
Protocol Code  ULUAVPMB
Tumour Group  Lung
Contact Physician  Dr. Christopher Lee

ELIGIBILITY:
- Advanced non-small cell lung cancer
- Second- or subsequent-line therapy for disease progression on or after prior platinum-based chemotherapy
- Tumor characteristics confirmed by an accredited laboratory:
  - PD-L1 expression > 1%
- ECOG 0-2
- Adequate hepatic and renal function
- Access to a treatment centre with expertise to manage immune-mediated adverse reactions of pembrolizumab
- Patients are eligible to receive either pembrolizumab or nivolumab, not both.
- BC Cancer Compassionate Access Program (CAP) approval must be obtained

EXCLUSIONS:
- ECOG performance status > 2
- Active, known or suspected autoimmune disease
- Use with caution 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, TSH, morning serum cortisol, chest x-ray
  - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH, sodium, potassium, TSH
  - If clinically indicated: chest x-ray, morning serum cortisol, lipase, glucose, serum or urine HCG (required for women 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
- If 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>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>pembrolizumab</td>
<td>2 mg/kg (maximum 200mg)</td>
<td>IV in 50 mL NS* over 30 minutes Using a 0.2 to 1.2 micron in-line filter</td>
</tr>
</tbody>
</table>

*Keep final concentration to 1 to 10 mg/mL

- Repeat every 3 weeks until disease progression, unacceptable toxicity, or a maximum of 35 cycles or 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:
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 Appendix for Immune-mediated Adverse Reaction Management Guide).

2. **Infusion-related reactions**: isolated cases of severe infusion reactions have been reported. Discontinue pembrolizumab with Grade 3 or 4 reactions. Patients with mild or moderate infusion reactions may receive pembrolizumab with close monitoring and use of premedication.

Contact Dr. Christopher Lee 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 pembrolizumab
- Monitor every 2 to 3 days
- Consider pulmonary and infectious disease consultation

**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

**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

**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

**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

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., inFLIXximab, cyclophosphamide, mycophenolate)
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 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 BC Cancer 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) 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 BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Consider repeat endoscopy
- **Physician notified, 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 BC Cancer Symptom Management Guidelines: Cancer-Related Diarrhea
- Book 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

**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
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 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

**Grade 3**
Creatinine >3.0 - 6.0 x ULN
- Grade 4 >6.0xULN
- 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
  - BEFORE resuming pembrolizumab 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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**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

**Grade 3**
Creatinine >3.0 - 6.0 x ULN
- Grade 4 >6.0xULN
- 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
  - BEFORE resuming pembrolizumab and routine creatinine

**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

<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>• Continue pembrolizumab</td>
<td>• Evaluate endocrine function</td>
<td>• Rule out sepsis</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>• Consider pituitary scan</td>
<td>• Withhold pembrolizumab</td>
</tr>
<tr>
<td>• Consider endocrinology consultation</td>
<td>• Endocrinology consultation</td>
<td>• Evaluate endocrine function</td>
</tr>
<tr>
<td></td>
<td>• predniSONE 1 to 2 mg/kg/day PO</td>
<td>• Endocrinology consultation</td>
</tr>
<tr>
<td></td>
<td>• Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</td>
<td>• Consider pituitary scan</td>
</tr>
<tr>
<td></td>
<td>• Appropriate hormone replacement if symptomatic with abnormal lab or pituitary scan</td>
<td>• Repeat labs in 1 to 3 weeks; MRI in 1 month if symptoms persist but normal lab or pituitary scan</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Endocrinology consult</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Stress dose of IV steroids with mineralocorticoid activity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV fluids</td>
</tr>
</tbody>
</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

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**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
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 BC Cancer 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 pembrolizumab
- 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 persists more than 1-2 weeks or recurs
- Consider skin biopsy
- Withhold pembrolizumab
- 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 pembrolizumab

If improves to Grade 1
- taper predniSONE over at least 1 month, add prophylactic antibiotics for opportunistic infections, and resume pembrolizumab
Other immune-mediated 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