event Management Algorithm
Rule out noninflammatory causes. If noninflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

<table>
<thead>
<tr>
<th>Grade of Diarrhea/Colitis</th>
<th>Management</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea &lt;4 stools/day over baseline; Colitis: asymptomatic</td>
<td>Continue I-O therapy per protocol; Symptomatic treatment</td>
<td>Close monitoring for worsening symptoms; Educate patient to report worsening immediately if persists; Treat as grade 2 or 3/4</td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea: 4–6 stools per day over baseline; iv fluids indicated &lt;24 hrs; not interfering with ADL; Colitis: abdominal pain; blood in stool</td>
<td>Delay I-O therapy per protocol; Symptomatic treatment</td>
<td>If improves to grade 1: Resume I-O therapy per protocol; If persists &gt;5–7 days or recurs: 55–60 mg/kg/day methylprednisolone or oral equivalent; When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol; If worsens or persists &gt;3–5 days with oral steroids: Treat as grade 3/4</td>
</tr>
<tr>
<td>Grade 3–4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea: 6 stools per day over baseline; incontinence; iv fluids ≥24 hrs; interfering with ADL; Colitis (G3): severe abdominal pain, medical intervention indicated, perianal signs; G4: life-threatening, perforation</td>
<td>Discontinue I-O therapy per protocol; 1.0 to 2.0 mg/kg per day methylprednisolone iv or oral equivalent; Add prophylactic antibiotics for opportunistic infections; Consider lower endoscopy</td>
<td>If improves: Continue steroids until grade 1, then taper over at least 1 month; If persists &gt;3–5 days, or recurs after improvement: Add infliximab 5 mg/kg per day (if no contraindication). Note Infliximab should not be used in cases of perforation or sepsis</td>
</tr>
</tbody>
</table>

Patients on iv steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Diarrhea/Colitis Management

<table>
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<th>Grade of Diarrhea/Colitis (NCI CTCAE v4)</th>
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</tr>
<tr>
<td>Grade 2: Diarrhea: 4-6 stools per day over baseline; IV fluids indicated ≤24 hrs; not interfering with ADL; Colitis; abdominal pain; blood in stool</td>
<td>Delay I-O therapy per protocol; Symptomatic treatment</td>
<td>If improves to grade 1: Resume I-O therapy per protocol. If persists &gt; 5-7 days or recurs: 5.5-10 mg/kg per day methylprednisolone or oral equivalent. When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists &gt; 3-5 days with oral steroids: Treat as grade 3/4</td>
</tr>
<tr>
<td>Grade 3-4: Diarrhea: ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs interfering with ADL; Colitis: severe abdominal pain, medical intervention indicated, peristomal signs; G4: life-threatening, perforation</td>
<td>Discontinue I-O therapy per protocol; 1.0 to 2.0 mg/kg per day methylprednisolone or equivalent. Add prophylactic antibiotics for opportunistic infections. Consider lower endoscopy</td>
<td>If improves: Continue steroids until grade 1, then taper over at least 1 month. If persists &gt; 3-5 days, or recurs after improvement, add infliximab 5 mg/kg per day (if no contraindications). Note: Infliximab should not be used in cases of perforation or sepsis.</td>
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If ongoing → may need other immunosuppressants such as tacrolimus or mycophenolate mofetil in steroid & infliximab refractory. Colectomy may be needed (involve surgery early).

Prophylaxis for Diarrhea?

- 115 stage III/IV melanoma patients
  - Ipilimumab + budesonide vs ipilimumab + placebo
    - Q3 weeks x 4 doses with daily budesonide (9mg daily) which was tapered down by week 16; maintenance ipilimumab at weeks 24, 26, 48 & q 12 weeks thereafter

Table 2. Rate of grade ≥2 diarrhea in patients given ipilimumab with or without prophylactic budesonide

