BCCA Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma Using Pembrolizumab

Protocol Code
USMAVPEM

Tumour Group
Skin and Melanoma

Contact Physician
Dr. Kerry Savage

ELIGIBILITY:
- Unresectable stage 3 or stage 4 metastatic melanoma in patients:
  - Ipilimumab naïve, regardless of BRAF V600 mutation status
  - ECOG 0 - 1
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab
- A BCCA “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
- Patients are eligible to receive pembrolizumab or ipilimumab or nivolumab but not sequential use of these agents

EXCLUSIONS:
- Active central nervous system metastases (should be asymptomatic and/or stable)
- Active autoimmune disease
- Use with cautions in patients with long term immunosuppressive therapy or systemic corticosteroids (Requiring more than 10 mg prednisone/day or equivalent)

TESTS:
- Baseline: CBC and differentials, platelets, creatinine, alkaline phosphatase, AST, ALT, total bilirubin, LDH, electrolytes, TSH, serum morning cortisol, chest x-ray
- Before each treatment: CBC and differentials, platelets, creatinine, alkaline phosphatase, AST, ALT, total bilirubin, LDH, electrolytes, TSH
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, glucose, serum or urine HCG (required for woman of child bearing potential if pregnancy suspected), Free T3 and Free T4, serum ACTH levels, testosterone, estradiol, FSH, LH, ECG
- Weekly telephone nursing assessment for signs and symptoms of side effects while on treatment (Optional).
PREMEDICATIONS:
- Antiemetics are not usually required.
- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- If prior infusion reactions to pembrolizumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 1000 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment.

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
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</thead>
<tbody>
<tr>
<td>pembrolizumab</td>
<td>2 mg/kg</td>
<td>IV in 50 mL* NS over 30 minutes using a 0.2 micron in-line filter</td>
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</tbody>
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*Keep final concentration to 1 to 10 mg/mL

- Repeat every 3 weeks until disease progression, unacceptable toxicity, or a maximum of 2 years of treatment

DOSE MODIFICATIONS:
No specific dose modifications. Toxicity managed by treatment delay and other measures (see Appendix for Immune-mediated Adverse Reaction Management Guide).

PRECAUTIONS:
- **Serious immune-mediated reactions**: these can be severe to fatal and usually occur during the treatment course. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see Appendix for Immune-mediated Adverse Reaction Management Guide).
- **Infusion-related reactions**: isolated cases of severe reaction have been reported. In case of a severe reaction (Grade 3 or 4), pembrolizumab infusion should be permanently discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive pembrolizumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered if there is a history of reaction.

Call Dr. Kerry Savage or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 1 Jun 2016
Date revised: 1 Apr 2017 (Tests clarified)
References:
Appendix. Immune-mediated adverse reaction management guide

Pneumonitis

Grade 1
Radiographic changes only

• Physician notified of assessment
• Consider withholding pembrolizumab
• Monitor every 2 to 3 days
• Consider pulmonary and infectious disease consultation

Reassess at least every 3 weeks

If improved
• Resume pembrolizumab (if withheld) when stable
If worsens
• Treat as Grade 2 or Grades 3 or 4

Grade 2
Mild to moderate symptoms, worsens from baseline

• Physician notified and collaborative symptom management initiated
• **Withhold pembrolizumab**
• Consider high resolution CT scan
• Monitor daily
• predniSONE 1 mg/kg/day PO
• Patient education of steroid use
• Pulmonary and infectious disease consultation
• Consider bronchoscopy, lung biopsy
• Book nursing follow up call as needed

Reassess every 1 to 3 days

If improved to baseline
• Taper steroid over at least 1 month
  BEFORE resuming pembrolizumab
• Consider prophylactic antibiotics for opportunistic infections
If persists or worsens after 2 weeks
• Treat as Grades 3 or 4

