### Grading Toxicity

**Definition:** An intense inflammatory condition associated with a robust immune response.

**Grade 1 (Mild)**
- Temperature ≥100.4 °F (38 °C) but no hypotension or hypoxia

**Grade 2 (Moderate)**
- Temperature ≥100.4 °F (38 °C) (but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**Grade 3 (Severe)**
- Temperature ≥100.4 °F (38 °C) (but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**Grade 4 (Potentially Life-Threatening)**
- Temperature ≥100.4 °F (38 °C) (but if fever is actively managed with antipyretic or anticytokine therapy, it is not a requirement for grading)

**Plus Conditions**
- Hemodynamic instability requiring multiple vasopressors
- Worsening hypoxia or respiratory distress despite oxygen administration, requiring positive pressure ventilation (CPAP, BiPAP, or intubation and mechanical ventilation)
- Coagulopathy requiring fresh frozen plasma or cryoprecipitate

### Management

**Overall Strategy**
- CRS toxicities with tebentafusp-tebn are generally milder than those seen with some other cellular-based therapies
- Assure adequate hydration/euvolemic status prior to starting tebentafusp-tebn
- Premedication of the first dose is not required, institutional practices vary. Examples of potential premedications include acetaminophen 650 mg PO, ondansetron 8 mg PO, diphényldimaines 25 mg PO, and famotidine 20 mg
- Medications that can be kept for PRN use include methylprednisolone for rash or CRS; saline bolus, meperidine for chills; diphényldimaines IV for rashes and itching, ondansetron IV for nausea, and acetaminophen for fevers, chills, and headache
- Fever is generally the first sign of CRS, so once the temperature starts increasing, monitor other vital signs more carefully. Consider active management to prevent CRS from escalating
- Monitor patients during the infusion and for at least 16 hours following the first 3 infusions (induction phase) and then as clinically indicated. For the maintenance phase, patients should be monitored a minimum of 30 minutes after administration
- Monitor temperature, pulse rate, respiratory rate, and blood pressure at least every 4 hours during the induction phase and twice post infusion in the maintenance phase. Increase frequency if patient develops symptoms
- Educate patients and caregivers About the importance of reporting concerning symptoms as soon as possible
- Emphasize that CRS occurs in the vast majority of patients (around 90%) and starts the day of the infusion. But it is manageable—very few patients discontinue because of it

### Grade 1 (Mild)
- Tebentafusp-tebn therapy to continue
  - Provide oral analgesics for discomfort (depending on labs, could be acetaminophen 650 mg PO)
  - Corticosteroid management not required
  - Provide ondansetron 8 mg IV PRN for nausea
  - No requirement for premedication for the next dose
  - Next dose can be escalated

### Grade 2 (Moderate)
- If hypotension or hypoxia lasts < 2 hours:
  - Continue tebentafusp-tebn
  - Corticosteroid management is not required
  - Premedication for the next dose is not required
  - Next dose can be escalated

- If hypotension or hypoxia lasts 2-3 hours or is recurrent:
  - Continue tebentafusp-tebn
  - Provide methylprednisolone 2 mg/kg or equivalent PRN
  - Corticosteroid premedication for the next dose is required
  - Next dose can be escalated

- If hypotension or hypoxia lasts >3 hours & is not responding to therapy:
  - Hold tebentafusp-tebn
  - Provide methylprednisolone 2 mg/kg or equivalent PRN
  - Corticosteroid premedication for the next dose is required
  - Next dose cannot be escalated; resume escalation schema once dosages is tolerated
  - All Grade 2 events:
    - Saline bolus (500 mL) PRN
    - Administer vasopressors as needed
    - Ondansetron 4 IV mg IV PRN for nausea
    - Give acetaminophen 650 mg PO PRN for fever/chills/headache
    - Administer low-flow nasal cannula (≤ 6 L/min as needed or blow by oxygen)

### Grade 3 (Severe)
- Hold tebentafusp-tebn
  - Administer vasopressors as required
  - Administer corticosteroids (methylprednisolone 2 mg/kg or equivalent PRN)
  - Corticosteroid premedication for the next dose is required
  - Next dose cannot be escalated; resume escalation schema once dosages is tolerated
  - Saline bolus (500 mL) as needed
  - Mepedrine 25 mg for chills
  - Ondansetron IV 4 mg IV PRN for nausea
  - Acetaminophen 650 mg PO PRN for fever/chills/headache
  - Administer high-flow nasal cannula (>6 L/min, as needed, or face mask)

### Grade 4 (Potentially Life-Threatening)
- Permanently discontinue tebentafusp-tebn
  - Administer vasopressors, typically multiple
  - Provide IV fluids as needed
  - Administer corticosteroids (methylprednisolone 2 mg/kg or equivalent)
  - If hypotension does not resolve rapidly (within 2-3 hours of onset) with intravenous crystalloidal therapy and corticosteroids, tocilizumab 8 mg/kg (IV not to exceed 800 mg/infusion) can be administered until hypotension resolves
  - Provide meperidine 25 mg for chills
  - Provide ondansetron 8 IV mg IV PRN for nausea
  - Administer positive pressure ventilation (CPAP, BiPAP, or intubation and mechanical ventilation) as required to maintain oxygenation
  - Administer analgesics as needed