<table>
<thead>
<tr>
<th>Patients with grade ≥2 diarrhea*</th>
<th>Ipilimumab + budesonide (group A: n = 58)</th>
<th>Ipilimumab + placebo (group B: n = 57)</th>
<th>Total (N = 115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2, n (%)</td>
<td>11 (19.0)</td>
<td>10 (17.5)</td>
<td>21 (18.3)</td>
</tr>
<tr>
<td>Grade 3, n (%)</td>
<td>6 (10.3)</td>
<td>10 (17.5)</td>
<td>16 (13.9)</td>
</tr>
<tr>
<td>Grade 4, n (%)</td>
<td>2 (3.4)</td>
<td>0</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Grade ≥2 diarrhea rate, n (%)</td>
<td>19/58 (32.7)</td>
<td>20/57 (35.0)</td>
<td>39/115 (33.9)</td>
</tr>
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95% CI1
Difference in rate of grade ≥2 diarrhea, %* 21.0-46.3 22.9-48.8
95% CI3

Colitis & Checkpoint Inhibitors

- Immune-related diarrhea/colitis less frequent with PD-1 inhibitors vs anti-CTLA-4 inhibitors
  - Diarrhea 14-19% vs 33%; colitis 1-3% vs 12%
- Can safely treat with anti-PD1 post anti-CTLA4 related GI toxicity
- Resolution of diarrhea occurred in ~90% of patients with median time to resolution of 1-2 weeks (with nivolumab)

Back to our case... Ms. AS

- Diarrhea resolved
- BUT biochemical progression **Feb 2015** (LDH 983 → 2047)
- CT showing new liver lesions & calvarial, L-spine lesions but other lesions stable or improved
- Started nivolumab **Apr 2015**
  - Grade 2 diarrhea off/on
  - LDH normalized, CT showing mixed response after 6 cycles
  - Cycle 7 delayed for diarrhea & upper abdominal pain in **July 2015**
    - LEs increased (AST, ALT 2x ULN; ALP slightly elevated, bilirubin N, LDH N)
    - Repeat CT showing mixed response & distended gallbladder (?acalculus cholecysitits)
Case 1 – Ms. AS

- VGH ED → general surgery → GI
  - Abdominal ultrasound showed no evidence of biliary dilatation or other abnormalities
  - Admitted under general surgery for presumed acalculous cholecystitis
  - General surgery did HIDA scan which was negative
  - GI involved given ongoing elevation in liver enzymes for further work up
  - Bloodwork for hepatitis including viral & autoimmune causes was negative
  - Upper endoscopy showing mild gastritis (not explaining extent of abdominal pain)
Case 1 – Ms. AS

- After ruling out other causes, diagnosed with drug-induced hepatitis secondary to nivolumab
  - Nivolumab permanently discontinued (after completing 6 cycles) and prednisone initiated with slow taper (40mg daily initially)
- Resolution over time with LEs followed weekly
- Surveillance...
### Immune-related Adverse Events

#### Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

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<tr>
<th>AE</th>
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<td>0.6</td>
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<td>Hypothyroidism</td>
<td>8.6</td>
<td>0</td>
<td>15.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophysisis</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.3</td>
<td>0.3</td>
<td>6.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Based on data from the phase 3 study CheckMate 067 [6]. Incidence of hypophysisis and pneumonitis is based on unpublished data from CheckMate 067.

<sup>b</sup>One treatment-related death (neutropenia) was reported.

<sup>c</sup>No treatment-related deaths were reported.

<sup>d</sup>One treatment-related death (cardiac arrest) was reported.

<sup>e</sup>Based on data from the phase 3 study KEYNOTE-006 every 3 week dosing group [4].

<sup>f</sup>No treatment-related deaths were reported.