Grade 3 or 4
Severe symptoms, new or worsening hypoxia, life-threatening

• Hospitalize
• **Discontinue pembrolizumab**
• Monitor daily
• predniSONE 2 to 4 mg/kg/day PO
• Patient education of steroid use
• Prophylactic antibiotics for opportunistic infections
• Pulmonary and infectious disease consultation
• Consider bronchoscopy, lung biopsy
• Upon discharge, book nursing follow up call as needed

If improved to baseline
• Taper steroid over at least 6 weeks
If persists or worsens after 2 days
• Consider non-steroid immunosuppressive agents (e.g., inFLIXimab, cyclophosphamide, mycophenolate)
**Enterocolitis**

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

**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 pembrolizumab
- 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

**Improvement to Grade 1 or less**
- Resume pembrolizumab
- If steroid used, taper over at least 1 month BEFORE resuming pembrolizumab
- Consider prophylactic antibiotics for opportunistic infections
- Patient education of steroid tapering per physician order

**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) pembrolizumab
- 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
- Prophylactic antibiotics for opportunistic infections
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea
- Physician notified and collaborative symptom management initiated
- Withhold (if Grade 3) or discontinue (if Grade 4 or persistent Grade 3) pembrolizumab
- 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
- Prophylactic antibiotics for opportunistic infections
- Patient education of steroid use
- Nursing management per BCCA Symptom Management Guidelines: Cancer-Related Diarrhea

**Improvement to Grade 1 or less**
- Taper prednisone over at least 1 month before resuming pembrolizumab
- 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
Monitoring
Abnormal liver function test, jaundice, tiredness

Grade 2
AST/ALT 3 to less than 5 X ULN
or
Total bilirubin 1.5 to 3 X ULN

- Physician notified and collaborative symptom management initiated
- Withhold pembrolizumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 3 days until resolution
- Book future nursing follow up call as needed

If AST/ALT 3 × ULN or lower and bilirubin 1.5 × ULN or lower, or return to baseline
- Resume pembrolizumab
If elevation persists more than 5-7 days or worsen
- predniSONE 0.5 to 1 mg/kg/day PO
- consider prophylactic antibiotics for opportunistic infections
- taper predniSONE over at least 1 month before resuming pembrolizumab
- Patient education of steroid tapering per physician order

Grades 3 or 4
AST/ALT more than 5 X ULN
or
Total bilirubin more than 3 X ULN
or
AST/ALT increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of AST/ALT

- Physician notified and collaborative symptom management initiated
- Discontinue pembrolizumab
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 1 to 2 days until resolution
- Gastroenterology consultation
- predniSONE 1 to 2 mg/kg/day PO
- Prophylactic antibiotics for opportunistic infections
- Patient education on steroid use
- Book future nursing follow up call as needed

If LFTs return to Grade 2 or less
- Taper predniSONE over at least 1 month
For persistent Grades 3 or 4 for more than 3 to 5 days, worsens, or recurs:
- Consider non-steroid immunosuppressive agents (e.g., mycophenolate)
Renal

Monitoring
Increase in serum creatinine, decreased urine output, hematuria, edema

Grade 1
Creatinine >1 - 1.5 x ULN
- Creatinine weekly

When return to baseline
- Resume routine creatinine

Grade 2
Creatinine >1.5 - 3.0 x ULN
- Physician notified and collaborative symptom management initiated
- Withhold pembrolizumab
- Nephrology consultation
- Creatinine every 2 to 3 days
- predniSONE 0.5 to 1 mg/kg/day PO
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If improved to Grade 1
- Taper steroid over at least 1 month
  BEFORE resuming pembrolizumab and routine creatinine
If persists for more than 7 days or worsens
- Treat as Grade 4

Grade 3
Creatinine >3.0 - 6.0 x ULN
Grade 4 >6.0 x ULN
- Physician notified and collaborative symptom management initiated
- Discontinue pembrolizumab
- Nephrology consultation
- Creatinine daily
- predniSONE 1 to 2 mg/kg/day PO
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If improved to Grade 1
- Taper steroid over at least 1 month
### Endocrine

