Royal Cornwall Hospitals
NHS Trust

Diagnosis and Management of Cytokine Release Syndrome (CRS) in Patients Receiving Bispecific Antibody Therapy in Non-Trial Patients
Clinical Guideline

V1.1

July 2025

This document is for UK Healthcare Professionals only.

Summary

Bispecific antibodies (e.g. Epcoritamab, Glofitamab, and Mosunetuzumab and Odronextamab*) engage and activate endogenous T cells to destroy tumour cells. They are used to treat non-Hodgkin lymphoma and myeloma. Treatment can be complicated by cytokine release syndrome (CRS), particularly during the first few doses. Treatment protocols already contain prophylaxis against this risk (e.g., weekly step-up dosing and prophylactic corticosteroids), however CRS can still occur and is important to recognise, as it usually resolves with prompt and appropriate treatment.

Cytokine release syndrome (CRS) is supra-physiologic response following any immune therapy that activates or engages endogenous or infused T-cells or other immune effector cells. Symptoms can be progressive but generally present with fever at the outset and may also include hypotension, capillary leak (hypoxia) and end-organ dysfunction. It is usually characterised clinically by fever, tachycardia, hypotension, chills and hypoxia. It usually occurs hours to days after the first few doses of treatment. In clinical trials, the incidence of CRS is 50-60% and most cases are mild (fever alone) and require minimal intervention such as supportive care. Approximately 1 – 4% of cases are severe, but up to 20% of cases may require corticosteroids and anti-cytokine therapy such as tocilizumab [1-11].

The common symptoms of CRS are not unique to CRS and practitioners must be cautious to exclude (or treat empirically) other causes of fever, hypotension, haemodynamic instability and or respiratory distress such as an overwhelming infection. There are no specific blood tests for CRS and changes in inflammatory markers, such as CRP and ferritin, may lag by up to 12 hours behind clinical features and are not specific to CRS. It is therefore a clinical diagnosis made based on timing of events and clinical features[11].

The management of CRS depends on the grade of severity and is defined in Tables 1 and 2 (see below). Patients who develop grade ≥2 CRS should be considered for early intervention with steroids and/or Tocilizumab (see Table 2) and discussed with the on-call haematology consultant (and ICU where appropriate) to obtain the necessary support and reduce the severity of CRS if possible.

(*Odronextamab is not yet licensed).

1. Aim/Purpose of this Guideline

1.1. To guide in the diagnosis and management of cytokine release syndrome in the context of bispecific antibody therapy and to support the inpatient overnight monitoring of such patients.

1.2. This version supersedes any previous versions of this document.

Data Protection Act 2018 (UK General Data Protection Regulation – GDPR) Legislation.

The Trust has a duty under the Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 to ensure that there is a valid legal basis to process personal and sensitive data. The legal basis for processing must be identified and documented before the processing begins. In many cases we may need consent; this must be explicit, informed, and documented. We cannot rely on opt out, it must be opt in.

Data Protection Act 2018 and UK General Data Protection Regulations 2016/679 is applicable to all staff; this includes those working as contractors and providers of services.

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2. The Guidance

2.1. **Planning Treatment for Patients Having Bispecifc Antibody Therapy**

There are slightly different CRS mitigation protocols for each antibody. All require weekly step-up dosing and prophylactic corticosteroids pre-treatment initially. Glofitamab requires a pre-dose infusion of Obinutuzumab on day 1 cycle 1 (a week before the first bispecific dose is given) and odronextamab mandates a split dose for cycle 1 day 1. During this time CRS is:

- Often predictable (during or 24hrs after infusion).
- Often mild (grade 1 requiring paracetamol only).
- Occasionally more severe requiring steroids +/- tocilizumab.

Inpatient monitoring for signs and symptoms of CRS for 24 hours post end of infusion is generally only required at the following time-points:

- For Glofitamab (*Columvi*):
    - **After completion of the infusion of the first dose of glofitamab** (2.5mg on Cycle 1 Day 8) (and for the subsequent infusion only if they experience a grade ≥2 CRS event with the previous dose)[8].

- For Epcoritamab (*Tepkinly*).
    - **After administration of the cycle 1 day 15 dose** of 48mg to monitor for signs and symptoms of CRS (and for the subsequent infusion only if they experience a grade ≥2 CRS event with the previous dose)[9].
- For Mosunetuzumab (*Lunsumio*).
    - **Hospitalisation is not mandated** as CRS is generally mild with its licensed use in follicular lymphoma[10].
- For Odronextamab.
    - Refer to clinical trial protocol and discuss with haematology trials team.

2.1.1. Planning outpatient treatment on the Headland Unit:

- Ensure patient has 24-hour hotline card and copy of CRS alert card (see CNS team).
- Encourage patient to make contact according to CRS alert card if they have any concerns.