<sup>g</sup>AE of special interest, regardless of attribution of study drug.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IPI, ipilimumab; NIVO, nivolumab; Pembro, pembrolizumab.
# Frequency and Timing

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<th>Condition</th>
<th>Frequency in OPDIVO (N=1994)</th>
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<td>3.3 (6 days to 9 months)</td>
<td>51 (13%)</td>
<td>2.1 (15 days to 11 months)</td>
</tr>
</tbody>
</table>

**Endocrinopathies**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
<th>Median Time to Onset (months, range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophysitis</td>
<td>12 (0.6%)</td>
<td>4.9 (14 months to 11 months)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>20 (1%)</td>
<td>4.3 (15 days to 21 months)</td>
</tr>
<tr>
<td>Hypothyroidism/thyroiditis</td>
<td>171 (9%)</td>
<td>2.9 (1 day to 16.6 months)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>54 (2.7%)</td>
<td>1.5 (1 day to 14.2 months)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17* (0.9%)</td>
<td>4.4 (15 days to 22 months)</td>
</tr>
<tr>
<td>Nephritis/Renal Dysfunction</td>
<td>23 (1.2%)</td>
<td>4.6 (23 days to 12.3 months)</td>
</tr>
<tr>
<td>Skin*</td>
<td>171 (9%)</td>
<td>2.8 (&lt;1 day to 25.8 months)</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>3* (0.2%)</td>
<td>-</td>
</tr>
</tbody>
</table>

*Fatal cases have been reported. \(^1\) Two cases of diabetic ketoacidosis occurred. \(^2\) Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids.

Source: OPDIVO Adverse Reactions Management Guide. BMS.
Hepatitis

- **History, physical**
  - Often asymptomatic elevation of AST, ALT (rarely bilirubin) but can have associated fever, malaise, nausea; fulminant hepatitis has been reported with ipilimumab
  - Most common onset between 8-14 weeks
  - R/O other etiology – viral, medication, alcohol, disease progression

- **Labs** – LEs, bilirubin, albumin, INR/PTT, glucose, hepatitis B/C serology, autoimmune W/U

- **Imaging** – CT scan to R/O disease progression, abdominal U/S

- **Consult** hepatology +/- biopsy

Hepatitis

• More common with nivo + ipi combo vs single agent PD1 (14% vs 1-2%)
• Generally reversible and able to be retreated however some may need permanent discontinuation
• Use with caution in patients with significant liver disease or elevated serum transaminases
  • Assess LEs at baseline & prior to each cycle

Hepatitis

Hepatic Adverse Event Management Algorithm

- Rule out noninflammatory causes. If noninflammatory cause, treat accordingly and continue I-O therapy.
- Consider imaging for obstruction.

**Grade 1**
- AST or ALT >3 to 5 x ULN and/or T. bilirubin >1.5 to 3 x ULN
  - Continue I-O therapy per protocol

**Grade 2**
- AST or ALT >3 to 5 x ULN and/or T. bilirubin >1.5 to 3 x ULN
  - Delay I-O therapy per protocol
  - Increase frequency of monitoring to every 3 days

**Grade 3-4**
- AST or ALT >5 x ULN and/or T. bilirubin >3 x ULN
  - Discontinue I-O therapy
  - Increase frequency of monitoring to every 1-2 days
  - 1.8 to 2.0 mg/kg per day methylprednisolone i.v. or i.v. equivalent
  - Add prophylactic antibiotics for opportunistic infections
  - Consult gastroenterologist

**Follow-up**
- If returns to baseline:
  - Resume routine monitoring, resume I-O therapy per protocol
- If elevations persist >5-7 days or worsen:
  - 0.5-1 mg/kg per day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
- If returns to grade 2:
  - taper steroids over at least 1 month
- If does not improve in >3-5 days, worsens or rebounds:
  - Add mycophenolate mofetil 1 g b.i.d.
  - If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

I-O therapy may be delayed rather than discontinued if AST/ALT 38 x ULN and T. bilirubin 55 x ULN.

