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

Protocol Code  USMAVFIFI

Tumour Group  Skin and Melanoma

Contact Physician  Dr. Vanessa Bernstein

ELIGIBILITY:
- Unresectable stage IIIC or stage IV melanoma
- ECOG 0 - 1
- Adequate hepatic and renal function
- 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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<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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</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. Vanessa Bernstein 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 Jul 2015
Date revised: 1 Mar 2017 (Eligibility Toxicities management updated)
References:
3. Pan-Canadian Oncology Drug Review. Expert Review Committee final recommendation on ipilimumab (Yervoy) for the first-line treatment of patients with advanced (unresectable or metastatic) melanoma. 22 December 2014.
### Appendix. Immune-mediated adverse reaction management guide

#### Enterocolitis

<table>
<thead>
<tr>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3 or 4</th>
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<tbody>
<tr>
<td>Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis</td>
<td>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,</td>
<td>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</td>
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- 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

- 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

**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

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**Warning**: The information contained in these documents are a statement of consensus of BC Cancer Agency professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer Agency's terms of use available at [www.bccancer.bc.ca/legal.htm](http://www.bccancer.bc.ca/legal.htm)
Liver

Abnormal liver function test, jaundice, tiredness

Monitoring

**Grade 2**
- AST/ALT 3 to less than 5 X ULN
- 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
- Total bilirubin more than 3 X ULN
- 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

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 ipilimumab
- 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 ipilimumab 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
- Physician notified and collaborative symptom management initiated
- Discontinue ipilimumab
- 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

Grade 4
Creatinine >6.0 x ULN
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

Asymptomatic TSH elevation
- Physician notified and collaborative symptom management initiated
- **Continue ipilimumab**
- 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
- Consider endocrinology consultation

Symptomatic endocrinopathy
- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function
- Consider pituitary scan
- **Withhold ipilimumab if abnormal lab or pituitary scan**
- Endocrinology consultation
- Prednison 1 to 2 mg/kg/day PO
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Appropriate hormone replacement if symptomatic with

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

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

Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)
- Physician notified and collaborative symptom management initiated
- Rule out sepsis
- **Withhold ipilimumab**
- Evaluate endocrine function
- Endocrinology consultation
- Consider pituitary scan
- Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan
- Endocrinology consult
- Stress dose of IV steroids with mineralocorticoid activity
- IV fluids

When adrenal crisis ruled out:
- Treat as symptomatic endocrinopathy

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Skin

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

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

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

If improves to Grade 1
- taper prednisone over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume ipilimumab
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