BC Cancer Protocol Summary for Management of Immune-Mediated Adverse Reactions to Checkpoint Inhibitor 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, tremelimumab)
- PD-1 inhibitors (e.g., nivolumab, pembrolizumab, dostarlimab)
- 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 toxicity management, see the following flow diagrams.

Infusion-related reactions

Isolated cases of severe reactions have been reported. In the case of a severe reaction, infusion of the checkpoint inhibitor(s) should be discontinued and appropriate medical therapy administered. Patients with a mild or moderate infusion reaction may receive checkpoint inhibitors with close monitoring. Premedication with acetaminophen and an antihistamine may be considered.

Potential immune-mediated adverse reactions include, but are not limited to:

If severe or clinically significant:

- Discontinue the checkpoint inhibitor(s)
- predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
- · Corticosteroid eye drops for uveitis, iritis or episcleritis
- Consider referring to a specialist
- 1. Blood and lymphatic: hemolytic anemia, immune thrombocytopenic purpura, hypereosinophilia
- 2. Cardiovascular: angiopathy, myositis, myocarditis, pericarditis, temporal arteritis, vasculitis
- 3. Endocrine: primary and secondary hypothyroidism, hyperthyroidism, autoimmune thyroiditis (with hyperthyroidism followed by hypothyroidism), hyperglycemia (with diabetic ketoacidosis), hypopituitarism, primary and secondary adrenal insufficiency, hypoparathyroidism
- **4. Eye:** blepharitis, conjunctivitis, episcleritis, iritis, scleritis, uveitis
- 5. Gastrointestinal: gastritis, colitis
- **6. Pancrease/liver:** pancreatitis, hepatitis
- 7. Musculoskeletal: arthritis, polymyalgia rheumatica
- 8. Skin: rash, eczema, psoriasis, Stevens-Johnson Syndrome, leukocytoclastic vasculitis
- 9. Neurologic: peripheral neuropathy, Guillan-Barré Syndrome, myasthenia gravis, meninaitis
- 10.Lung: pneumonitis, bronchiolitis obliterans organizing pneumonia

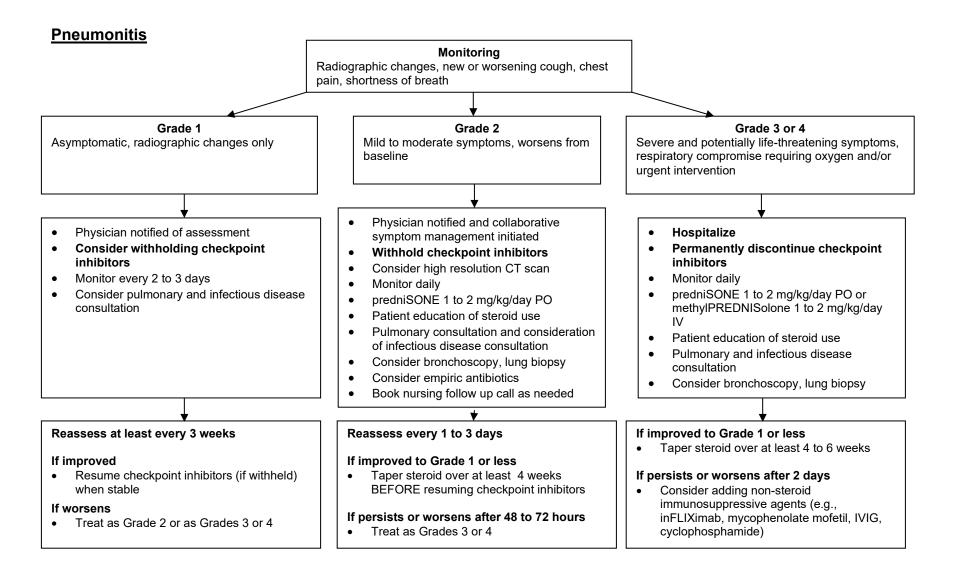
Dosing of PD-1/PD-L1 checkpoint inhibitors and immune-related adverse events8-12