The recommended starting dose for grade 4 hepatitis is 2 mg/kg per day methylprednisolone i.v.
Case 1 – Ms. AS

- LDH increasing and CT showing evidence of disease progression in Nov 2015
- Progression of symptoms with pain
- LEs improved & off steroids
- Chemotherapy offered but patient declined. Offered pembrolizumab which she started...
Case 1 – Ms. AS

- 3 cycles of pembrolizumab (LDH 4401 → 1830)
- LEs remaining normal but progression of disease
- Pembrolizumab stopped
- Patient passed away
Takeaway Points

• Patient had toxicity but early recognition and management allowed to get treated for adverse events and continue being treated for melanoma

• She was able to be on all three available checkpoint inhibitors successfully despite previous toxicity
Case 2 – Mr. JT

- **ID** – 56 year old man with metastatic melanoma
- **PMHx** – otherwise healthy
- **History of Presenting Illness:**
  - **1996** - Stage 2a (pT3a) cutaneous melanoma of the right arm, treated with excision
  - **2010** – Relapsed with right axillary mass (biopsy confirmed), managed with right ALND and adjuvant IFN
  - **2013** – Recurrence with metastatic disease
    - **PET scan**: FDG-avid deposits in liver and left biceps muscle and FDG-avid portocaval LAD
    - **US guided biopsy of liver**: metastatic melanoma, BRAF wild-type
Case 2 – Mr. JT

- Started on ipilimumab 3mg/kg IV q3 weeks (given for up to four cycles)

- Developed a rash one week after cycle 1
  - Pruritic erythematous, scaly eruption affecting the upper torso
Skin Toxicity

- One of the most common immune-related adverse events seen with checkpoint inhibitors

<table>
<thead>
<tr>
<th>Incidence</th>
<th>&gt;20%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manifestations</td>
<td>Rash typically focal with a maculopapular appearance occurring on the trunk, back or extremities</td>
</tr>
</tbody>
</table>
| Management | Symptomatic management  
  • Topical corticosteroids for rashes  
  • Anti-histamines for pruritus |
| Note | Some skin reactions can be severe/life-threatening and require hospitalization |
Skin Toxicity

- Iplimumab:
  - Dermatitis, vitiligo, Grover’s disease, dermatomyositis
  - **Timing**: typically starts within weeks of treatment starting

- PD-1 inhibitors:
  - Lichenoid dermatitis, pruritus, vitiligo, inverse psoriasiform eruption, bullous pemphigoid, sarcoidosis (cutaneous nodules)
  - **Timing**: usually takes longer to onset, and can occur anytime in treatment course

Lichenoid dermatitis

Inverse psoriasiform rash
Grade 1-2 (Covering ≤ 30% of BSA)

Management:
• Symptomatic therapy (e.g. antihistamines, topical steroid creams)
• Continue immunotherapy

If persists >1-2 wks:
• Consider skin biopsy
• Delay immunotherapy
• Consider 0.5-1mg/kg/day prednisone or equivalent.

Grade 3-4 (Covering > 30% of BSA or life-threatening)

Management:
• Delay or discontinue immunotherapy
• 1mg/kg/day Prednisone (or equivalent)
• Consider skin biopsy, dermatology consult

If improves to Grade 1:
• Taper steroids over at least 1 month
• Consider resuming immunotherapy
Case 2 - Mr JT

- Seen by dermatologist → ipilimumab-related rash
- Managed with steroid cream with good effect
  - Rx: betamethasone valerate 0.1% cream BID
- Received 4 cycles of ipilimumab, then observation
- Several months after completing ipilimumab, evidence of progression on CT scan
Case 2 - Mr JT

• Started on PD1 inhibitor pembrolizumab
• Issues with recurrent AP and N/V, but CT scan showed regression in metastases after just 1 cycle of pembrolizumab
• Received cycles 2-9
• Worsening fatigue, weight loss, ongoing N/V
• Repeat CT Oct 2014 showed further reduction in tumor burden
Case 2 - Mr JT

- Immune-related endocrine toxicity
- Serum cortisol 93 (120-620)
- ACTH undetectable

→ Central adrenal insufficiency
Endocrine Immune-Related Adverse Events - Adrenal Insufficiency

• Low levels of cortisol secreted by the adrenal glands
  • 1º Adrenal insufficiency – failure of adrenal glands
    • Low cortisol, High ACTH (hyperpigmentation, electrolyte abnormalities)
  • 2º Adrenal insufficiency – failure of the pituitary gland
    • Low cortisol, Low ACTH

• Presents with non-specific, insidious symptoms
  • Fatigue, anorexia, weight loss, GI symptoms, myalgias

• Adrenal crisis
  • Life-threatening medical emergency
  • Shock, delirium, hypoglycemia, electrolyte abnormalities, GI distress
  • Typically precipitated by abrupt withdrawal of exogenous glucocorticoids, or acute illness/stress that body isn’t able to respond to by increasing cortisol production
Adrenal Insufficiency

**Diagnosis:**
- AM cortisol
  - >415 nmol/L – normal
  - <275 nmol/L – Sn 62%, Sp 77%
  - <138 nmol/L – Sn 36%, Sp 99%
- ACTH stimulation test
  - Cosyntropin 250mcg IV, measure cortisol at 0, 30, 60 mins
  - Normal: cortisol level doubles to an absolute value > 500 nmol/L

**Treatment:**
- Hydrocortisone, dosed to mimic endogenous cortisol secretion
  (20mg qAM, 10mg qPM)
- Patient education important – 3x3 rule, Medic Alert
Endocrine irAEs

- Autoimmune endocrinopathies can affect any organ in the endocrine system
- This includes:
  - Pituitary gland
    - Hypophysitis
    - Adrenal insufficiency
  - Thyroid gland
    - Hypo or hyperthyroidism (VERY common!)
Hypophysitis

- Hypophysitis is a rare, yet serious complication of checkpoint inhibitors
- Inflammation of the pituitary gland
- Manifests clinically as adrenal insufficiency, hypothyroidism and hypogonadism
- Non-specific symptoms - **clues:** lethargy, N/V, headaches, visual change
- Diagnosed based on MRI showing pituitary swelling (CT can be normal)
- Need to check all pituitary hormones
  - LH, FSH, cortisol, IGF, free T3 and T4, testosterone
- **Management:**
  - Endocrinology referral
  - Systemic glucocorticoids – Prednisone 1mg/kg/day
    - +/- stress dose steroids if evidence of adrenal crisis
  - Hormone replacement
  - Long-term monitoring
Case 2 - Mr JT

- Endocrinology referral
- Started on Hydrocortisone
- Marked improvement in energy level and general well-being
- Other pituitary hormone levels checked – all within normal limits
- Remained on pembrolizumab for a total of 2 years
Immune-related Adverse Events

### Table 2. Recommended monitoring for patients on PD-1 inhibitors

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Baseline testing</th>
<th>Suggested ongoing monitoring&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>● TSH, T3, and T4</td>
<td>● TSH every 4–6 weeks (every other dose)</td>
</tr>
<tr>
<td></td>
<td>● No other baseline hormonal testing needed</td>
<td>● No routine monitoring of other hormones needed</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>● LFTs</td>
<td>● LFTs prior to each cycle</td>
</tr>
<tr>
<td></td>
<td>● Hepatitis B surface antigen (HBsAg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Hepatitis B surface antibody (anti-HBs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Hepatitis B core antibody (anti-HBc)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>● Anti-HCV</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>● Chest radiograph</td>
<td>● Chest imaging every 4–6 weeks (every other dose)</td>
</tr>
<tr>
<td></td>
<td>● High-resolution chest CT scan with and without injection of contrast</td>
<td>● If symptoms, resting and exertion pulse oximetry and high-resolution chest CT scan (consider spirometry with measurement of carbon monoxide-diffusing capacity)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Immune-related adverse events’ surveillance should be continued every 12 weeks up to 1 year after discontinuation of immunotherapy.

Abbreviations: CT, computed tomography; HCV, hepatitis C virus; LFTs, liver function tests; PD-1, programmed cell death protein-1; TSH, thyroid-stimulating hormone.

