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

Protocol Code
USMAVIPI

Tumour Group
Skin and Melanoma

Contact Physician
Dr. Kerry Savage

ELIGIBILITY:
- Unresectable stage III or stage IV melanoma
- ECOG 0 - 1
- Adequate hepatic and renal function
- At least one prior systemic therapy (Note: ipilimumab after pembrolizumab or nivolumab is not currently funded by BCCA)
- Life expectancy of at least 4 months
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of ipilimumab
- 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
- Concurrent 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
- Before each treatment: CBC and differentials, platelets, creatinine, alkaline phosphatase, AST, ALT, total bilirubin, LDH, electrolytes, TSH
- If clinically indicated: 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 but recommended).
PREMEDICATIONS:
Antiemetics are not usually required.
- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- If prior infusion reactions to ipilimumab: 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>ipilimumab</td>
<td>3 mg/kg IV every 3 weeks</td>
<td>IV in 100 mL NS over 1 hour 30 minutes* using a 0.22 micron in-line filter</td>
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</tbody>
</table>

* if no reactions at second dose, may infuse over 30 minutes

- Repeat every 3 weeks for 4 cycles
- If stable disease (more than 3 months) or complete / partial response, consider repeating treatment course (reinduction) at disease progression

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, ipilimumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab with close monitoring. Premedications with acetaminophen and anti-histamine may be considered.

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 November 2012
Date revised: 1 Mar 2017 (Eligibility and toxicities management updated)
References:
4. Pan-Canadian Oncology Drug Review. Final clinical guidance report for ipilimumab (Yervoy) for advanced melanoma. 18 April 2012.
7. Sosman JA. Ipilimumab (anti-CTLA-4) immunotherapy in advanced melanoma. UpToDate. (Accessed on December 13, 2011)
Appendix. Immune-mediated adverse reaction management guide

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 ipilimumab**
- **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

**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) ipilimumab**
- 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
- Book nursing follow up call as needed

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

**Improvement to Grade 1 or less**
- Taper predniSONE over at least 1 month before resuming ipilimumab
- 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

BC Cancer Agency Protocol Summary USMAVIP1
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Liver

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 ipilimumab**
- 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 ipilimumab

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 ipilimumab
- 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 ipilimumab**
- 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

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Creatinine &gt;1 - 1.5 x ULN</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Creatinine weekly</td>
</tr>
<tr>
<td></td>
<td>When return to baseline</td>
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<tr>
<td></td>
<td>• Resume routine creatinine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
<th>Creatinine &gt;1.5 - 3.0 x ULN</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Physician notified and collaborative symptom management initiated</td>
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<tr>
<td></td>
<td>• Withhold ipilimumab</td>
</tr>
<tr>
<td></td>
<td>• Nephrology consultation</td>
</tr>
<tr>
<td></td>
<td>• Creatinine every 2 to 3 days</td>
</tr>
<tr>
<td></td>
<td>• PredniSONE 0.5 to 1 mg/kg/day PO</td>
</tr>
<tr>
<td></td>
<td>• Patient education on steroid use</td>
</tr>
<tr>
<td></td>
<td>• Consider renal biopsy</td>
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<tr>
<td></td>
<td>• Book future nursing follow up call as needed</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
<th>Creatinine &gt;3.0 - 6.0 x ULN</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>• Physician notified and collaborative symptom management initiated</td>
</tr>
<tr>
<td></td>
<td>• Discontinue ipilimumab</td>
</tr>
<tr>
<td></td>
<td>• Nephrology consultation</td>
</tr>
<tr>
<td></td>
<td>• Creatinine daily</td>
</tr>
<tr>
<td></td>
<td>• PredniSONE 1 to 2 mg/kg/day PO</td>
</tr>
<tr>
<td></td>
<td>• Patient education on steroid use</td>
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<tr>
<td></td>
<td>• Consider renal biopsy</td>
</tr>
<tr>
<td></td>
<td>• Book future nursing follow up call as needed</td>
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</tbody>
</table>

