Chemotherapy Protocol

LYMPHOMA

EPCORITAMAB -Cycle 1 - (28 Day -Priming)

Regimen

- Lymphoma-Epcoritamab – Cycle 1- (28 day -Priming)

Indication

- Treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy
- **This protocol is to be used for dose titration of epcoritamab to 48mg (full dose). Once this dose is reached the Cycle 2 onwards regimen protocol should be used.**
- Blueteq form must be completed for funding -NICE TA954

Toxicity

Drug	Adverse Effect
Epcoritamab	Cytokine release syndrome (CRS), immune effector-cell associated neurotoxicity syndrome (ICANS), serious infection, tumour flare, tumour lysis syndrome, cytopenia, thrombocytopenia, neutropenia, hypophosphatemia, hypokalemia, hypomagnesemia, headache, abdominal pain, nausea and vomiting, diarrhoea, elevated ALT, AST & ALP.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Symptoms of CRS can occur weeks after administration and therefore the patient must be issued with an alert card to carry with them at all times.

See Trust Protocol for management and grading of CRS and ICANS following bispecific antibody treatment.

Monitoring

Regimen

- FBC, LFTs, U&Es, bone profile, CRP and LDH prior to day one of treatment
- Documented viral screen – CMV, HSV, EBV, VZV, HIV
- Check hepatitis B status before starting. Patients with positive hepatitis B serology should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis re-activation

CRS:

Symptoms: pyrexia, tiredness, cardiac failure, tachycardia, cardiac arrythmias, dyspnoea, hypoxia, capillary leak syndrome, chills, renal impairment, headache, malaise, transaminitis, nausea, diarrhoea, hypotension.

- Temperature, blood pressure and oxygen saturation monitored 4-hourly after epcoritamab administration on cycle 1 day 15 and then twice daily as directed in accordance with local procedures.
- This must be documented, and CRS graded on the CRS Assessment Form in the patient's notes, as per local policy.

See Trust Protocol following bispecific antibody treatment for CRS guidelines for monitoring requirement and grading.

The prescriber must inform the patient of the risk of CRS and signs and symptoms of CRS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of CRS. Patients should be provided with an alert card and instructed to carry the card at all times. This card states their treatment regimen and emergency contact details in case of reaction or CRS.

ICANS

Symptoms: seizures, somnolence, headaches, confusion, agitation, speech disorders, tremor, encephalopathy, ataxia, memory impairment, mental status changes, hallucinations, depressed level of consciousness, delirium, dysmetria.

No formal ICANS assessment is required following epcoritamab administration. However, the prescriber, clinical team and patient must be aware of the risk of ICANS and the signs and symptoms of ICANS. Patients must be instructed to seek immediate medical attention if they experience signs and symptoms of ICANS.
See Trust Protocol following bispecific antibody treatment for ICANS grading and management.

Patient monitoring

- All patients **must be hospitalised on Cycle 1 Day 15 (i.e. first dose of 48mg) for 24 hours after administration of epcoritamab** to monitor for the signs and symptoms of CRS and ICANS.
- At least 1 dose of tocilizumab for use in the event of CRS must be available on the ward, or pre-specified location, prior to epcoritamab administration, during dosing of Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.
- Patients who experienced Grade ≥ 2 CRS or received tocilizumab with their most recent infusion should be hospitalised for their next scheduled infusion.

Tumour Lysis Syndrome

- Tumour lysis syndrome (TLS) has been reported with epcoritamab. Patients should be assessed for risk of tumour lysis prior to each administration. Ensure patients are well hydrated.
- In patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count (greater than $25x10^9$/L) and/or renal impairment (CrCl less than 70 ml/min) should receive prophylaxis.

- Prophylaxis should consist of adequate hydration and administration of allopurinol or a suitable alternative such as rasburicase prior to the infusion.
- All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed.

Dose Modifications

No dose reductions of epcoritamab are recommended. Adverse events should be managed with dose interruption or treatment discontinuation.
Please discuss all dose delays with the relevant consultant before prescribing. The approach may be different depending on the clinical circumstances.
Patients should permanently discontinue epcoritamab after a Grade 4 CRS or ICANS event.