# Immune-related Adverse Events

## Table 1. Incidence of treatment-related AEs of interest associated with immune checkpoint inhibitors

<table>
<thead>
<tr>
<th>AE</th>
<th>NIVO&lt;sup&gt;a,b&lt;/sup&gt;</th>
<th>NIVO + IPI&lt;sup&gt;a,c&lt;/sup&gt;</th>
<th>IPI&lt;sup&gt;a,d&lt;/sup&gt;</th>
<th>Pembro&lt;sup&gt;e,f&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Pruritus</td>
<td>18.8</td>
<td>0</td>
<td>33.2</td>
<td>1.9</td>
</tr>
<tr>
<td>Rash</td>
<td>25.9</td>
<td>0.6</td>
<td>40.3</td>
<td>4.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19.2</td>
<td>2.2</td>
<td>44.1</td>
<td>9.3</td>
</tr>
<tr>
<td>Colitis</td>
<td>1.3</td>
<td>0.6</td>
<td>11.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>3.8</td>
<td>1.3</td>
<td>17.6</td>
<td>8.3</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>3.8</td>
<td>1.0</td>
<td>15.3</td>
<td>6.1</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>8.6</td>
<td>0</td>
<td>15.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Hypophysitis</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>1.3</td>
<td>0.3</td>
<td>6.4</td>
<td>1.0</td>
</tr>
</tbody>
</table>

# Immunotherapy vs Chemotherapy

## Table 2. Incidence and RR of summary toxicity endpoints, including 95% CI and number of trials in each analysis

<table>
<thead>
<tr>
<th>Summary AE endpoints</th>
<th>No. of trials</th>
<th>PD-1/PD-L1 inhibitor incidence % (95% CI)</th>
<th>Chemotherapy incidence % (95% CI)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any all-grade AEs</td>
<td>7</td>
<td>67.6 (64.2–70.8)</td>
<td>82.9 (78.9–86.2)</td>
<td>0.82 (0.76–0.88)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Any high-grade AEs</td>
<td>7</td>
<td>11.4 (9.9–13.1)</td>
<td>35.7 (26.0–46.8)</td>
<td>0.32 (0.22–0.45)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment discontinuation</td>
<td>7</td>
<td>4.5 (3.5–5.7)</td>
<td>11.1 (8.5–14.3)</td>
<td>0.44 (0.33–0.57)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Treatment-related deaths</td>
<td>3</td>
<td>0.6 (0.3–1.1)</td>
<td>1.4 (0.7–2.5)</td>
<td>0.42 (0.16–1.13)</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: AE, adverse event; CI, confidence interval; PD-1, programmed death receptor-1; PD-L1, programmed death-ligand 1; RR, relative risk.

Figure 1. Timing of occurrence of immune-related adverse events following ipilimumab treatment.

Nivolumab (PD-1 Inhibitor)

Time to onset of select treatment-related irAEs seen with Nivolumab
(Any grade, N = 474)

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

<table>
<thead>
<tr>
<th>The Common</th>
<th>The Life Threatening</th>
<th>The Weird &amp; Wonderful</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fatigue</td>
<td>• Pneumonitis</td>
<td>Neurologic irAEs</td>
</tr>
<tr>
<td>• Rash</td>
<td>• Colitis</td>
<td>• Guillain-Barre Syndrome</td>
</tr>
<tr>
<td>• Pruritus</td>
<td>• Hepatitis</td>
<td>• Inflammatory myopathies</td>
</tr>
<tr>
<td>• Diarrhea</td>
<td>• Nephritis</td>
<td>• Aseptic meningitis</td>
</tr>
<tr>
<td>• Endocrinopathies</td>
<td>• Type 1 Diabetes and DKA</td>
<td>• CIPD</td>
</tr>
<tr>
<td>- Thyroid (hyper or hypo)</td>
<td>• Pancreatitisis</td>
<td>• PRES</td>
</tr>
<tr>
<td></td>
<td>• Hypophysitis</td>
<td>• Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>- Adrenal insufficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mimickers of progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pseudoprogession</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sarcoidosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Awareness and Education is important

- irAEs are typically **low grade** and **easily managed**, but early **recognition** is important to prevent significant morbidity and mortality
- Patient and care team education is required to help with diagnosis of immune-related adverse events, which can present with non-specific, insidious symptoms
- The cornerstone of treatment is systemic **glucocorticoids** and **withholding** or permanent discontinuation of the immunotherapy

