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)
- 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 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, meningitis
10. **Lung:** pneumonitis, bronchiolitis obliterans organizing pneumonia

Dosing of PD-1/PD-L1 checkpoint inhibitors and immune-related adverse events[8-12]

- 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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14. Cancer Care Ontario. Immune checkpoint inhibitor toxicity management – clinical practice guideline. March 23, 2018.
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17. Puzanov I, Diab A, Abdallah K, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017;5:95-123.
18. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. November 27, 2017.
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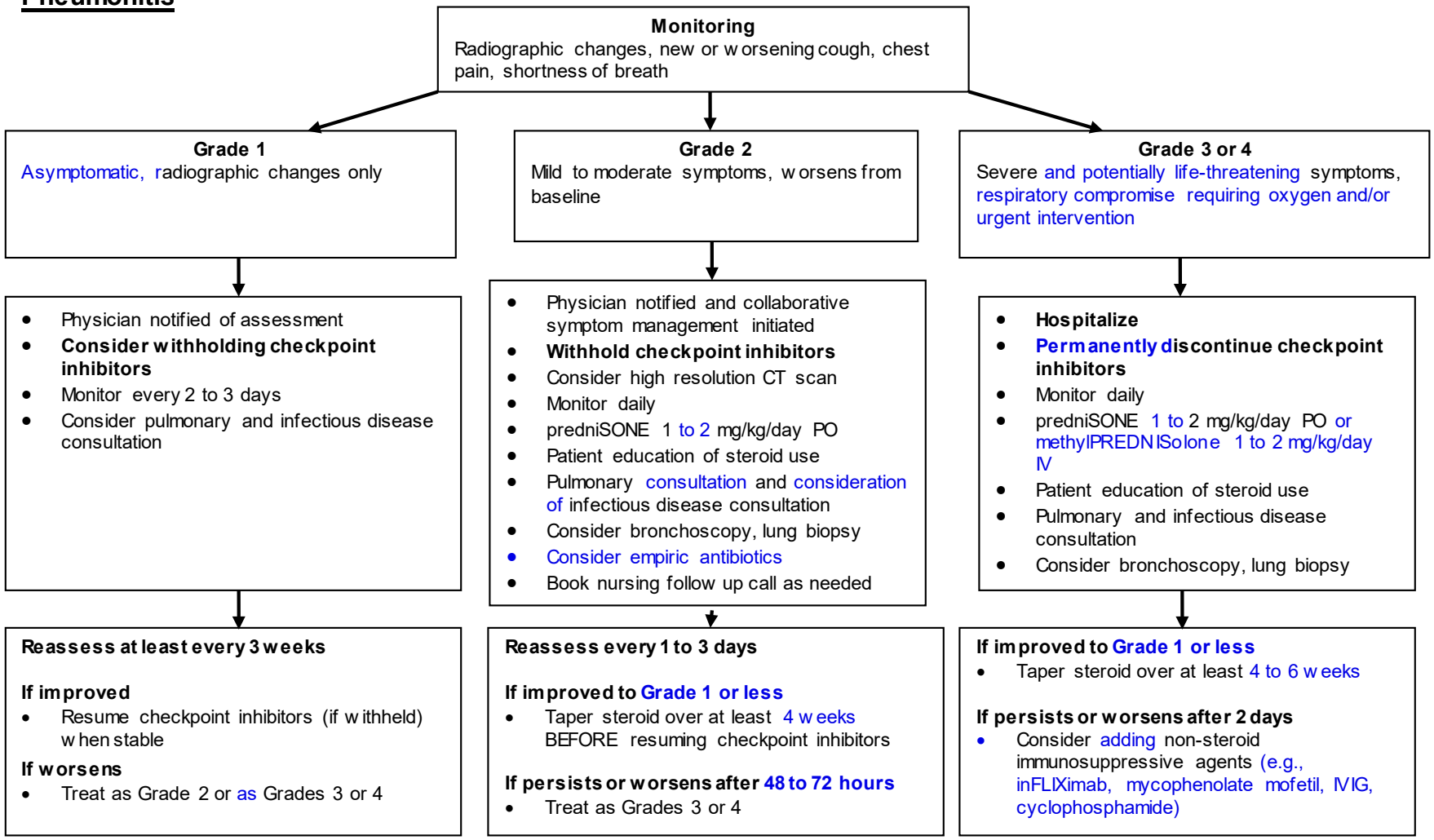
For grading details, see: *Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy*, below chart

Pneumonitis



Enterocolitis

Monitoring
Diarrhea, abdominal pain, mucus or blood in stools- with or without fever, ileus, peritoneal signs

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

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 self-care 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

Monitoring
Abnormal liver function test, jaundice, tiredness

Grade 2
ALT (or AST) 3 to 5 X ULN
or
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
or
Total bilirubin more than 3 X ULN
or
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)

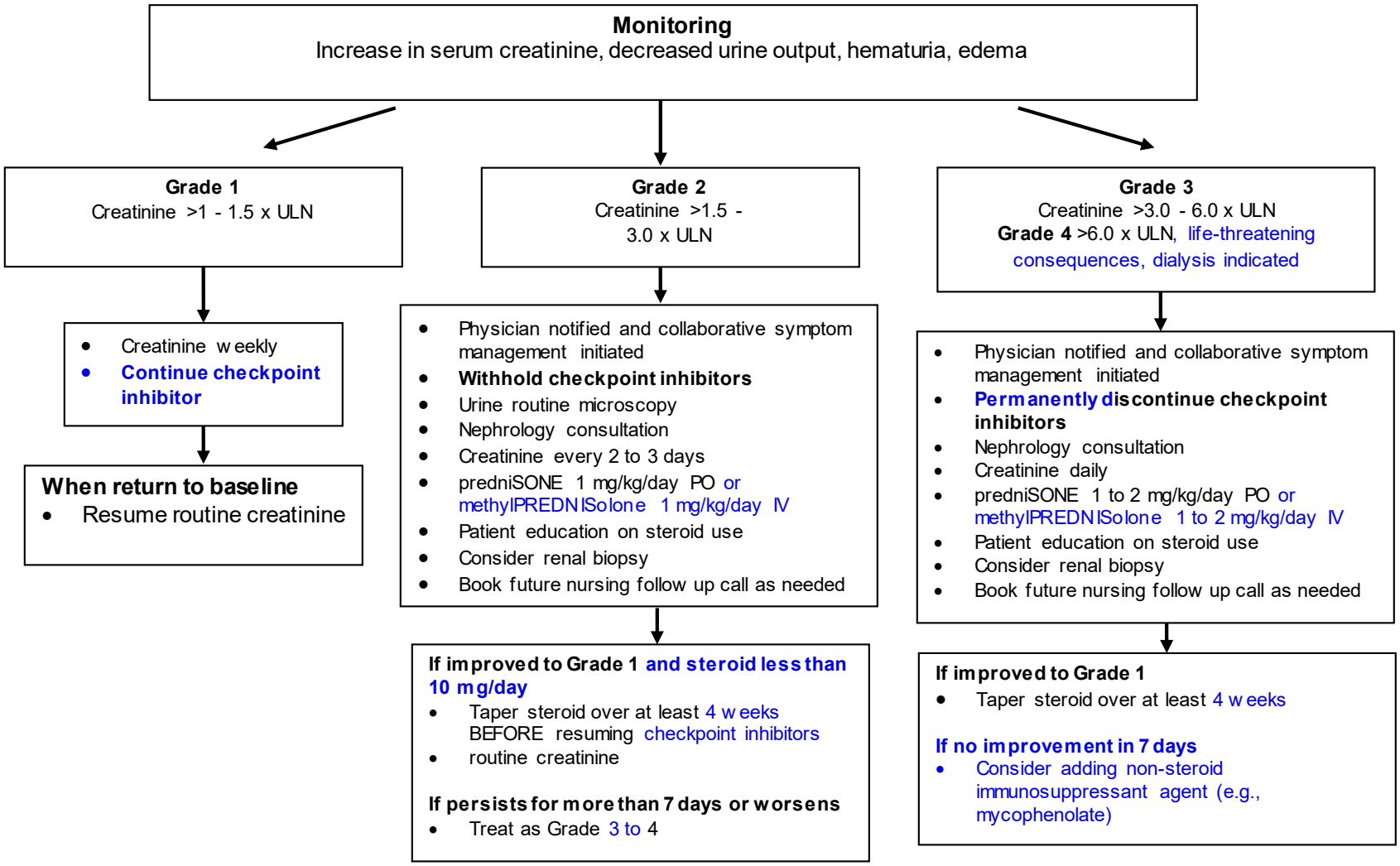
- Physician notified and collaborative symptom management initiated
- **Permanently discontinue checkpoint inhibitors**
- Rule out infectious or malignant causes or obstruction
- Increase LFTs monitoring to every 1 to 5 days until resolution
- Gastroenterology (hepatology) consultation
- predniSONE 1 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)

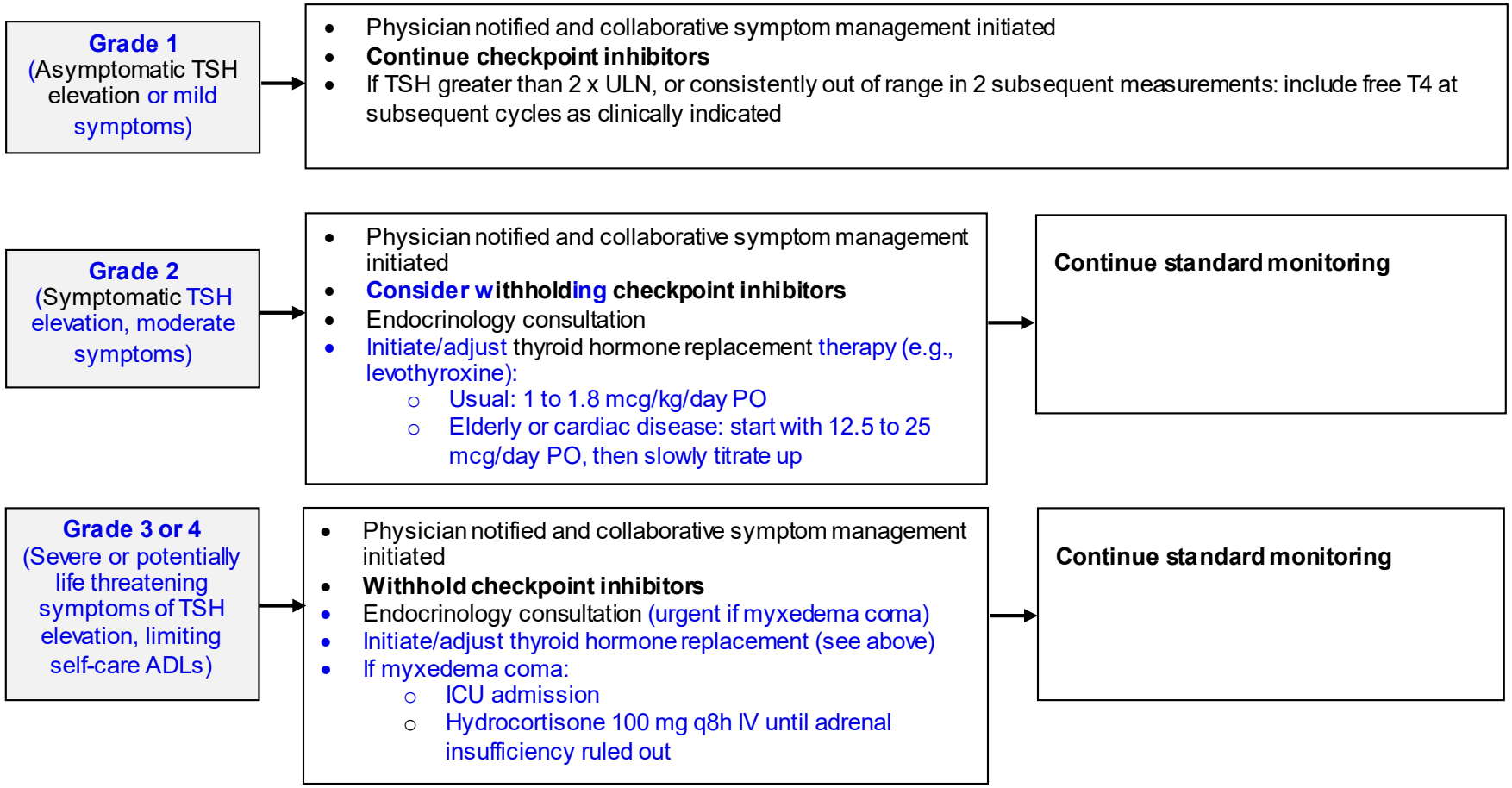
Nephritis



Endocrine: Hypothyroidism

Monitoring

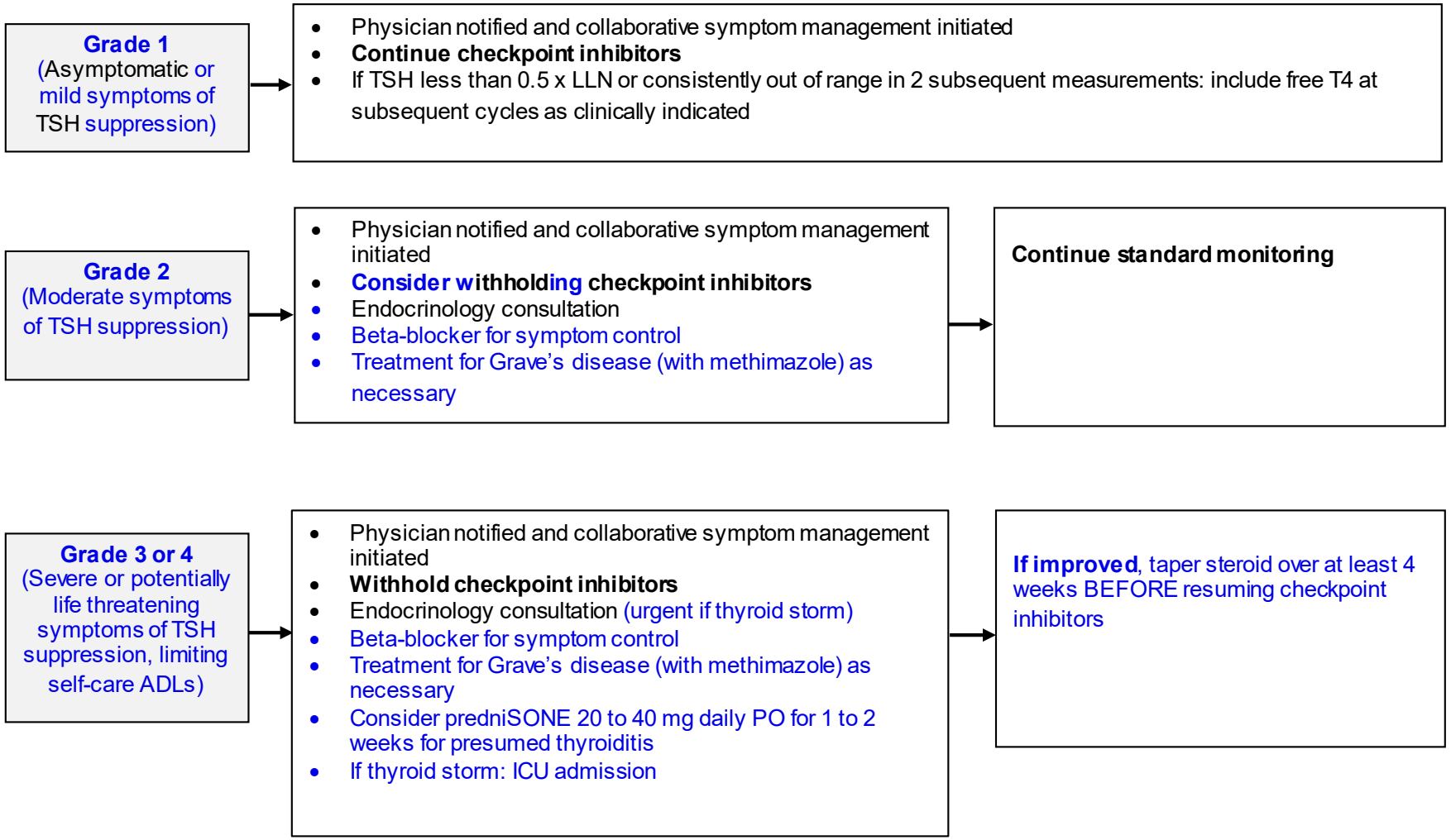
Extreme tiredness, weight gain, mood or behaviour changes (e.g., decreased libido, confusion, forgetfulness), dizziness or fainting, hair loss, feeling cold, constipation, hoarseness



Endocrine: Hyperthyroidism

Monitoring

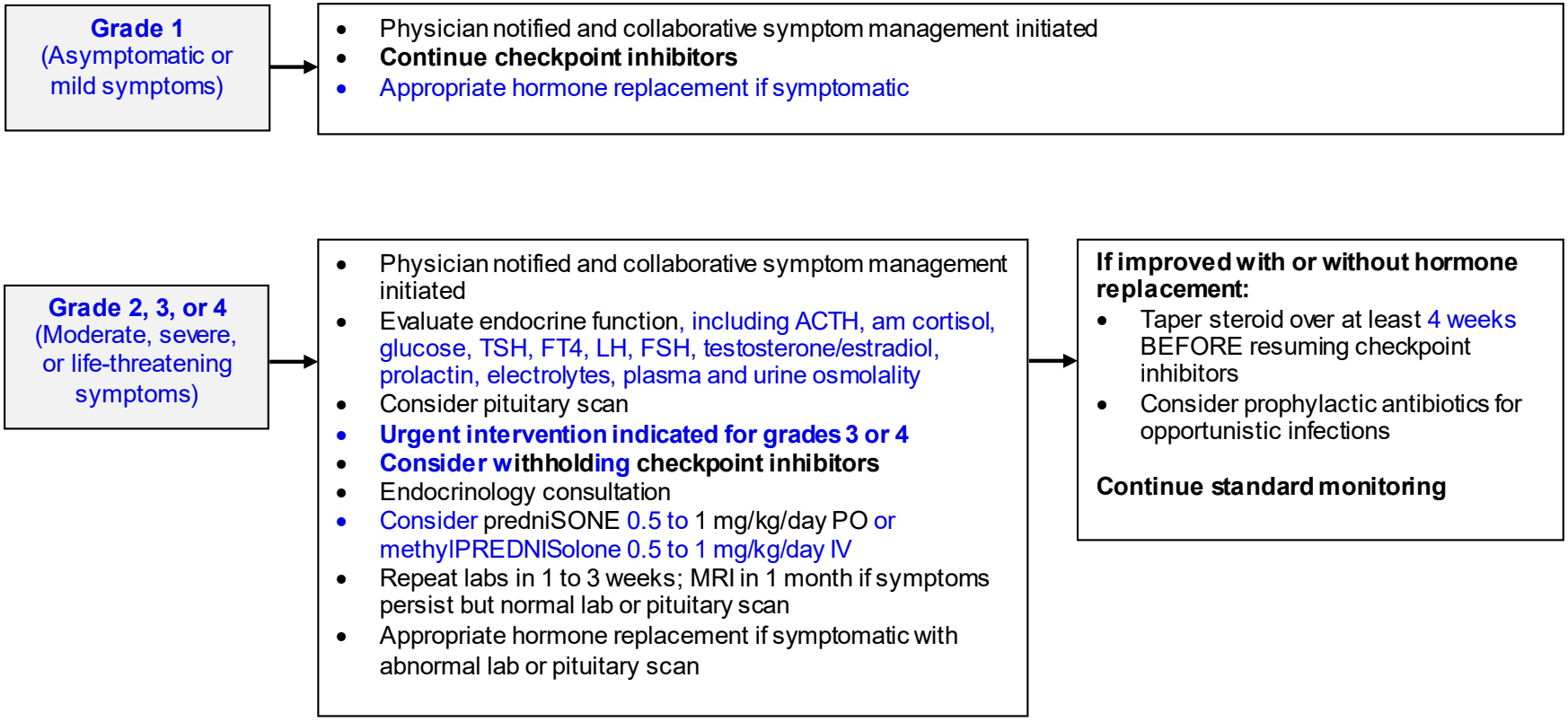
Weight loss, increased frequency of bowel movements, heat intolerance, sweating, tremor, palpitations, anxiety, fatigue, goiter



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



Endocrine: Adrenal Insufficiency

Monitoring

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

Grade 1
(Asymptomatic or mild symptoms)

- Physician notified and collaborative symptom management initiated
- **Continue checkpoint inhibitors**
- Consider endocrinology consultation
- Hydrocortisone 15 to 20mg daily (in 2 to 3 divided doses) or prednisone 5 to 10mg daily; may need to consider mineralocorticoid replacement if primary adrenal insufficiency

Grade 2
(Moderate symptoms)

- Physician notified and collaborative symptom management initiated
- Evaluate endocrine function, including ACTH, cortisol, glucose, electrolytes
- Consider pituitary scan if low ACTH
- **Withhold checkpoint inhibitors if abnormal lab or pituitary scan**
- Endocrinology consultation
- ACTH and am cortisol BEFORE steroids, if feasible
- Hydrocortisone 15 to 30 mg daily in two divided doses or predniSONE 10 mg daily PO to start
- 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

- Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component

Grade 3 or 4
(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; consider permanent discontinuation for grade 4 symptoms**
- Evaluate endocrine function (as above)
- 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:
  - Hydrocortisone 25 to 50 mg PO/IV or prednisone 40 to 60 mg PO
  - Hydrocortisone 50 to 100 mg IV for severe adrenal crisis
- IV fluids

When adrenal crisis ruled out:

- Treat as grade 2

Skin Toxicities

Monitoring
Rash, pruritus (unless an alternate etiology has been identified)

Grade 1 to 2
Rash covering 30% of skin surface or less, with or without associated symptoms (pruritus, etc.)

- Physician notified of assessment
- **Continue checkpoint inhibitors**
- Nursing management per ASCO Skin Reactions to Targeted Therapies
  - Sun safety (see Your Medication Sun Sensitivity and Sunscreens)
  - Skin care; moisturizers, soaps
  - Topical corticosteroids (e.g., betamethasone)
  - diphenhydrAMINE PO
- Book nursing follow up call for next business day and/or create care plan if BC Cancer nurse unable to follow up

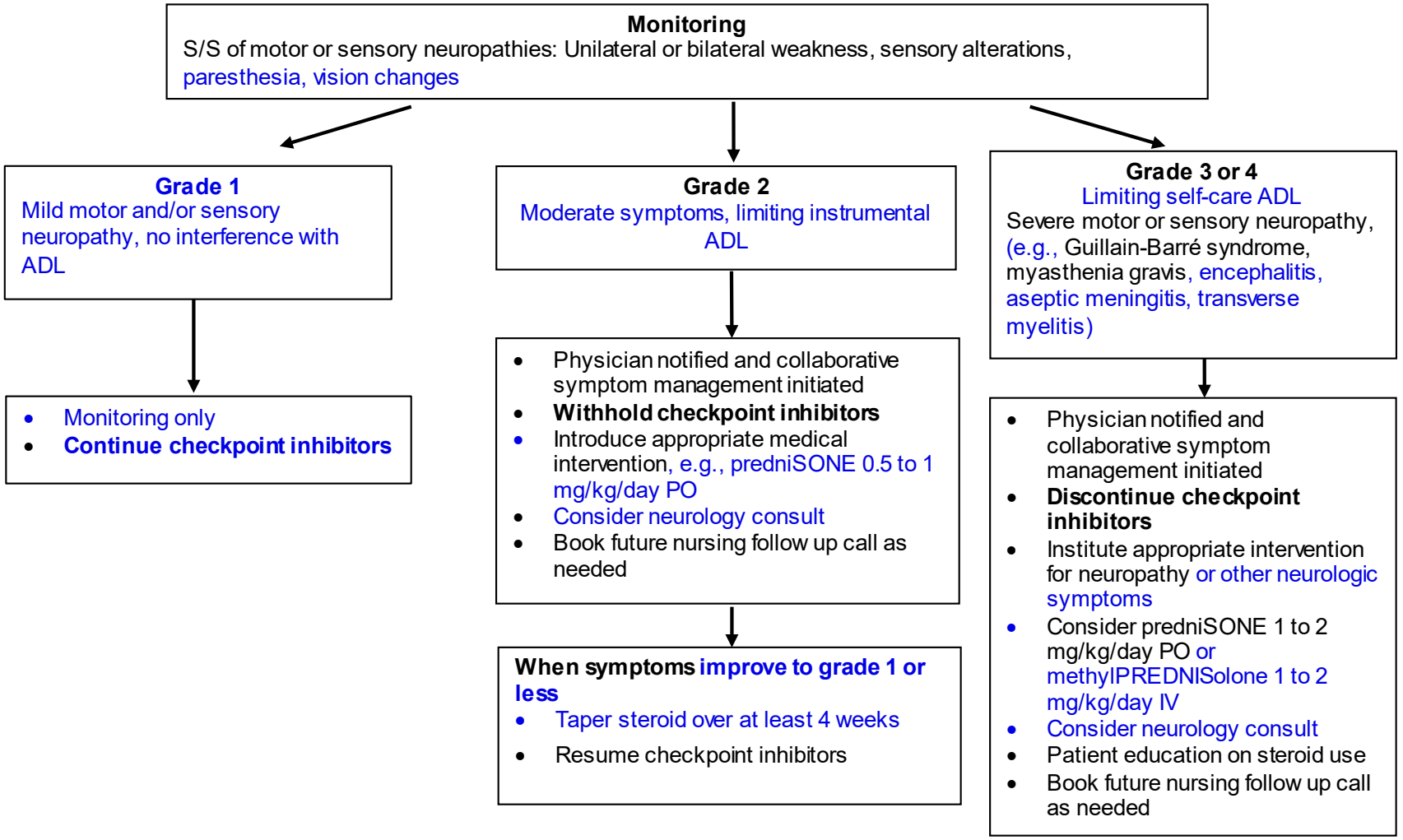
If persists more than 1-2 weeks or recurs
- Consider skin biopsy
- **Withhold checkpoint inhibitors**
- predniSONE 0.5 to 1 mg/kg/day PO
- Patient education on steroid use
- Once improving, taper predniSONE over at least 4 weeks then resume checkpoint inhibitors

Grade 3 or 4
Rash covering more than 30% of skin surface, moderate to severe symptoms, limiting self-care ADL, life-threatening

- Physician notified and collaborative symptom management initiated
- **Withhold or discontinue checkpoint inhibitors**
- Consider skin biopsy
- Dermatology consult
- predniSONE 0.5 to 1 mg/kg/day PO or methylPREDNISolone 0.5 to 1 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 steroid over at least 4 weeks
- Consider adding prophylactic antibiotics for opportunistic infections
- 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)	