Treatment Guideline: Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab

INTRODUCTION

This document has been developed to assist management of patients enrolled on the CELESTIMO phase 3 clinical trial[1], which is open at Gloucestershire Hospitals NHSFT (Principal Investigator: Dr Rory McCulloch). This trial randomises patients with relapsed follicular lymphoma to receive either a standard of care arm, rituximab plus lenalidomide, or mosunetuzumab plus lenalidomide.

Mosunetuzumab is a bispecific antibody used in the treatment of B-cell non-Hodgkin lymphoma[2]. It has two binding sites, one that targets an antigen expressed on the lymphoma cell surface (CD20), and a second that targets a T-cell surface marker (CD3). This interaction enhances host cytotoxic T-cell activity against lymphoma cells. Although efficacious, it is important to recognise that this agent is associated with specific toxicities related to its mode of action, including Cytokine Release Syndrome (CRS). Management of this complication is described in this document.

TREATMENT SETTING

As the overall risk of a severe reaction is deemed to be sufficiently low (Grade 3-4 CRS risk 2%[2]), mosunetuzumab will normally be delivered as an outpatient on the Edward Jenner Unit (GRH). However, if a patient's risk of CRS is deemed elevated the treating clinician may elect to admit them to Rendcomb/Lilleybrook (CGH) to receive the infusion. This is most likely to occur for the first infusion dose. In this setting the patient will be observed for 24 hours post infusion. If the patient remains well, they will then be discharged. When patients are admitted for treatment, the DCC team at CGH should be informed on the morning of the infusion before 08:30 AM.

CYTOKINE-RELEASE SYNDROME

CRS is an identified risk for mosunetuzumab. Mild to moderate presentation of infusion-related reactions (IRRs) and/or CRS may include symptoms, such as fever, chills, vomiting, dizziness, hypertension, hypotension, dyspnoea, restlessness, sweating, flushing, skin rash, tachycardia, tachypnoea, headache, tumour pain, nausea, and/or myalgia, and may be treated symptomatically with analgesics, antipyretic medicines, and anti-histamines, as indicated. Such reactions typically occur during or shortly after an infusion or within 24 hours after study drug infusion predominantly at the first infusion.

The incidence and severity of CRS and IRRs typically decrease with subsequent infusions. Patients may also develop IgE-mediated hypersensitivity reactions to study treatment. CRS and IRRs may be indistinguishable from an anaphylactic reaction. Severe or life-threatening presentations of IRRs and/or CRS, such as hypotension, tachycardia, dyspnoea or chest discomfort, should be treated aggressively with supportive and resuscitative measures as indicated below, including the use of high-dose corticosteroids, IV fluids, and other supportive measures. Severe CRS may be associated with other clinical sequelae, such as disseminated intravascular coagulation, capillary leak syndrome, or macrophage activation syndrome.

Table 1 presents management guidelines for CRS and IRRs for patients receiving mosunetuzumab, adapted from the CELESTIMO trial protocol (v4.0).

Table 1: Recommendations for Management of Infusion-Related Reactions and Cytokine-Release Syndrome for Patients Receiving Mosunetuzumab

Please note: all reactions grade 1 or above should be discussed with a ***Consultant Haematologist.***