Haematological toxicities

Dose modifications for haematological toxicity in the table below are for general guidance only. Any haematological abnormalities will be evaluated with clinical judgement. Always refer to the responsible consultant as any dose delays will be dependent on clinical circumstances and treatment intent. The patient may require blood products and/or growth factor support.

Neutrophils ($x10^9$/L)	**Dose modifications**
<0.5	Withhold until ANC is ≥ 0.5
Platelets ($x10^0$ /L)	**Dose modifications**
<50	Withhold until platelet count is ≥ 50
Haemoglobin (g/L)	**Dose modifications**
<80	Withhold until returns to <LLN – 100 or baseline.

Hepatic Impairment

No dose adjustment is required in patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin 1 to 1.5 times ULN and any AST).

There is limited data in moderate hepatic impairment (total bilirubin >1.5 to 3 times ULN and any AST). Therefore, the effects of epcoritamab are unknown.

The safety and efficacy of epcoritamab has not been established in patients with severe hepatic impairment (total bilirubin >3 times ULN and any AST).

Renal Impairment

Dose adjustment is not considered necessary in patients with mild or moderate renal impairment (CrCL 30 to < 90 mL/min).

The safety and efficacy of epcoritamab has not been established in patients with severe to end-stage renal impairment (CrCl <30mL/min).

Other

For all NCI-CTC grade 3 and above toxicities/ adverse events delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or baseline.

Withhold epcoritamab in patients with active infection, until the infection resolves.

Regimen

Epcoritamab dosing begins with a step-up dosing schedule (cycle 1 comprises: priming dose, followed by intermediate dose before full dose) to decrease the risk of CRS, leading to the recommended dose of 48 mg. Therefore cycle 1 is a 28 day priming cycle before leading onto the maintenance dose of 48mg (see Epcoritamab - Cycle 2 onwards - 28 day protocol).
Each cycle of epcoritamab is 28 days, and the treatment duration is until disease progression or unacceptable toxicity. Patients should permanently discontinue epcoritamab after a Grade 4 CRS or ICANS event.

Aria regimen is built as an in-patient regimen on Cycle 1 Day 15 and all other treatment days are built as an out-patient regimen. If the patient is admitted as an in-patient on any other days, the supportive medicines must be prescribed on the in-patient prescribing system.

Cycle 1

Drug	Days	Dose	Administration
Epcoritamab	1	0.16 mg	Subcutaneous injection
Epcoritamab	8	0.8 mg	Subcutaneous injection
Epcoritamab	15	48 mg	Subcutaneous injection[2]
Epcoritamab	22	48 mg	Subcutaneous injection

[2]First full dose of Epcoritamab must be administered as an in-patient.

Dose Information

Delayed or missed doses

A re-priming (identical to Cycle 1 with standard CRS prophylaxis) is required if:

- > 8 days between the priming dose (0.16 mg) and intermediate dose (0.8 mg), or
- > 14 days between the intermediate dose (0.8 mg) and first full dose (48 mg), or
- > 6 weeks between full doses (48 mg)

After the re-priming cycle, the patient should resume treatment with Day 1 of the next planned treatment cycle (subsequent to the cycle during which the dose was delayed).

Administration Information

Pre-medications
Epcoritamab should be administered to well-hydrated patients. Premedication to reduce the risk of CRS as outlined.

Pre-medication (30 minutes prior to epcoritamab)	**Cycle 1**
	All Patients
Dexamethasone 15mg oral [1]	√
Chlorphenamine 10mg oral	√
Paracetamol 1000mg oral	√

[1]On these days, the steroid prophylaxis is to continue for 3 consecutive days following each weekly administration of epcoritamab.

Epcoritamab should be administered by subcutaneous injection, preferably in the lower part of the abdomen or the thigh.
Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3).