- Both standard and extended dosing regimens have similar pharmacokinetics and appear to have similar efficacy and safety
- Incidence of immune-related adverse effects does not appear to increase with increased doses used in extended interval dosing
- Extended dosing regimens reduce the number of clinic visits, thereby:
 - Decreasing workload within the healthcare system
 - Decreasing travel burden for patients
 - Reducing potential infectious disease exposure by limiting the physical interaction between staff and patients
- See Systemic Therapy Update, Dec 2020, for further details

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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
- Continue checkpoint inhibitors
- Book nursing follow up call for next business day and/or create care plan if BC Cancer nurse unable to follow up

Monitoring

Diarrhea, abdominal pain, mucus or blood in stoolswith or without fever, ileus, peritoneal signs

Grade 2

Diarrhea of 4 to 6 stools per day over baseline, limiting instrumental ADL, abdominal pain, mucus or blood in stool.

- Physician notified and collaborative symptom management initiated
- Withhold checkpoint inhibitors
- Antidiarrheal treatment
- If diarrhea and colitis symptoms (abdominal pain, blood in stool), start predniSONE 1 mg/kg/day PO immediately
- Stool cultures, including C, difficile toxin
- Gastroenterology consult
- If diarrhea only and persists beyond 2 to 3 days* or recur, start predniSONE 1 mg/kg/day PO
- Consider 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
- * 1-2 days if combination checkpoint inhibitors

Improvement to Grade 1 or less

- Resume checkpoint inhibitors
- If steroid used, taper over at least 4 to 6 weeks BEFORE resuming checkpoint inhibitors
- If no improvement within 72 hours, treat as Grade 3 or 4
- 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, ileus, fever, limiting selfcare ADLs: colitis with severe abdominal pain. hospitalization indicated

Grade 4: life-threatening colitis, perforation

- Physician notified and collaborative symptom management initiated
- Withhold (if Grade 3) or permanently 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 or methylPREDNISolone 1 to 2 mg/kg/day IV
- 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 steroid over 4 to 6 weeks before resuming checkpoint inhibitors
- Patient education of steroid tapering per physician order

If no response within 1 to 5 days or recurs

- Consider treatment with inFLIXimab; if refractory to inFLIXimab, consider vedolizumab
- Continually evaluate for evidence of gastrointestinal perforation or peritonitis
- Consider repeat endoscopy

Hepatitis

Monitorina

Abnormal liver function test, jaundice, tiredness

Grade 2

ALT (or AST) 3 to 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 3 to 5 days or worsens

- predniSONE 0.5 to 1 mg/kg/day PO or methylPREDNISolone 0.5 to 1 mg/kg/day IV
- consider prophylactic antibiotics for opportunistic infections
- taper steroid over at least 4 weeks before resuming checkpoint inhibitors
- Patient education of steroid tapering per physician order

Grade 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
- Permanently discontinue checkpoint inhibitors
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 1 to 5 days until resolution
- Gastroenterology (hepatology) consultation
- predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
- Patient education on steroid use
- Book future nursing follow up call as needed

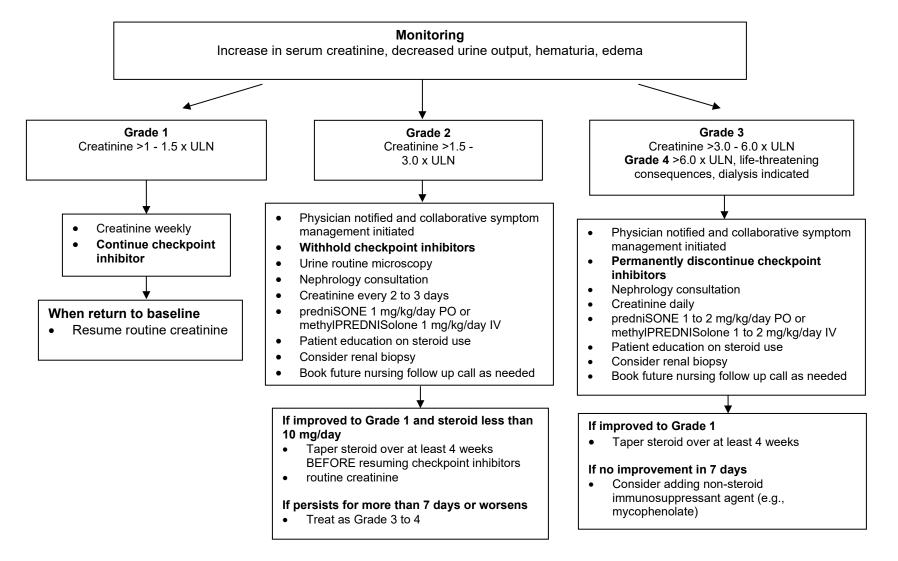
If LFTs return to Grade 2 or less

Taper steroid over at least 4 weeks

For persistent Grades 3 or 4 for more than 3 days, worsens, or recurs:

Consider non-steroid immunosuppressive agents (e.g., mycophenolate; avoid infliximab due to hepatotoxicity potential)

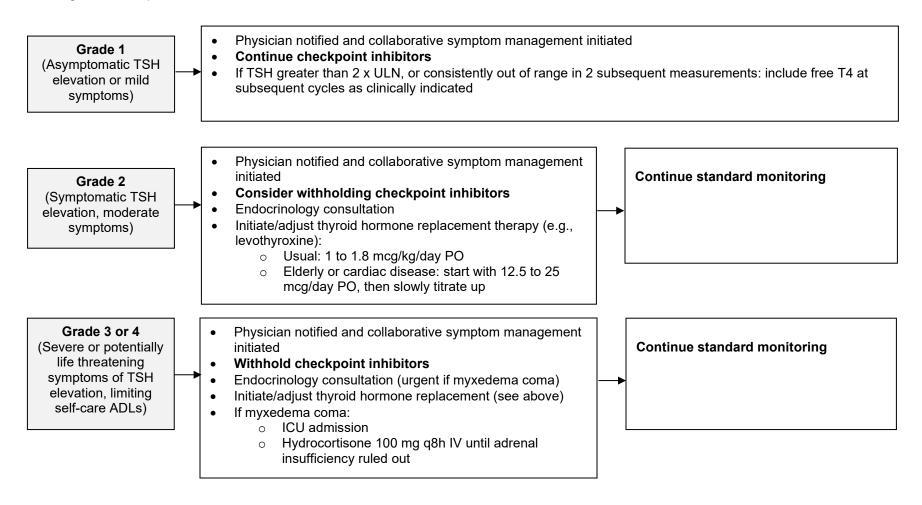
Nephritis



Endocrine: Hypothyroidism

Monitoring

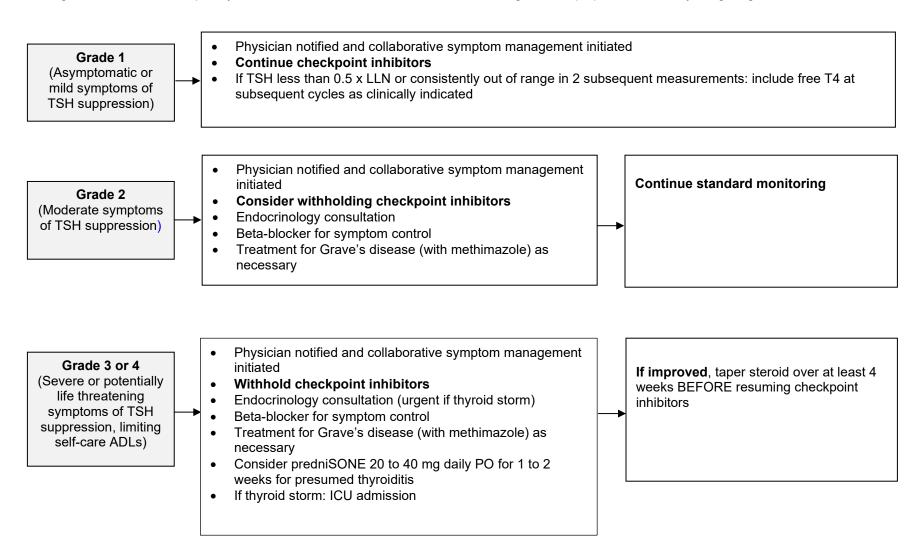
Extreme tiredness, weight gain, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness



Endocrine: Hyperthyroidism

Monitoring

Weight loss, increased frequency of bowel movements, heat intolerance, sweating, tremor, palpitations, anxiety, fatigue, goiter