---

Also, not everything is an immune-related AE....
And not everyone needs steroids...
ASSESS AND ASK THE PATIENT ABOUT THE FOLLOWING SIGNS OR SYMPTOMS

**GASTROINTESTINAL**
- Any changes in normal bowel habits or changes from baseline (e.g., last week, last visit)
  - Diarrhea
  - Abdominal pain
  - Blood or mucus in stool with or without fever
  - Peritoneal signs consistent with bowel perforation
  - Ileus

**LIVER**
- Elevations in liver function tests
  - AST >2.5 times upper limit of normal (ULN)
  - ALT >2.5 times ULN
  - Total bilirubin >1.5 times ULN

**NOTE:** Always check lab values prior to each infusion.

**SKIN**
- Pruritus
- Rash

**NEUROLOGIC**
- Monitor for symptoms of motor and sensory neuropathy
  - Unilateral or bilateral weakness
  - Sensory alterations
  - Paresthesia

**ENDOCRINE**
- Fatigue
- Headache
- Mental status changes
- Abdominal pain
- Unusual bowel habits
- Hypotension
- Abnormal thyroid function tests and/or serum chemistries

MEDICAL ALERT

NAME __________________________

has received

NIVOLUMAB: Immune-Mediated Adverse Reactions

SEVERE IMMUNE-MEDIATED ADVERSE REACTIONS
Including enterocolitis, intestinal perforation, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, endocrinopathy, pneumonitis and toxicities in other organ systems. Duration of risk after treatment is unknown.

FOR MORE INFORMATION:
Abbottsford - Abbotsford Centre............................................. 604-851-4710
Kelowna - Centre for the Southern Interior.......................... 250-712-3900
Prince George - Centre for the North................................... 250-645-7300
Surrey - Fraser Valley Centre.............................................. 604-930-4055
Vancouver - Vancouver Centre............................................. 604-877-6000
Victoria - Vancouver Island Centre.................................... 250-519-5500

www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual

Rev 1 March 2017

ALWAYS CARRY THIS CARD AND SHOW TO PHYSICIANS INCLUDING ANESTHETISTS
To Whom It May Concern:

RE: __________________________________________

Medical Oncologist ______________________________
Immunotherapy Regimen __________________________

This patient is receiving immunotherapy at the BCCA and is at risk of immune-related toxicities which may be life threatening and require urgent management.

Immunotherapy toxicities are different from those encountered with standard chemotherapy or targeted therapies. The immune system may become dysregulated during immunotherapy treatment, leading to symptoms and findings which mimic autoimmune disorders. Adverse events can occur during or following treatment and can be life threatening. Any organ system in the body is at risk including, but not limited to:

- Lungs (pneumonitis, pleuritis, sarcoidosis)
- Gastrointestinal (colitis, ileitis, pancreatitis)
- Liver (hepatitis)
- Skin (rash, Stevens-Johnson syndrome)
- Endocrine (hypophysitis, adrenal insufficiency, hypo/hyperthyroidism, type 1 diabetes mellitus)
- Renal (interstitial nephritis)
- Blood (hemolytic anemia, thrombocytopenia, neutropenia)
- Neurologic (encephalitis, Guillain-Barré syndrome, meningitis, myasthenia gravis, neuropathy)
- Musculoskeletal (myositis, arthritis)
- Cardiovascular (pericarditis, myocarditis, vasculitis)
- Ophthalmologic (uveitis, scleritis, episcleritis, conjunctivitis, retinitis)

Management of immune-related toxicities necessitates prompt coordination with a medical oncologist with prompt initiation of high dose corticosteroids. Referral to the appropriate subspecialty. If you suspect your patient is presenting with immune-related toxicity, please contact the patient’s medical oncologist directly or if after-hours contact the on-call physician. For additional information on immunotherapy toxicity treatment algorithms, located at the end of the above posted protocol at www.bccancer.bc.ca.
Resources and Education