CRS Grade† *(definition below)*	**Action with current mosunetuzumab infusion**	**Supportive care**	**Tociluzimab or corticosteroids therapy**
Grade 1 Fever ≥ 38ºC	• Slow infusion to ≤ 50% or interrupt infusion until symptoms resolve; restart at same rate • If symptoms recur with rechallenge, interrupt study treatment, do not resume, and manage per Grade 2.	• Symptomatic management of constitutional symptoms and organ toxicities • Consider empiric broad-spectrum antibiotics • Consider G-CSF if patient is neutropenic • Maintenance IV fluids for hydration • Give paracetamol 1 g oral/IV, up to QDS. • Consider hospitalisation until symptoms completely resolve	• For prolonged CRS (> 2 days) in patients with significant symptoms and/or comorbidities (per investigator discretion, e.g., impaired cardiovascular function, reduced pulmonary reserve), consider tocilizumab* and corticosteroids as per Grade 2
Grade 2 Fever ≥ 38ºC Hypotension not requiring vasopressors *and/or* Hypoxia requiring low-flow oxygen‡ by nasal cannula or blow-by	• Hold further study treatment until symptoms resolved; consider restarting infusion at 50% rate • If symptoms recur with rechallenge at decreased infusion rate, interrupt study treatment, do not resume, and manage per Grade 3	• Symptomatic management of constitutional symptoms and organ toxicities • **Consider DCC admission for haemodynamic monitoring** • For hypotension: IV fluid bolus as needed (recommend 250 ml normal saline or Hartman's); for persistent refractory hypotension (e.g., after 2 fluid boluses and tociluzimab therapy), start vasopressors and manage per Grade 3 • Rule out other inflammatory conditions, which can mimic severe CRS (e.g., infections/sepsis), undertake Covid19 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH (Appendix 4 in the study protocol).	• Consider tocilizumab (discuss with consultant Haematologist) • For persistent refractory hypotension after 1 or 2 doses of tociluzimab therapy (see dosing in additional notes*), consider 10 mg IV dexamethasone every 6 hours (or equivalent) • Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab

CRS Grade† *(definition below)*	Action with current mosunetuzumab infusion	Supportive care	Tociluzimab or corticosteroids therapy
Grade 3 Fever ≥ 38ºC Hypotension requiring a vasopressor (with or without vasopressin) *and/or* Hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask	• Stop infusion, do not resume	• Symptomatic management of organ toxicities, ***admit patient to DCC for haemodynamic monitoring*** • For hypotension: IV fluid bolus and vasopressors as needed • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis), undertake Covid19 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work-up and assess for signs and symptoms of HLH (see Appendix 4 in study protocol) *(see additional points on managing severe CRS below)*	• Administer tocilizumab* • Dexamethasone 10 mg IV every 6 hours (or equivalent). If refractory, manage as per Grade 4 • Manage per Grade 4, if no improvement within 18–24 hours after second dose of tocilizumab
Grade 4 Fever ≥ 38ºC Hypotension requiring multiple vasopressors (excluding vasopressin) *and/or* Hypoxia requiring oxygen by positive pressure (e.g., C-PAP, BiPAP, intubation, and mechanical ventilation)	• Stop infusion, do not resume	• ***Arrange DCC admission and haemodynamic monitoring*** • Mechanical ventilation as needed • IV fluids and vasopressors as needed • Symptomatic management of organ toxicities • Rule out other inflammatory conditions that can mimic severe CRS (e.g., infections or sepsis), undertake Covid19 diagnostic PCR • Consider empiric broad-spectrum antibiotics • If no improvement within 24 hours, initiate work up and assess for signs and symptoms HLH (see additional points on managing severe CRS (below), and Appendix 4 in study protocol)	• Administer tocilizumab* • For patient's refractory to tocilizumab, consider anakinra^ based on discretion of the consultant in charge; management should be discussed with the Medical Monitor • Administer 10 mg IV dexamethasone every 6 hours (or equivalent) • If refractory, consider 1000 mg/day IV methylprednisolone

BiPAP, bilevel positive airway pressure; C-PAP, continuous positive airway pressure; CRS, cytokine release syndrome; DCC, Department of Critical Care; G-CSF, growth colony stimulating factor; HLH, Haemophagocytic Lymphohistiocytosis; IV, intravenous; PCR, polymerase chain reaction.

