**Table Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab**

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

| **irAEs** | **Toxicity Grade (CTCAE v5.0)** | **Action With Pembrolizumab** | **Corticosteroid and/or Other Therapies** | **Monitoring and Follow-up** |
|---|---|---|---|---|
| Pneumonitis | Grade 2 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper<br>• Add prophylactic antibiotics for opportunistic infections | • Monitor participants for signs and symptoms of pneumonitis<br>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment |
| | Recurrent Grade 2, Grade 3 or 4 | Permanently discontinue | | |
| Diarrhea/Colitis | Grade 2 or 3 | Withhold | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | • Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | and of bowel perforation (ie, peritoneal signs and ileus)<br>• Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis<br>• Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion |
| AST or ALT Elevation or Increased Bilirubin | Grade 2 [a] | Withhold | • Administer corticosteroids (initial dose of 0.5 to 1 mg/kg prednisone or equivalent) followed by taper | • Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable) |
| | Grade 3 [b] or 4 [c] | Permanently discontinue | • Administer corticosteroids (initial dose of 1 to 2 mg/kg prednisone or equivalent) followed by taper | |
| T1DM or Hyperglycemia | New onset T1DM or Grade 3 or 4 hyperglycemia associated | Withhold [d] | • Initiate insulin replacement therapy for participants with T1DM<br>• Administer antihyperglycemic in participants with hyperglycemia | • Monitor participants for hyperglycemia or other signs and symptoms of diabetes |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| | with evidence of β-cell failure | | | |
| Hypophysitis | Grade 2 | Withhold | • Administer corticosteroids and initiate hormonal replacements as clinically indicated | • Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency) |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hyperthyroidism | Grade 2 | Continue | • Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate | • Monitor for signs and symptoms of thyroid disorders |
| | Grade 3 or 4 | Withhold or permanently discontinue [d] | | |
| Hypothyroidism | Grade 2, 3 or 4 | Continue | • Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care | • Monitor for signs and symptoms of thyroid disorders |
| Nephritis: grading according to increased creatinine or acute kidney injury | Grade 2 | Withhold | • Administer corticosteroids (prednisone 1 to 2 mg/kg or equivalent) followed by taper | • Monitor changes of renal function |
| | Grade 3 or 4 | Permanently discontinue | | |
| | Grade 2 | Withhold | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|
| Neurological Toxicities | Grade 3 or 4 | Permanently discontinue | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| Myocarditis | Grade 1 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology and/or exclude other causes |
| | Grade 2, 3 or 4 | Permanently discontinue | | |
| Exfoliative Dermatologic Conditions | Suspected SJS, TEN, or DRESS | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Confirmed SJS, TEN, or DRESS | Permanently discontinue | | |
| All Other irAEs | Persistent Grade 2 | Withhold | • Based on severity of AE administer corticosteroids | • Ensure adequate evaluation to confirm etiology or exclude other causes |
| | Grade 3 | Withhold or discontinue based on the event [e] | | |
| | Recurrent Grade 3 or Grade 4 | Permanently discontinue | | |

| irAEs | Toxicity Grade (CTCAE v5.0) | Action With Pembrolizumab | Corticosteroid and/or Other Therapies | Monitoring and Follow-up |
|---|---|---|---|---|

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

**Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.**

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

**Dose modification and toxicity management of infusion-reactions related to pembrolizumab**

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 4.

| NCI CTCAE Grade | Treatment | Premedication at Subsequent Dosing |
|---|---|---|
| **Grade 1**<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. | None |
| **Grade 2**<br>Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose.<br>**Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment** | Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of _____ with:<br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic). |
| **Grades 3 or 4**<br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br>Grade 4: | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>Epinephrine**<br>IV fluids<br>Antihistamines<br>NSAIDs<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated. | No subsequent dosing |

| | | |
|---|---|---|
| Life-threatening; pressor or ventilatory support indicated | **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.** | |
| Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.<br>For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) | | |

**Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines**

**Other allowed dose interruption for pembrolizumab**

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Participants should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.