2.1.2. For Inpatient doses refer to the following checklist:

Question	Confirm
Admit to Lowen ward the evening before infusion.	
Pharmacy to ensure tocilizumab is available on ward before infusion starts.	
Take baseline bloods on day of infusion (FBC, UEs, LFTs, CRP).	
Inform nursing team at morning board-round that monitoring is required on day of infusion.	
Commence infusion no later than 12:00 noon.	
Monitor the patient with 4 hourly vital signs for 24 hours post infusion. If well (grade 1 or no CRS) patient can be discharged with advice on symptoms and contact details in case of delayed reaction.	

2.2. Management of Cytokine Release Syndrome

The management depends on the grade of severity[11]:

Severity Grade of CRS	Clinical Features
1	Fever* with or without constitutional symptoms (e.g., myalgia, arthralgia, malaise).

Severity Grade of CRS	Clinical Features
2	Fever* with hypotension† not requiring vasopressors and/or hypoxia‡ requiring the use of low flow oxygen (<6L/minute).
3	Fever* with hypotension† requiring 1 vasopressor and/or hypoxia‡ requiring high flow oxygen (>6L/min).
4	Fever* with hypotension† requiring multiple vasopressors and or hypoxia‡ requiring positive pressure ventilation (e.g. CPAP) not attributable to any other cause.

Table 1. Severity grading of CRS according to clinical features (taken from Lee *et al.* 2018)[11].

*Fever: defined as temperature ≥38.0^{o}C. 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, in this case CRS grading is driven by hypotension or hypoxia.

†Hypotension should be determined on a case-by-case basis, accounting for patient's age and the patient's individual baseline.

‡ hypoxia is defined as the requirement of supplemental oxygen to correct a deficit in oxygenation from the patient's individual baseline.

Initial Assessment Should Include:

1. Evaluation of the patient for other causes of fever, hypoxia, hypotension (consider infection and broad-spectrum antibiotics).

2. Regular vital signs (hourly until symptoms resolve).

3. For Grade ≥2 CRS:

   A. FBC, U&Es, LFTs, Ca^{2+}, phosphorus, uric acid, LDH, CRP, ferritin, PT/APTT, fibrinogen.

   B. Urinalysis, urine culture, blood cultures, sputum culture, COVID19 PCR.

   C. Chest x-ray: if respiratory signs / symptoms or reduced oxygen saturations.

   D. ECG: baseline at onset of CRS and then as dictated by clinical signs and symptoms.

2.3. Management of Cytokine Release Syndrome

Severity	Grade 1	Grade 2	Grade 3	Grade 4
Intervention	Treat symptoms[1]. Consider other causes of fever. Consider corticosteroids and anti-cytokine therapy in certain cases, e.g., advanced age, high tumour burden, circulating tumour cells, fever refractory to antipyretics.[3,4].	Treat symptoms[1]. Give anti-cytokine therapy (tocilizumab)[4]. For hypotension: 0.9% saline fluid challenge in 500mL boluses. If >1000mL is administered, consider vasopressor support[2]. Hypoxia: administer oxygen at a flow needed to correct deficit. Consider a further dose of corticosteroids.	As per Grade 2 with ITU support: Give anti-cytokine therapy (tocilizumab)[4]. Administer corticosteroids[3] Administer broad spectrum antibiotics. If CRS is refractory to initial anti-cytokine therapy, initiate / increase dose of corticosteroids and consider an alternative anti-cytokine therapy e.g., anakinra.	As per Grade 3 with ITU supervision. Give anti-cytokine therapy[4]. Administer corticosteroids[3] Administer broad spectrum antibiotics. If CRS is refractory to initial anti-cytokine therapy, initiate / increase dose of corticosteroids and consider alternative anti-cytokine therapy e.g., anakinra.

Severity	Grade 1	Grade 2	Grade 3	Grade 4
If CRS occurs during bispecific Antibody infusion	Interrupt infusion Restart infusion at slower rate when symptoms resolve. If symptoms recur, discontinue infusion.	Discontinue current infusion.	Discontinue current infusion.	Permanently discontinue bispecific antibody.

Severity	Grade 1	Grade 2	Grade 3	Grade 4
For next scheduled bispecific infusion	Ensure symptoms are resolved for >72 hours prior to next infusion. Consider slower rate of infusion (duration may be up to 8 hours).	Ensure symptoms are resolved for >72 hours prior to next infusion. Consider slower rate of infusion (duration may be up to 8 hours). Inpatient monitoring post-infusion.	Ensure symptoms are resolved for >72 hours prior to next infusion. Consider slower rate of infusion (duration may be up to 8 hours). Inpatient monitoring post-infusion. If grade ≥3 CRS recurs, stop infusion and permanently. discontinue therapy.	Not applicable.