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Endocrine: Hypophysitis

Monitoring

Persistent or unusual headaches, vision changes, extreme tiredness, weight gain or loss, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness

Grade 1

(Asymptomatic or mild symptoms)

- Physician notified and collaborative symptom management initiated
- Continue checkpoint inhibitors
- Appropriate hormone replacement if symptomatic

Grade 2, 3, or 4 (Moderate, severe, or life-threatening

symptoms)

- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function, including ACTH, am cortisol, glucose, TSH, FT4, LH, FSH, testosterone/estradiol, prolactin, electrolytes, plasma and urine osmolality
- Consider pituitary scan
- Urgent intervention indicated for grades 3 or 4
- Consider withholding checkpoint inhibitors
- **Endocrinology consultation**
- Consider predniSONE 0.5 to 1 mg/kg/day PO or methylPREDNISolone 0.5 to 1 mg/kg/day IV
- 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 4 weeks BEFORE resuming checkpoint inhibitors
- Consider prophylactic antibiotics for opportunistic infections

Continue standard monitoring

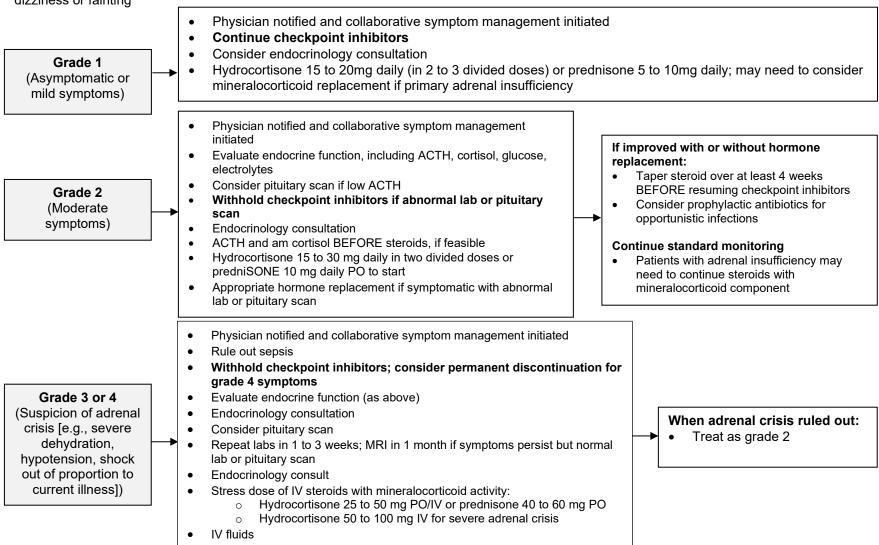
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Endocrine: Adrenal Insufficiency

Monitoring

Persistent or unusual headaches, extreme tiredness, weakness, dehydration, mood or behaviour changes (e.g., confusion, forgetfulness), dizziness or fainting