**Monitoring**

Persistent or unusual headaches, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, irritability, forgetfulness) dizziness or fainting, hair loss, feeling cold, constipation, voice gets deeper

<table>
<thead>
<tr>
<th>Asymptomatic TSH elevation</th>
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<tbody>
<tr>
<td>• Physician notified and collaborative symptom management initiated</td>
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<tr>
<td>• <strong>Continue pembrolizumab</strong></td>
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<tr>
<td>• If TSH less than 0.5 x LLN, or TSH greater than 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated</td>
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<tr>
<td>• Consider endocrinology consultation</td>
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<table>
<thead>
<tr>
<th>Symptomatic endocrinopathy</th>
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<tbody>
<tr>
<td>• Physician notified and collaborative symptom management initiated</td>
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<tr>
<td>• Evaluate endocrine function</td>
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<tr>
<td>• Consider pituitary scan</td>
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<tr>
<td>• <strong>Withhold pembrolizumab if abnormal lab or pituitary scan</strong></td>
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<tr>
<td>• Endocrinology consultation</td>
</tr>
<tr>
<td>• prednisone 1 to 2 mg/kg/day PO</td>
</tr>
<tr>
<td>• Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</td>
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<thead>
<tr>
<th>Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)</th>
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<tbody>
<tr>
<td>• Physician notified and collaborative symptom management initiated</td>
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<tr>
<td>• Rule out sepsis</td>
</tr>
<tr>
<td>• <strong>Withhold pembrolizumab</strong></td>
</tr>
<tr>
<td>• Evaluate endocrine function</td>
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<tr>
<td>• Endocrinology consultation</td>
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<tr>
<td>• Endocrinology consult</td>
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<tr>
<td>• Stress dose of IV steroids with mineralocorticoid activity</td>
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<tr>
<td>• IV fluids</td>
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</table>

If improved with or without hormone replacement:

- Taper steroid over at least 1 month BEFORE resuming pembrolizumab
- Consider prophylactic antibiotics for opportunistic infections

**Continue standard monitoring**

- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

When adrenal crisis ruled out:

- Treat as symptomatic endocrinopathy
**Skin**

**Monitoring**
Rash, pruritus (unless an alternate etiology has been identified)

**Grade 1 to 2**
30% of skin surface or less

- Physician notified of assessment
- Nursing management per ASCO Skin Reactions to Targeted Therapies
  - Sun safety (see Your Medication Sun Sensitivity and Sunscreens)
  - Skin care; moisturizers, soaps
  - Topical corticosteroids
diphenhydramine PO
- Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up

If persists more than 1-2 weeks or recurs
- Consider skin biopsy
- **Withhold pembrolizumab**
- prednison 0.5 to 1 mg/kg/day PO
- Patient education on steroid use
- Once improving, taper prednison over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume pembrolizumab

**Grade 3-4**
More than 30% of skin surface, life-threatening

- Physician notified and collaborative symptom management initiated
- **Withhold or discontinue pembrolizumab**
- Consider skin biopsy
- Dermatology consult
- prednison 1 to 2 mg/kg/day PO (or methylprednisolone 1 to 2 mg/kg/day IV)
- Patient education on steroid use
- Book nursing follow up call for next business day and/or create care plan if BCCA nurse unable to follow up

If improves to Grade 1
- taper prednison over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume pembrolizumab
Other immune-mediated or treatment-related adverse reactions

If severe or clinically significant:
- Withhold (Grade 3) or permanently discontinue pembrolizumab (Grade 4)
- prednisONE 1 to 2 mg/kg/day PO
- Corticosteroid eye drops for uveitis
- Consider referring to a specialist

1. Eye: uveitis
2. Gastrointestinal: pancreatitis
3. Musculoskeletal: myositis
4. Skin: severe skin reactions