Key and Additional notes:

† Cytokine-release syndrome will be assessed according to the ASTCT Consensus Grading Criteria[3]. Fever is defined as temperature ≥ 38ºC not attributable to any other cause. In patients who have CRS and then receive antipyretic or anti-cytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. Cytokine-release syndrome grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low-flow also includes blow-by oxygen delivery. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

***** **Tocilizumab dosing:** should be administered by IV infusion at a dose of 8 mg/kg for patients weighing ≥ 30 kg only and 12 mg/kg for patients weighing < 30 kg given over 60 minutes (doses exceeding 800 mg per infusion are not recommended); repeat every 8 hours as necessary (for up to a maximum of 4 doses)[4]. See Appendix 7 in trial protocol for schedule of activities for tocilizumab treatment of CRS. S:\Oncology\Cancer Clinical Trials\1 OPEN CANCER CLINICAL TRIALS - PROTOCOLS\CELESTIMO (Lymphoma) (RM)

^ **Anakinra**: If considering use discuss urgently with on-call pharmacy. For further information on dosage and administration please see University Hospitals Bristol and Weston standard operating procedure: http://nww.avon.nhs.uk/dms/download.aspx?did=23516 see also SPC for administration details[5].

Additional points on managing severe CRS (grade 3 or 4):

The development of a severe reaction necessitates immediate notification of the on-call Consultant Haematologist. Immediate assessment should include:

- Intensive observation monitoring: Pulse, temperature, blood pressure and respiration rate, pulse oximetry +/- ABG.
- Lab studies: FBC, comprehensive metabolic panel (U&Es, LFTs, Ca^{2+}, Mg^{2+}, Phosphate, uric acid, LDH, CRP, lactate, ferritin), PT/APTT, fibrinogen, urinalysis, consider cytokines as feasible (IFN-γ, IL-6, TNF-, IL-2, IL-2R). Ferritin, procalcitonin and fibrinogen should be monitored daily until cytokine storm has resolved.
- If considering HLH consider using the H-score to help guide clinical management: https://www.mdcalc.com/calc/10089/hscore-reactive-hemophagocytic-syndrome
- Chest X-Ray: if respiratory signs / symptoms or reduced oxygen saturations (urgent mobile)
- ECG: baseline at onset of CRS and then as dictated by clinical signs and symptoms.
- Microbiological studies: blood cultures, urine, sputum if present.
- Physical examination: to include neurological checks in patients with neurologic symptoms.
- The patient should be referred to DCC for immediate review and transfer to DCC as appropriate.
- Tocilizumab and corticosteroids should be readily available on Rendcomb ward and Edward Jenner Unit, but early involvement of pharmacy staff is recommended to confirm access to treatments for refractory CRS.

REFERENCES

1. Phase III randomized, open-label, multicenter study evaluating efficacy and safety of Mosunetuzumab in combination with Lenalidomide in comparison to Rituximab in combination with Lenalidomide in patients with Follicular Lymphoma after at least one line of systemic therapy. *Protocol number GO42909.* 2021 Sep; v4. S:\Oncology\Cancer Clinical Trials\1 OPEN CANCER CLINICAL TRIALS - PROTOCOLS\CELESTIMO (Lymphoma) (RM)
2. Budde, L.E. *et al.* Safety and efficacy of mosunetuzumab, a bispecific antibody, in patients with relapsed or refractory follicular lymphoma: a single-arm, multicentre, phase 2 study. *Lancet Onc*. 2022 Aug;23(8):1055-1065.
3. Lee, D.W. *et al.* ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biol Blood Marrow Transplant.* 2019 Apr;25(4):625-638.
4. Roche Products Ltd (2022) EMC *RoActemra 20mg/ml Concentrate for Solution for Infusion* Available via https://www.medicines.org.uk/emc/product/6673/smpc#gref
5. Swedish Orphan Biovitrum Ltd (2022) EMC *Kineret 100 mg solution for injection in a pre-filled syringe* Available via https://www.medicines.org.uk/emc/product/559

CONTACTS

- Haematology Consultant: If out of hours, contact the oncall Haematology Consultant via Switchboard
- Department of Critical Care (DCC): contact Acute Care Response Team (ACRT) via bleep 1700, or contact the oncall DCC consultant via switchboard depending on level of clinical concern.
- Pharmacy oncall out of hours: via Switchboard
- Clinical Trials Team: if a patient on trial is admitted please email: ghn-tr.haematologytrials@nhs.net