BC Cancer Protocol Summary for the Treatment of Unresectable or Metastatic Melanoma Using Ipilimumab and Nivolumab

**Protocol Code**  
USAVIPNI

**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
- No prior systemic therapy for advanced disease with the exception of BRAF and/or MEK inhibitors for BRAF mutant metastatic melanoma
- Patients on or completed anti-PD-1 monotherapy for advanced disease without progression, particularly if at high risk for disease progression
- Patients who relapse after a response > 2 years with ipilimumab started prior to 1 April 2019 for advanced disease
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of immunotherapy checkpoint inhibitors
- A BC Cancer “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
- Note:
  - No replacement of nivolumab with pembrolizumab in the maintenance phase

**EXCLUSIONS:**
- Progressing on anti-PD-1 monotherapy for advanced disease
- Prior treatment with combination immunotherapy for advanced disease
- Retreatment with ipilimumab and nivolumab would not be funded for patients on relapse
- Active central nervous system metastases (if CNS mets present they should be asymptomatic and/or stable)
- 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 & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, glucose, TSH, morning serum cortisol, chest x-ray
- Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): HBsAg, HBcoreAb
- Note: tuberculin skin test recommended
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH, creatinine kinase, glucose
- If clinically indicated: chest x-ray, morning serum cortisol, lipase, 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 induction phase with ipilimumab and nivolumab. Optional when patients are on nivolumab

PREMEDICATIONS:
- Antiemetics are not usually required.
- Antiemetic protocol for low emetogenicity (see SCNAUSEA).
- If prior infusion reactions to ipilimumab or nivolumab: diphenhydrAMINE 50 mg PO, acetaminophen 325 to 1000 mg PO, and hydrocortisone 25 mg IV 30 minutes prior to treatment

TREATMENT:

Induction Phase

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>nivolumab</td>
<td>1 mg/kg</td>
<td>IV in 50 mL* NS over 30 minutes using a 0.2 or 0.22 micron in-line filter***</td>
</tr>
<tr>
<td>ipilimumab</td>
<td>3 mg/kg</td>
<td>IV in 100 mL NS over 1 hour 30 minutes** using a 0.2 or 0.22 micron in-line filter***</td>
</tr>
</tbody>
</table>

*Keep final concentration to 1 to 10 mg/mL
** If no infusion reactions after 2 treatments, may infuse subsequent doses over 30 minutes
***Use a separate infusion line and filter for each drug
- Repeat every 3 weeks for 4 cycles

Maintenance Phase

<table>
<thead>
<tr>
<th>Drug</th>
<th>2-Weekly Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>nivolumab</td>
<td>3 mg/kg (maximum 240 mg)</td>
<td>IV in 100 mL* NS over 30 minutes using a 0.2 or 0.22 micron in-line filter</td>
</tr>
</tbody>
</table>

*Keep final concentration to 1 to 10 mg/mL
- Start 3 weeks after last induction phase dose and repeat every 2 weeks until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 6 weeks. Discontinue treatment if confirmatory progression on subsequent scan (6-10 weeks)

OR

<table>
<thead>
<tr>
<th>Drug</th>
<th>4-Weekly Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>nivolumab</td>
<td>6 mg/kg</td>
<td>IV in 100 mL* NS over 30 minutes using a 0.2 or 0.22 micron in-line filter</td>
</tr>
</tbody>
</table>
*Keep final concentration to 1 to 10 mg/mL

- Start 6 weeks after last induction phase dose and repeat every 4 weeks until disease progression or unacceptable toxicity
- If pseudo progression on imaging is suspected, may continue treatment for another 8 weeks. Discontinue treatment if confirmatory progression on subsequent scan (8-12 weeks)

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 and/or nivolumab infusion should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive ipilimumab and/or nivolumab 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.
References:
Appendix. Immune-mediated adverse reaction management guide

Pneumonitis

**Monitoring**
Radiographic changes, new or worsening cough, chest pain, shortness of breath

**Grade 1**
Radiographic changes only

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

**Reassess at least every 3 weeks**
If improved
- Resume nivolumab (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 nivolumab**
- 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 nivolumab
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 nivolumab**
- Monitor daily
- predniSONE 2 to 4 mg/kg/day PO
- Patient education of steroid use
- 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 1 month
- **If persists or worsens after 2 days**
  - Consider non-steroid immunosuppressive agents

Warning: The information contained in these documents are a statement of consensus of BC Cancer 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's terms of use available at www.bccancer.bc.ca/legal.htm
Enterocolitis

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

- Physician notified of assessment
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Antidiarrheal treatment
- Book nursing follow up call for next business day and/or create care plan if BC Cancer 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 and nivolumab**
- Antidiarrheal treatment
- If persists beyond 1-2 days or recur, start prednisone 0.5 to 1 mg/kg/day PO
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Improvement to Grade 1 or less
- Resume ipilimumab and nivolumab
- If steroid used, taper over at least 1 month BEFORE resuming ipilimumab and nivolumab
- 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) ipilimumab and 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
- Prophylactic antibiotics for opportunistic infections
- Patient education of steroid use
- Nursing management per BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book nursing follow up call as needed

Improvement to Grade 1 or less
- Taper prednisone over at least 1 month before resuming ipilimumab and 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

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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 and nivolumab**
- 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 and nivolumab

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 and nivolumab
- 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 and nivolumab**
- 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 and nivolumab
- 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 nivolumab
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 and nivolumab
- 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
>6.0 x ULN
- Physician notified and collaborative symptom management initiated
- Discontinue ipilimumab and nivolumab
- 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 persists for more than 7 days or worsens
- Treat as Grade 4
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 and nivolumab**
- 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 and nivolumab if abnormal lab or pituitary scan**
- Endocrinology consultation
- prednisONE 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 abnormal lab or pituitary scan

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 and nivolumab**
- 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

If improved with or without hormone replacement:
- Taper steroid over at least 1 month
- BEFORE resuming ipilimumab and nivolumab
- 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)

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 BC Cancer nurse unable to follow up

If persists more than 1-2 weeks or recurs
- Consider skin biopsy
- Withhold ipilimumab and nivolumab
- 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 and nivolumab

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

- Physician notified and collaborative symptom management initiated
- Withhold or discontinue ipilimumab and nivolumab
- 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 BC Cancer nurse unable to follow up

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

**Monitoring**

S/S of motor or sensory neuropathies: Unilateral or bilateral weakness, sensory alterations, paresthesia

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**Grade 2**
Not interfering with daily activities

- Physician notified and collaborative symptom management initiated
- **Withhold ipilimumab and nivolumab**
- Introduce appropriate medical intervention
- Book future nursing follow up call as needed

When symptoms resolve or return to baseline
- Resume ipilimumab and nivolumab to complete planned doses or 16 weeks from first dose, whichever earlier

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**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 and nivolumab**
- 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
Other immune-mediated adverse reactions

If severe or clinically significant:
- Discontinue ipilimumab and nivolumab
- 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