Management of Bispecific Antibody Treatment Related Cytokine Release Syndrome (CRS)

All reactions grade 1 or above should be discussed with a Consultant Haematologist. For patients requiring ITU input: Registrar Bleep #702 Outreach Nurses Bleep #421/422		
Presenting Symptoms	**Initial management**	**Ongoing management**
Grade 1 CRS		
Temperature ≥38°C No hypotension No Hypoxia	• Interrupt bispecific infusion (if running) • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • Supportive care e.g. IV fluids and oxygen as appropriate • If fever persists for 6-8 hours, consider **dexamethasone 10 mg IV 6 hourly** until symptoms have resolved. Consider taper. • Consider **tocilizumab*** in cases of protracted fever (e.g. >48 hours despite dexamethasone)	• Restart infusion at slower rate once symptoms have resolved • If symptoms recur, discontinue infusion • Ensure symptoms are resolved for >72 hours prior to next infusion and consider slower rate of infusion (may be extended up to 8 hours.) • If symptoms persist for >3 days or refractory fever, treat as Grade 2 CRS • Consider **antifungal prophylaxis** in patients receiving steroids
Grade 2 CRS – Inform ICU and Consider Transfer		
Temperature ≥38°C **AND** Hypotension responsive to fluids **AND/OR** Hypoxia requiring <6L/min oxygen	• Discontinue current infusion • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • Administer **Dexamethasone 10 mg IV 6 hourly** until symptoms have resolved. Consider taper. • IV fluids bolus 500-1000 mL to maintain SBP >90mm/Kg and oxygen as appropriate • Consider **tocilizumab*** in cases of protracted fever (e.g. >48 hours despite dexamethasone) • If hypotension persistent after 2 x fluid boluses and tocilizumab, consider low-dose vasopressor	• Ensure symptoms are resolved for >72 hours prior to next infusion and consider slower rate of infusion • Inpatient monitoring for next infusion (may be extended up to 8 hours.) • If no improvement within 24 hours, treatment as Grade 3 CRS • Consider **antifungal prophylaxis** in patients receiving steroids

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Grade 3 (Medical Emergency) – Transfer to ICU		
Temperature ≥38°C **AND** Hypotension requiring vasopressors **AND/OR** Hypoxia requiring >6L/min oxygen	• Discontinue current infusion • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • Administer vasopressors as required • Administer oxygen as required • Administer **tocilizumab*** • Administer **IV methylprednisolone 1mg/kg BD**. If refractory, consider methylprednisolone 1g/day IV. Consider taper once symptoms resolved.	• Ensure symptoms are resolved for >72 hours prior to next infusion and consider slower rate of infusion (may be extended up to 8 hours.) • Inpatient monitoring for next infusion • If grade ≥3 CRS recurs, stop infusion and permanently discontinue therapy • Consider **antifungal prophylaxis** in patients receiving steroids
Grade 4 (Medical Emergency) – Transfer to ICU		
Temperature ≥38°C **AND** Hypotension requiring multiple vasopressors **AND/OR** Hypoxia requiring CPAP/BiPAP/Ventilation	• Discontinue current infusion • Treat as per neutropenic sepsis guideline • Give **paracetamol 1000 mg IV/PO** (ensure at least 4 hours gap if given as pre-med) and **chlorphenamine 10 mg IV** • Administer **tocilizumab*** • Administer **methylprednisolone 1g/day IV.** Consider taper once symptoms resolved. • If multiple doses of tocilizumab have been used and still symptomatic, consider **Anakinra****	• Permanently discontinue bispecific antibody • Consider **antifungal prophylaxis** in patients receiving steroids

***Tocilizumab Guidance (20mg/mL concentration solution for infusion)**

- 8mg/kg (max. 800 mg per dose) IV over 60 minutes
- Repeat dose every 8 hours if no improvement. Maximum 4 doses.
- Stock on Laurel 3, ITU and Emergency Drug Cupboard (by Pharmacy)
- Blueteq required (can be done retrospectively)

****Anakinra Guidance (100mg/0.67 mL solution for injection PFS)**

- Patient must have had at least 2 doses of tocilizumab and still symptomatic
- 100 mg daily SC or via slow IV bolus if platelets <20.
- Can increase in 100 mg increments to a maximum dose of 10mg/kg/day as needed
- Continue until 24 hours after resolution of CRS (usually no more than 3-5 days required.)
- Stock on ITU

Monitoring:

- NEWS score hourly
- FBC, U&Es, LFTs, Ca2+, Mg2+ , PO43- , uric acid, LDH, CRP, lactate, PT/APTT
- Ferritin, procalcitonin and fibrinogen should be monitored daily until CRS has resolved
- Microbiological studies: urinalysis, urine culture, blood cultures, sputum culture if present, COVID19 PCR
- 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