Guidelines:
- “Management of immunotherapy-related toxicities” – *NCCN Clinical Practice Guidelines in Oncology, 2021* (https://www.nccn.org/professionals/physician_gls/pdf/immunotherapy.pdf) → you do need to log in but it’s free to sign up

Drug Monographs:
- Pembrolizumab (https://www.merck.ca/static/pdf/KEYTRUDA-PM_E.pdf)

Articles:
- “Management of adverse events following treatment with anti-PD 1 Agents” – *The Oncologist*, 2016
- “Safety and tolerability of PD-1/PD-L1 inhibitors compared with chemotherapy: a Meta-Analysis“ – *Oncologist, 2017*
- “Monitoring and management of immune-related AEs associated with PD-1 axis inhibitors in lung cancer” – *The Oncologist, 2016*

Protocols:
- **BC Cancer protocols**: BC Cancer website → Health Professionals → Chemotherapy Protocols → Immunotherapy → SCIMMUNE Protocol
Call your local medical oncologist for advice...

• These drugs can cause any ‘itis’ and toxicity can present in a myriad of ways

• Call us for patients on these drugs if you suspect potential toxicity

• AND don’t forget the usual suspects in patients including infection, other drug toxicity, progressive malignancy etc.
SCIMMUNE Protocol

Enterocolitis

Grade 1
Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis

- Physician notified of assessment
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Antidiarrheal treatment
- Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up

Grade 2
Diarrhea of 4 to 6 stools per day over baseline, IV fluids less than 24 h, normal daily activities, abdominal pain, mucus or blood in stool

- Physician notified and collaborative symptom management initiated
- Withhold nivolumab
- Antidiarrheal treatment
- If persists beyond 3-5 days or recur, start prednisone 0.5 to 1 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Monitoring
Diarrhea, abdominal pain, mucus or blood in stools-with or without fever, ileus, peritoneal signs

Grade 3 or 4
Grade 3: diarrhea of 7 or more stools per day over baseline, incontinence, IV fluids for 24 h or more, impaired daily activities; colitis with severe abdominal pain, requiring medical interventions, peritoneal signs of bowel perforation
Grade 4: life-threatening colitis, perforation

- Physician notified and collaborative symptom management initiated
- Withhold (if Grade 3) or discontinue (if Grade 4 or persistent Grade 3) nivolumab
- Gastroenterology consultation
- Rule out bowel perforation; if bowel perforation is present, DO NOT administer corticosteroids
- Consider endoscopic evaluation
- Prednisone 1 to 2 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Improvement to Grade 1 or less
- Resume nivolumab
- If steroid used, taper over at least 1 month before resuming nivolumab
- Patient education of steroid tapering per physician order

Improvement to Grade 1 or less
- Taper prednisone over at least 1 month before resuming nivolumab
- Patient education of steroid tapering per physician order
- If no response within 5 days or recur
- Consider treatment with infliximab; if refractory to infliximab, consider mycophenolate
- Continually evaluate for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy

Conclusions

• Checkpoint inhibitors are immunomodulatory agents that are used to amplify T-cell mediated immunity and allow the patient to mount an effective anti-tumor immune response
• Checkpoint inhibitors have improved the prognosis for patients in a number of different disease sites
• These agents are associated with unique immune-related toxicities, with skin and the GI tract being most commonly affected
• CTLA-4 inhibitors are associated with higher rates of immune-related adverse events than PD-1 inhibitors, with combination immunotherapy showing significantly increased risk of Grade 3 or 4 toxicity
• Overall, however, immunotherapy is better tolerated than chemotherapy
Conclusions

• Immune-related adverse events are typically low grade and easily managed, but require early recognition to prevent significant morbidity and mortality
• Patient and care team education is required to help with the diagnosis of immune-related adverse events, which can present with non-specific, insidious symptoms
• The cornerstone of treatment is systemic glucocorticoids and withholding or permanent discontinuation of the immunotherapy

Also, not everything is an immune-related AE....
POLL – How comfortable would you feel seeing a patient on IO?

1. Very comfortable
2. Somewhat comfortable
3. Neutral
4. Somewhat uncomfortable
5. Not comfortable at all
Questions?