Appendix. Management of Cytokine Release Syndrome Recommendations Adapted from Clinical Trial Protocols

BsAb Agent	Grade 1	Grade 2	Grade 3	Grade 4
Glofitamab[24] CRS graded according to the Lee Criteria[70]	Interrupt infusion (if symptoms occur during infusion) Treat symptomatically including antihistamine, antipyretics, and or analgesics as needed Treat fever and neutropenia if present Monitor fluid balance, administer IV fluids as clinically indicated Consider IV steroids and tocilizumab for prolonged CRS (>2 days) in patients with significant symptoms or comorbidities Consider extending infusion time for subsequent dose Hospitalize for subsequent dose	Discontinue infusion (if symptoms occur during infusion) As per grade 1 Monitor cardiac and other organ function Hemodynamic support as indicated Oxygen for hypoxia ICU if appropriate Tocilizumab IV corticosteroids Manage as per grade 3 if no improvement within 8-12 hours after starting tocilizumab. Patients with extensive comorbidities should follow grade 3 management guidelines Consider extending infusion time for subsequent dose Hospitalize for subsequent dose	Discontinue infusion (if symptoms occur during infusion) Consider ICU Maintain fluid balance; administer IV fluids as indicated Oxygen for hypoxia Vasopressor support for hypotension Supportive care as clinically indicated Tocilizumab IV steroids Consider extending infusion time for subsequent dose Hospitalize for subsequent dose	Discontinue infusion (if symptoms occur during infusion) ICU admission, follow all grade 3 guidelines Further treatment must be discussed with medical monitor
Mosunetuzumab[23] CRS graded using modified CRS grading system	Slow or interrupt infusion (if symptoms occur during infusion) Symptom management Consider broad spectrum antibiotics Treat neutropenia	Interrupt infusion until symptoms resolve, and consider restarting at half infusion rate (if symptoms occur during infusion) Symptom management Consider ICU for hemodynamic monitoring	Stop infusion and do not resume (if symptoms occur during infusion) Symptom management Admit to ICU for hemodynamic monitoring	Stop infusion and do not resume (if symptoms occur during infusion) Symptom management Admit to ICU for hemodynamic monitoring Mechanical ventilation as required

	Maintenance IV fluids for hydration Consider hospitalization until symptoms resolve Consider corticosteroids / tocilizumab for prolonged CRS (>2 days) in patients with significant symptoms and/or comorbidities Subsequent doses: premedicate, consider reducing infusion rate, consider hospitalization	IV fluid boluses as needed; vasopressors for refractory hypotension (e.g. after 2 fluid boluses and tocilizumab) Consider broad spectrum antibiotics Consider tocilizumab Consider dexamethasone 10 mg QID for refractory hypotension after 1-2 doses of tocilizumab Manage as Grade 3 if no improved after 24 hours of starting tocilizumab Subsequent doses: may receive subsequent doses if symptoms resolve to grade ≤1 for 3 consecutive days.[a] Consider enhanced premedications, reduce rate by half or lower, hospitalization	IV fluid boluses and vasopressors as needed for hypotension Consider broad spectrum antibiotics Administer tocilizumab Dexamethasone 10mg QID (or equivalent). If refractory manage as grade 4. Manage as grade 4 if no improvement within 18-24 hours. May receive next dose if CRS event was responsive to treatment and symptoms resolve to grade ≤1 for 3 consecutive days.[a] Enhanced premedications, reduce rate by half or lower, hospitalization	IV fluid boluses and vasopressors as needed for hypotension Consider broad spectrum antibiotics Administer tocilizumab For patients refractory to tocilizumab, consider siltuximab, anakinra, dasatinib and emapalumab Dexamethasone 10mg QID (or equivalent) If refractory consider methylprednisolone 1000mg/day IV. Permanently discontinue mosunetuzumab
Epcoritamab[25] CRS graded according to the ASTCT grading for CRS[72]	Hospitalization Septic work up NSAIDs Tocilizumab for specific cases (ie. patients with reduced ability to compensate)	As per grade 1 Fluids for hypotension (limit fluid boluses due to the vasodilation and capillary leak associated with CRS) Low flow oxygen via nasal canula Tocilizumab for patients with co-morbidities	As per grade 1 and 2 Vasopressors for hypotension High-flow oxygen, face mask or non-rebreather mask or Venturi mask Tocilizumab Consider steroids	As per grade 1-3 Two vasopressors for hypotension Positive pressure ventilation for hypoxia Tocilizumab Steroids

Abbreviations: BsAb, Bispecific Antibody; CRS, cytokine release syndrome; ICU, intensive care unit; IV, intravenous; NSAIDs, non-steroidal anti-inflammatory drugs; QID, four times a day.

[a]Protocol required discussion with medical monitor of the clinical trial for further treatment.