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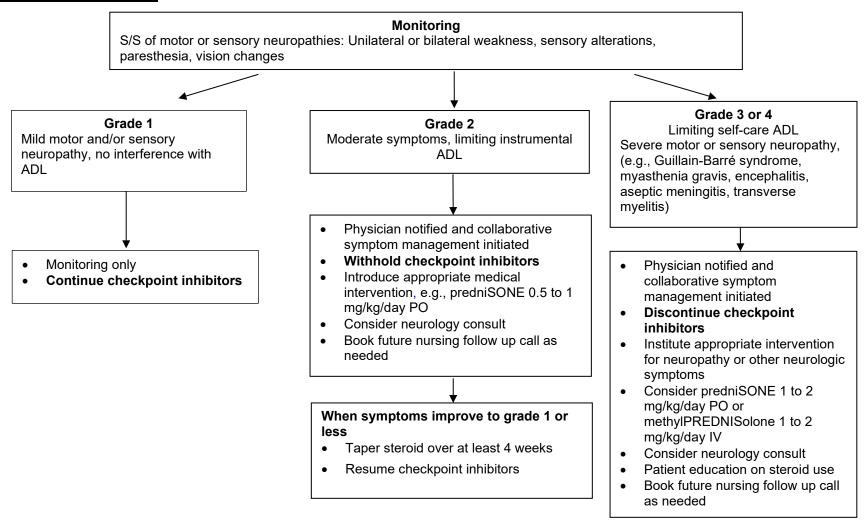
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Skin Toxicities Monitoring Rash, pruritus (unless an alternate etiology has been identified) Grade 1 to 2 Grade 3 or 4 Rash covering 30% of skin surface or less, Rash covering more than 30% of skin with or without associated symptoms surface, moderate to severe symptoms, (pruritus, etc.) limiting self-care ADL, life-threatening Physician notified of assessment Physician notified and collaborative symptom management **Continue checkpoint inhibitors** initiated Nursing management per ASCO Skin Reactions to Withhold or discontinue checkpoint inhibitors **Targeted Therapies** Consider skin biopsy Sun safety (see Your Medication Sun Sensitivity and Dermatology consult Sunscreens) predniSONE 0.5 to 1 mg/kg/day PO or methylPREDNISolone Skin care; moisturizers, soaps 0.5 to 1 mg/kg/day IV Topical corticosteroids (e.g., betamethasone) Patient education on steroid use diphenhydrAMINE PO Book nursing follow up call for next business day and/or Book nursing follow up call for next business day and/or create care plan if BC Cancer nurse unable to follow up create care plan if BC Cancer nurse unable to follow up If persists more than 1-2 weeks or recurs If improves to Grade 1 Consider skin biopsy Taper steroid over at least 4 weeks Withhold checkpoint inhibitors Consider adding prophylactic antibiotics for opportunistic predniSONE 0.5 to 1 mg/kg/day PO infections

- Patient education on steroid use
- Once improving, taper predniSONE over at least 4 weeks then resume checkpoint inhibitors

Consider resuming checkpoint inhibitors once steroid taper complete

Neurologic Toxicities



Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy

Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Pneumonitis	Asymptomatic, radiographic changes only	Mild to moderate symptoms, worsens from baseline	Severe symptoms, respiratory compromise requiring oxygen	Potentially life-threatening symptoms, respiratory compromise requiring oxygen and/or urgent intervention
Enterocolitis	Diarrhea of less than 4 stools per day over baseline; asymptomatic colitis	Diarrhea of 4 to 6 stools per day over baseline, limiting instrumental ADL, abdominal pain, mucus or blood in stool.	Diarrhea of 7 or more stools per day over baseline, incontinence, ileus, fever, limiting self-care ADLs; colitis with severe abdominal pain, hospitalization indicated	life-threatening colitis, perforation
Hepatitis		ALT (or AST) 3 to 5 X ULN or Total bilirubin 1.5 to 3 X ULN	ALT (or AST) more than 5 X ULN or 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)
Nephritis	Creatinine >1 - 1.5 x ULN	Creatinine >1.5 - 3.0 x ULN	Creatinine >3.0 - 6.0 x ULN	Creatinine >6.0 x ULN, life- threatening consequences, dialysis indicated
Hypothyroidism	Asymptomatic TSH elevation or mild symptoms	Symptomatic TSH elevation, moderate symptoms	Severe symptoms of TSH elevation	Potentially life threatening symptoms of TSH elevation
Hyperthyroidism	Asymptomatic or mild symptoms of TSH suppression	Moderate symptoms of TSH suppression	Severe symptoms of TSH suppression	Potentially life threatening symptoms of TSH suppression
Hypophysitis	Asymptomatic or mild symptoms	Moderate symptoms	Severe symptoms	Life-threatening symptoms
Adrenal Insufficiency	Asymptomatic or mild symptoms	Moderate symptoms	Suspicion of adrenal crisis (e.g., severe dehydration, hypotension, shock out of proportion to current illness)	

Immune-Related Adverse Events	Grade 1	Grade 2	Grade 3	Grade 4
Skin Toxicities	Rash covering 30% of skin surface or less, with or without associated symptoms (pruritus, etc.)		Rash covering more than 30% of skin surface, moderate to severe symptoms, limiting self-care ADL, life-threatening	
Neurologic Toxicities	Mild motor and/or sensory neuropathy, no interference with ADL	Moderate symptoms, limiting instrumental ADL	Limiting self-care ADL Severe motor or sensory neuropathy, (e.g., Guillain- Barré syndrome, myasthenia gravis, encephalitis, aseptic meningitis, transverse myelitis)	