1. Treat symptoms: paracetamol 1g IV (if not already received within 4 hours).

2. CRS is associate with capillary leak: excess IV fluids can lead to worsening hypoxia and a deteriorating clinical picture; therefore, early ITU involvement and consideration of vasopressor is encouraged.

3. Corticosteroid dosing: dexamethasone 10mg IV given every 6 hours. In refractory grade 4 CRS consider methylprednisolone 1g once daily.

4. Anti-cytokine therapy: Tocilizumab dosing: 8mg/kg IV infusion over 1 hour (not exceeding 800mg per dose); repeat tocilizumab after at least 8 hours as needed. Maximum of 2 doses in a 24hr period.

2.4. References

1. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Dickinson M. *et al.* NEJM Dec. 2022.

2. Epcoritamab, a Novel, Subcutaneous CD3xCD20 Bispecific T-Cell-Engaging Antibody, in Relapsed or Refractory Large B-Cell Lymphoma: Dose Expansion in a Phase I/II Trial. Thieblemont C. *et al.* JCO Apr 2023.

3. Subcutaneous Epcoritamab with Rituximab + Lenalidomide in Patients with Relapsed or Refractory Follicular Lymphoma:Phase 1/2 Trial Update. Falchi L. et al. BLOOD Suppl 2022.

4. Mosunetuzumab monotherapy is active and tolerable in patients with relapsed/refractory diffuse large B-cell lymphoma. Bartlett N. et al. BLOOD Apr 2023.

5. Mosunetuzumab Monotherapy Demonstrates Durable Efficacy with a Manageable Safety Profile in Patients with Relapsed/Refractory Follicular Lymphoma Who Received ≥2 Prior Therapies: Updated Results from a Pivotal Phase II Study. Bartlett N. et al. BLOOD Nov 2022.

6. Final Analysis of the Phase 2 ELM-2 Study: Odronextamab in Patients with Relapsed/Refractory (R/R) Diffuse Large B-Cell Lymphoma (DLBCL). Ayyappan S. et al. Blood 2023.

7. Results of a Second, Prespecified Analysis of the Phase 2 Study ELM-2 Confirm High Rates of Durable Complete Response with Odronextamab in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL) with Extended Follow-up. Villasboas J. et al. BLOOD ASH 2023.

8. Columvi https://www.medicines.org.uk/emc/product/15176/smpc

9. Tepkinly, https://www.medicines.org.uk/emc/product/15187/smpc#gref

10. Lunsumio https://www.medicines.org.uk/emc/product/14121/smpc#gref

11. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Lee D W. et al. American Transplantation and Cellular Therapy Vol 25 Issue 4 2018. https://doi.org/10.1016/j.bbmt.2018.12.758

3. Monitoring compliance and effectiveness

Information Category	Detail of process and methodology for monitoring compliance
Element to be monitored	Incidence of cytokine release syndrome and outcomes of management according to above guideline.
Lead	Dr David Tucker, Consultant Haematologist.
Tool	Digital patient records, eCARE, Nervecentre, patient notes.
Frequency	Annually.
Reporting arrangements	The results of this will be reviewed by the haematology clinical governance structure and annual audit review in haematology.
Acting on recommendations and Lead(s)	Dr Tucker (Consultant Haematologist) and Bispecific therapy lead.
Change in practice and lessons to be shared	Clinical Governance reports and meetings in haematology; medical grand-round educational meetings.

4. Equality and Diversity

4.1. This document complies with the Royal Cornwall Hospitals NHS Trust service Equality and Diversity statement which can be found in the Equality Diversity And Inclusion Policy or the Equality and Diversity website.

4.2. Equality Impact Assessment

The Initial Equality Impact Assessment Screening Form is at Appendix 2.

Appendix 1. Governance Information

Information Category	Detailed Information
Document Title:	Diagnosis and Management of Cytokine Release Syndrome (CRS) in Patients Receiving Bispecific Antibody Therapy in Non-Trial Patients Clinical Guideline V1.1
This document replaces (exact title of previous version):	Diagnosis and Management of Cytokine Release Syndrome (CRS) in Patients Receiving Bispecific Antibody Therapy in Non-Trial Patients Clinical Guideline V1.0
Date Issued/Approved:	September 2024
Date Valid From:	July 2025
Date Valid To:	December 2027
Directorate/Department responsible (author/owner):	Dr David Tucker, Consultant Haematologist
Contact details:	01872 252524
Brief summary of contents:	Guidance on the management of common complications of bispecific antibody therapy in lymphoma patients including the diagnosis and management of cytokine release syndrome.
Suggested Keywords:	Cytokine Release Syndrome, Bispecific Antibody Therapy, Odronextamab, Glofitamab, Epcoritamab.
Target Audience:	**RCHT:** Yes **CFT:** No **CIOS ICB:** No
Executive Director responsible for Policy:	Chief Medical Officer
Approval route for consultation and ratification:	Haematology Clinical Governance Meeting
Manager confirming approval processes:	Dr Bryson Pottinger
Name of Governance Lead confirming consultation and ratification:	Suzanne Atkinson
Links to key external standards:	None required