**If improved to Grade 1**
• Taper steroid over at least 1 month
BEFORE resuming ipilimumab and routine creatinine

**If persists for more than 7 days or worsens**
• Treat as Grade 4

**If improved to Grade 1**
• Taper steroid over at least 1 month

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## 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>
<th>Symptomatic endocrinopathy</th>
<th>Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Physician notified and collaborative symptom management initiated</td>
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</tr>
<tr>
<td>- <strong>Continue ipilimumab</strong></td>
<td>- <strong>Evaluate endocrine function</strong></td>
<td>- <strong>Rule out sepsis</strong></td>
</tr>
<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>
<td>- <strong>Consider pituitary scan</strong></td>
<td>- <strong>Withhold ipilimumab</strong></td>
</tr>
<tr>
<td>- <strong>Endocrinology consultation</strong></td>
<td>- <strong>Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</strong></td>
<td>- <strong>Evaluate endocrine function</strong></td>
</tr>
<tr>
<td>- <strong>Prednisone 1 to 2 mg/kg/day PO</strong></td>
<td>- <strong>Appropriate hormone replacement if symptomatic with</strong></td>
<td>- <strong>Endocrinology consultation</strong></td>
</tr>
<tr>
<td>- <strong>Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</strong></td>
<td></td>
<td>- <strong>Consider pituitary scan</strong></td>
</tr>
<tr>
<td>- <strong>Endocrinology consultation</strong></td>
<td>- <strong>Withhold ipilimumab if abnormal lab or pituitary scan</strong></td>
<td>- <strong>Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</strong></td>
</tr>
<tr>
<td>- <strong>Prednisone 1 to 2 mg/kg/day PO</strong></td>
<td></td>
<td>- <strong>Endocrinology consultation</strong></td>
</tr>
<tr>
<td>- <strong>Stress dose of IV steroids with mineralocorticoid activity</strong></td>
<td>- <strong>Continue ipilimumab</strong></td>
<td>- <strong>Stress dose of IV steroids with mineralocorticoid activity</strong></td>
</tr>
<tr>
<td>- <strong>IV fluids</strong></td>
<td>- If improved with or without hormone replacement:</td>
<td>- <strong>IV fluids</strong></td>
</tr>
<tr>
<td></td>
<td>- <strong>Taper steroid over at least 1 month</strong></td>
<td>- <strong>Withhold ipilimumab if abnormal lab or pituitary scan</strong></td>
</tr>
<tr>
<td></td>
<td>- <strong>Before resuming ipilimumab</strong></td>
<td>- <strong>Evaluate endocrine function</strong></td>
</tr>
<tr>
<td></td>
<td>- <strong>Consider prophylactic antibiotics for opportunistic infections</strong></td>
<td>- <strong>Endocrinology consultation</strong></td>
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<td>- <strong>Endocrinology consultation</strong></td>
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<tr>
<td></td>
<td></td>
<td>- <strong>Stress dose of IV steroids with mineralocorticoid activity</strong></td>
</tr>
</tbody>
</table>

### If improved with or without hormone replacement:
- Taper steroid over at least 1 month **Before resuming ipilimumab**
- 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

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**Skin**

Monitoring

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

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**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

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**Grade 3-4**

More than 30% of skin surface, life-threatening

- Physician notified and collaborative symptom management initiated
- Withhold or discontinue ipilimumab
- Consider skin biopsy
- Dermatology consult
- predniSONE 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

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If persists more than 1-2 weeks or recurs

- Consider skin biopsy
- Withhold ipilimumab
- predniSONE 0.5 to 1 mg/kg/day PO
- Patient education on steroid use
- Once improving, taper predniSONE over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume ipilimumab

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If improves to Grade 1

- taper predniSONE over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume ipilimumab

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Neurologic

**Monitoring**
S/S of motor or sensory neuropathies: Unilateral or bilateral weakness, sensory alterations, parenthesis

**Grade 2**
Not interfering with daily activities
- Physician notified and collaborative symptom management initiated
- **Withhold ipilimumab**
- Introduce appropriate medical intervention
- Book future nursing follow up call as needed

**Grades 3 or 4**
(interfering with daily activities)
Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
- Physician notified and collaborative symptom management initiated
- **Discontinue ipilimumab**
- Institute appropriate intervention for neuropathy
- Consider predniSONE 1 to 2 mg/kg/day PO
- Patient education on steroid use
- Book future nursing follow up call as needed

When symptoms resolve or return to baseline
- Resume ipilimumab to complete planned doses or 16 weeks from first dose, whichever earlier
Other immune-mediated adverse reactions

If severe or clinically significant:

- Discontinue ipilimumab
- prednISONE 1 to 2 mg/kg/day PO
- Corticosteroid eye drops for uveitis, iritis or episcleritis
- Consider referring to a specialist

1. Blood and lymphatic: hemolytic anemia
2. Cardiovascular: angioathy, myocarditis, pericarditis, temporal arteritis, vasculitis
3. Endocrine: autoimmune thyroiditis
4. Eye: blepharitis, conjunctivitis, episcleritis, iritis, scleritis, uveitis
5. Gastrointestinal: pancreatitis
6. Infectious: meningitis
7. Musculoskeletal: arthritis, polymyalgia rheumatica
8. Renal and urinary: nephritis
9. Respiratory: pneumonitis
10. Skin: psoriasis, leukocytoclastic vasculitis