BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitors Immunotherapy

Protocol Code                      SCIMMUNE
Tumour Group                       Supportive Care
Contact Physician                  Dr. Kerry Savage

Eligibility

Patients treated with immunotherapy agents with checkpoint inhibition, including:

- CTLA-4 inhibitors (e.g., ipilimumab)
- PD-1 inhibitors (e.g., nivolumab, pembrolizumab)
- PD-L1 inhibitors (e.g., atezolizumab, avelumab, durvalumab)

These agents are associated with immune-mediated adverse reactions, although the incidence may vary from agent to agent. Reactions 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. For specific toxicities management, see the following flow diagrams.

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. For specific toxicities management, see the following flow diagrams.

Infusion-related reactions

Isolated cases of severe reaction have been reported. In case of a severe reaction, infusion of checkpoint inhibitors should be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive checkpoint inhibitors with close monitoring. Premedications with acetaminophen and anti-histamine may be considered.
Other immune-mediated adverse reactions
If severe or clinically significant:

- **Discontinue the checkpoint inhibitors.**
- 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:** angiopathy, myositis, 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

References:
Pneumonitis

Grade 1
Radiographic changes only
- Physician notified of assessment
- Consider withholding checkpoint inhibitors
- 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
- WITHOLD checkpoint inhibitors
- 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 checkpoint inhibitors
- 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

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

Reassess at least every 3 weeks
- If improved
  - Resume checkpoint inhibitors (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 checkpoint inhibitors
- If persists or worsens after 2 weeks
  - Treat as Grades 3 or 4

If improved to baseline
- Taper steroid over at least 1 month

If persists or worsens after 2 days
- Consider non-steroid immunosuppressive agents
**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 checkpoint inhibitors
- 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
  - *1-2 days if combination check-point inhibitors

**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) checkpoint inhibitors
- 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**
- Resume checkpoint inhibitors
- If steroid used, taper over at least 1 month BEFORE resuming checkpoint inhibitors
- 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 checkpoint inhibitors
- 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

**Warning:** The information contained in these documents is 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
**Liver**

**Monitoring**
Abnormal liver function test, jaundice, tiredness

**Grade 2**
- ALT (or AST) 3 to less than 5 X ULN
- Total bilirubin 1.5 to 3 X ULN

- Physician notified and collaborative symptom management initiated
- **Withhold checkpoint inhibitors**
- 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 checkpoint inhibitors

*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 checkpoint inhibitors
- Patient education of steroid tapering per physician order

**Grades 3 or 4**
- ALT (or AST) more than 5 X ULN
- Total bilirubin more than 3 X ULN
- ALT (or AST) increases ≥50% baseline and lasts ≥1 week in patients with liver metastasis who begin treatment with Grade 2 elevation of ALT (or AST)

- Physician notified and collaborative symptom management initiated
- **Discontinue checkpoint inhibitors**
- 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 checkpoint inhibitors
- 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 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
Grade 4 >6.0 x ULN

- Physician notified and collaborative symptom management initiated
- Discontinue checkpoint inhibitors
- 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

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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

- Physician notified and collaborative symptom management initiated
- **Continue checkpoint inhibitors**
  - 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

Asymptomatic TSH elevation

- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function
- Consider pituitary scan
- **Withhold checkpoint inhibitors 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

Symptomatic endocrinopathy

- Physician notified and collaborative symptom management initiated
- Rule out sepsis
- **Withhold checkpoint inhibitors**
  - 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
- 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

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 checkpoint inhibitors**
  - 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
- Consider prophylactic antibiotics for opportunistic infections
- **Continue standard monitoring**
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Asymptomatic TSH elevation

- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function
- Consider pituitary scan
- **Withhold checkpoint inhibitors 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

If improved with or without hormone replacement:
- Taper steroid over at least 1 month
- Consider prophylactic antibiotics for opportunistic infections
- **Continue standard monitoring**
  - Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

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 checkpoint inhibitors
- 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 checkpoint inhibitors

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

- Physician notified and collaborative symptom management initiated
- Withhold or discontinue checkpoint inhibitors
- 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 checkpoint inhibitors
**Neurologic**

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

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

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**When symptoms resolve or return to baseline**
- Resume checkpoint inhibitors 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 checkpoint inhibitors**
- 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