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 or within 6 months of completing adjuvant anti-PD1 therapy
- 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 prednisolone/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 975 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
** Keep final concentration to 1 to 4 mg/mL
***Use a separate infusion line and filter for each drug
**** If no infusion reactions after 2 treatments, may infuse subsequent doses over 30 minutes

- 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 (maximum 480 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 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:


PRECAUTIONS:

1. **Serious immune-mediated reactions**: can be severe to fatal and usually occur during the treatment course, but may develop months after discontinuation of therapy. They may include enterocolitis, intestinal perforation or hemorrhage, hepatitis, dermatitis, neuropathy, endocrinopathy, pneumonitis, as well as toxicities in other organ systems. Early diagnosis and appropriate management are essential to minimize life-threatening complications (see SCIMMUNE protocol for...

2. **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. Vanessa Bernstein or tumour group delegate at (250) 519 5572 or 1-800-670-3322 local 5572 with any problems or questions regarding this treatment program.

References: