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 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
References:

Pneumonitis

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

**Grade 1**
Asymptomatic, 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
- **Withdraw checkpoint inhibitors**
- Consider high resolution CT scan
- Monitor daily
- predniSONE 1 to 2 mg/kg/day PO
- Patient education of steroid use
- Pulmonary consultation and consideration of infectious disease consultation
- Consider bronchoscopy, lung biopsy
- **Consider empiric antibiotics**
- Book nursing follow up call as needed

**Grade 3 or 4**
Severe and potentially life-threatening symptoms, respiratory compromise requiring oxygen and/or urgent intervention
- Hospitalize
- **Permanently discontinue checkpoint inhibitors**
- Monitor daily
- predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
- Patient education of steroid use
- Pulmonary and infectious disease consultation
- Consider bronchoscopy, lung biopsy

**Reassess at least every 3 weeks**
If improved
- Resume checkpoint inhibitors (if withheld) when stable

If worsens
- Treat as Grade 2 or as Grades 3 or 4

**Reassess every 1 to 3 days**
If improved to **Grade 1 or less**
- Taper steroid over at least 4 to 6 weeks

If persists or worsens after 48 to 72 hours
- Treat as Grades 3 or 4

If persists or worsens after 2 days
- Consider adding non-steroid immunosuppressive agents (e.g., inFLIXimab, mycophenolate mofetil, IVIG, cyclophosphamide)

For grading details, see: *Grading System of Immune-Related Adverse Events Associated with Checkpoint Immunotherapy*, below chart
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

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

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

* 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

BC Cancer Protocol Summary SCIMMUNE
Activated: 1 Jan 2019 Revised: 1 Feb 2022 (Flow diagram grading and management updated, detailed grading table added)

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### Monitoring

**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)

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**Hepatitis**
Nephritis

Monitoring
Increase in serum creatinine, decreased urine output, hematuria, edema

Grade 1
Creatinine >1 - 1.5 x ULN
- Creatinine weekly
- Continue checkpoint inhibitor

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
- Urine routine microscopy
- Nephrology consultation
- Creatinine every 2 to 3 days
- predniSONE 1 mg/kg/day PO or methylPREDNISolone 1 mg/kg/day IV
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If improved to Grade 1 and steroid less than 10 mg/day
- Taper steroid over at least 4 weeks
- BEFORE resuming checkpoint inhibitors
- routine creatinine

If persists for more than 7 days or worsens
- Treat as Grade 3 to 4

Grade 3
Creatinine >3.0 - 6.0 x ULN
- Physician notified and collaborative symptom management initiated
- Permanently discontinue checkpoint inhibitors
- Nephrology consultation
- Creatinine daily
- predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
- Patient education on steroid use
- Consider renal biopsy
- Book future nursing follow up call as needed

If no improvement in 7 days
- Consider adding non-steroid immunosuppressant agent (e.g., mycophenolate)

Grade 4
Creatinine >6.0 x ULN, life-threatening consequences, dialysis indicated
- Withhold checkpoint inhibitors
- Permanently discontinue checkpoint inhibitors
- Nephrology consultation
- Creatinine daily
- predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
- 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 4 weeks

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**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

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**Grade 1**
(Asymptomatic TSH elevation or mild symptoms)
- Physician notified and collaborative symptom management initiated
- **Continue checkpoint inhibitors**
- If TSH greater than 2 x ULN, or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated

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**Grade 2**
(Symptomatic TSH elevation, moderate symptoms)
- Physician notified and collaborative symptom management initiated
- **Consider withholding** checkpoint inhibitors
- Endocrinology consultation
- Initiate/adjust thyroid hormone replacement therapy (e.g., levothyroxine):
  - Usual: 1 to 1.8 mcg/kg/day PO
  - Elderly or cardiac disease: start with 12.5 to 25 mcg/day PO, then slowly titrate up

**Continue standard monitoring**

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**Grade 3 or 4**
(Severe or potentially life threatening symptoms of TSH elevation, limiting self-care ADLs)
- Physician notified and collaborative symptom management initiated
- **Withhold checkpoint inhibitors**
- Endocrinology consultation (urgent if myxedema coma)
- Initiate/adjust thyroid hormone replacement (see above)
- If myxedema coma:
  - ICU admission
  - Hydrocortisone 100 mg q8h IV until adrenal insufficiency ruled out

**Continue standard monitoring**

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**Endocrine: Hyperthyroidism**

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

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**Grade 1**
(Assymptomatic or mild symptoms of TSH suppression)

- Physician notified and collaborative symptom management initiated
- **Continue checkpoint inhibitors**
- If TSH less than 0.5 x LLN or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated

**Grade 2**
(Moderate symptoms of TSH suppression)

- Physician notified and collaborative symptom management initiated
- **Consider withholding checkpoint inhibitors**
- Endocrinology consultation
- Beta-blocker for symptom control
- Treatment for Grave's disease (with methimazole) as necessary

**Grade 3 or 4**
(Severe or potentially life threatening symptoms of TSH suppression, limiting self-care ADLs)

- Physician notified and collaborative symptom management initiated
- **Withhold checkpoint inhibitors**
- Endocrinology consultation (urgent if thyroid storm)
- Beta-blocker for symptom control
- Treatment for Grave’s disease (with methimazole) as necessary
- Consider predniSONE 20 to 40 mg daily PO for 1 to 2 weeks for presumed thyroiditis
- If thyroid storm: ICU admission

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**Continue standard monitoring**

- If improved, taper steroid over at least 4 weeks BEFORE resuming checkpoint inhibitors

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**Endocrine: Hyperthyroidism**

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

---

**Grade 1**
(Assymptomatic or mild symptoms of TSH suppression)

- Physician notified and collaborative symptom management initiated
- **Continue checkpoint inhibitors**
- If TSH less than 0.5 x LLN or consistently out of range in 2 subsequent measurements: include free T4 at subsequent cycles as clinically indicated

**Grade 2**
(Moderate symptoms of TSH suppression)

- Physician notified and collaborative symptom management initiated
- **Consider withholding checkpoint inhibitors**
- Endocrinology consultation
- Beta-blocker for symptom control
- Treatment for Grave’s disease (with methimazole) as necessary

**Grade 3 or 4**
(Severe or potentially life threatening symptoms of TSH suppression, limiting self-care ADLs)

- Physician notified and collaborative symptom management initiated
- **Withhold checkpoint inhibitors**
- Endocrinology consultation (urgent if thyroid storm)
- Beta-blocker for symptom control
- Treatment for Grave’s disease (with methimazole) as necessary
- Consider predniSONE 20 to 40 mg daily PO for 1 to 2 weeks for presumed thyroiditis
- If thyroid storm: ICU admission

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**Continue standard monitoring**

- If improved, taper steroid over at least 4 weeks BEFORE resuming checkpoint inhibitors

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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

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**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

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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**
**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

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 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 2 divided doses or prednisone 10 mg daily PO to start
- Appropriate hormone replacement if symptomatic with abnormal lab or pituitary scan

When adrenal crisis ruled out:
- Treat as grade 2

**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)

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**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

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**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

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**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

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**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

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**Neurologic Toxicities**

- **Monitoring**
  - S/S of motor or sensory neuropathies: Unilateral or bilateral weakness, sensory alterations, paresthesia, vision changes

- **Grade 1**
  - Mild motor and/or sensory neuropathy, no interference with ADL
  - Monitoring only
  - Continue checkpoint inhibitors

- **Grade 2**
  - Moderate symptoms, limiting instrumental ADL
  - Physician notified and collaborative symptom management initiated
  - Withhold checkpoint inhibitors
  - Introduce appropriate medical intervention, e.g., predniSONE 0.5 to 1 mg/kg/day PO
  - Consider neurology consult
  - Book future nursing follow up call as needed

- **Grade 3 or 4**
  - Limiting self-care ADL
  - Severe motor or sensory neuropathy, (e.g., Guillain-Barré syndrome, myasthenia gravis, encephalitis, aseptic meningitis, transverse myelitis)
  - Physician notified and collaborative symptom management initiated
  - Discontinue checkpoint inhibitors
  - Institute appropriate intervention for neuropathy or other neurologic symptoms
  - Consider predniSONE 1 to 2 mg/kg/day PO or methylPREDNISolone 1 to 2 mg/kg/day IV
  - Consider neurology consult
  - Patient education on steroid use
  - Book future nursing follow up call as needed

- **When symptoms improve to grade 1 or less**
  - Taper steroid over at least 4 weeks
  - Resume checkpoint inhibitors

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<th>Grade 3</th>
<th>Grade 4</th>
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