Information Category	Detailed Information
Related Documents:	See 2.4.
Training Need Identified?	No
Publication Location (refer to Policy on Policies – Approvals and Ratification):	Internet and Intranet
Document Library Folder/Sub Folder:	Clinical / Haematology

Version Control Table

Date	Version Number	Summary of Changes	Changes Made by
September 2024	V1.0	Initial issue	Dr David Tucker, Consultant Haematologist
July 2025	V1.1	Infromationm added to front page to state 'This document is for UK Healthcare Professionals only'.	Dr David Tucker, Consultant Haematologist

All or part of this document can be released under the Freedom of Information Act 2000.

All Policies, Strategies and Operating Procedures, including Business Plans, are to be kept for the lifetime of the organisation plus 6 years.

This document is only valid on the day of printing.

Controlled Document.

This document has been created following the Royal Cornwall Hospitals NHS Trust The Policy on Policies (Development and Management of Knowledge Procedural and Web Documents Policy). It should not be altered in any way without the express permission of the author or their Line Manager.

Appendix 2. Equality Impact Assessment

Section 1: Equality Impact Assessment (EIA) Form

The EIA process allows the Trust to identify where a policy or service may have a negative impact on an individual or particular group of people.

For guidance please refer to the Equality Impact Assessment Policy (available from the document library) or contact the Equality, Diversity, and Inclusion Team rcht.inclusion@nhs.net

Information Category	Detailed Information
Name of the strategy/policy/proposal/service function to be assessed:	Diagnosis and Management of Cytokine Release Syndrome (CRS) in Patients Receiving Bispecific Antibody Therapy in Non-Trial Patients Clinical Guideline V1.1
Directorate and service area:	Haematology/ General Surgery and Cancer Services
Is this a new or existing Policy?	New
Name of individual completing EIA (Should be completed by an individual with a good understanding of the Service/Policy):	Dr David Tucker, Consultant Haematologist
Contact details:	01872 252524

Information Category	Detailed Information
1. Policy Aim - Who is the Policy aimed at? (The Policy is the Strategy, Policy, Proposal or Service Change to be assessed)	This guideline is developed to assist clinicians in the safe and effective Diagnosis and Management of Cytokine Release Syndrome (CRS) in Patients Receiving Bispecific Antibody Therapy in Non-Trial Patients.
2. Policy Objectives	As above.
3. Policy Intended Outcomes	As above.
4. How will you measure each outcome?	Audit.
5. Who is intended to benefit from the policy?	Staff and patients.

Information Category	Detailed Information
6a. Who did you consult with? (Please select Yes or No for each category)	• Workforce: Yes • Patients/visitors: No • Local groups/system partners: No • External organisations: No • Other: No
6b. Please list the individuals/groups who have been consulted about this policy.	**Please record specific names of individuals/groups:** Haematology Clinical Governance Meeting.
6c. What was the outcome of the consultation?	Approved.
6d. Have you used any of the following to assist your assessment?	**National or local statistics, audits, activity reports, process maps, complaints, staff, or patient surveys:** No.

7. The Impact

Following consultation with key groups, has a negative impact been identified for any protected characteristic? Please note that a rationale is required for each one.

Where a negative impact is identified without rationale, the key groups will need to be consulted again.

Protected Characteristic	(Yes or No)	Rationale
Age	No	
Sex (male or female)	No	
Gender reassignment (Transgender, non-binary, gender fluid etc.)	No	
Race	No	
Disability (e.g. physical or cognitive impairment, mental health, long term conditions etc.)	No	
Religion or belief	No	
Marriage and civil partnership	No	

Protected Characteristic	(Yes or No)	Rationale
Pregnancy and maternity	No	
Sexual orientation (e.g. gay, straight, bisexual, lesbian etc.)	No	

A robust rationale must be in place for all protected characteristics. If a negative impact has been identified, please complete section 2. If no negative impact has been identified and if this is not a major service change, you can end the assessment here.

I am confident that section 2 of this EIA does not need completing as there are no highlighted risks of negative impact occurring because of this policy.

Name of person confirming result of initial impact assessment: Dr David Tucker, Consultant Haematologist.

If a negative impact has been identified above OR this is a major service change, you will need to complete section 2 of the EIA form available here:
Section 2. Full Equality Analysis