Supportive Treatments

- Tocilizumab must be prescribed as when required in advance of epcoritamab infusion, in the event of CRS.Tocilizumab (8 mg/kg, maximum dose 800 mg) intravenously 8-hourly if required. *See CRS management* in *Trust Bi-specific Antibody Protocol.*
  - One dose of tocilizumab must be available on the ward or pre-specified location prior to infusion of epcoritamab.
  - Follow local procedures for administration.

- Corticosteroids may be indicated (*See CRS management* in *Trust Bi-Specific Antibody Protocol)* can be either:
    - 10 mg intravenous dexamethasone, 100 mg intravenous prednisolone, 1-2 mg/kg intravenous methylprednisolone per day, or equivalent

- Tumour lysis syndrome (TLS) prophylaxis should be prescribed according to the individual patient TLS risk and at consultant review:
  - In high risk patients, consider 3 mg rasburicase intravenous once prior to first dose epcoritamab followed by 300 mg once daily oral allopurinol starting the day after rasburicase.
  - For low to moderate risk patients, start allopurinol 300 mg oral (100 mg if renal impairment)

- This must be assessed prior to epcoritamab treatment and at each dose increment.

- **Administration related reactions on a required basis:**
  - salbutamol 2.5mg nebulised
  - chlorphenamine 10mg intravenous
  - hydrocortisone sodium succinate 100mg intravenous
  - paracetamol 1000mg oral
  - oxygen as required
  - sodium chloride 0.9% 500ml intravenous
  - consider pethidine 25-50mg intravenous for infusion related rigors that fail to respond to steroids.

- **Anti-infective prophylaxis**
  - Aciclovir 400mg oral twice a day
  - Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral

- **Gastric protection** with a proton pump inhibitor or a H_2 antagonist according to local formulary choice;
  - esomeprazole 20mg once a day oral
  - omeprazole 20mg once a day oral
  - lansoprazole 15mg once a day oral
  - pantoprazole 20mg once a day oral
  - rabeprazole 20mg once a day oral
  - cimetidine 400mg twice a day oral
  - famotidine 20mg once a day oral
  - nizatidine 150mg twice a day oral

- **Growth factors (GCSF)** may be considered to support during neutropenia. To be discussed with consultant.

Extravasation

- Epcoritamab -neutral

References

1. Summary of Product Characteristics for Tepkinyl 48mg solution for injection (AbbVie Limited) -Last updated 28 November 2023.
2. Summary of Product Characteristics for Tepkinyl 4mg/0.8ml concentrate for solution for injection (AbbVie Limited) -Last updated 28 November 2023.
3. Lee D, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biology of Blood

REGIMEN SUMMARY

Epcoritamab - Cycle 1 - (28 day -Priming)

Cycle 1

Day ONE

1. Warning – Ensure TLS assessment completed.
   - TLS prophylaxis allopurinol supplied as pick-up internal on day 1.
   - Rasburicase if required will need prescribing on Aria internal prescription.

2. Warning - Ensure patient has been issued with treatment alert card.

3. Chlorphenamine 10mg oral
   Administration Instructions
   Administer 30 minutes prior to epcoritamab

4. Dexamethasone 15mg oral
   Administration Instructions
   Administer 30 minutes prior to epcoritamab

5. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient takes regular paracetamol for pain control and take dose into account.
   Administer 30 minutes prior to epcoritamab

6. Epcoritamab 0.16mg subcutaneous injection
   Administration Instructions
   Epcoritamab should be administered by subcutaneous injection, preferably in the lower part of abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3)

7. Chlorphenamine 10mg when required for infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

8. Hydrocortisone sodium succinate 100mg intravenous when required for the relief of infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

9. Paracetamol 1000mg oral when required for pyrexia
   Administration Instructions
   For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

10. Salbutamol 2.5mg nebule once only when required for the relief of infusion related bronchospasm

11. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly if required in the event of CRS. Maximum 3 doses.
    Administration Instructions
    See Trust Protocol for CRS management post epcoritamab.
    One dose of tocilizumab must be available on the ward or pre-specified location prior to infusion of epcoritamab. Follow local procedures for administration.

Take home medicines (Day 1)

12. Dexamethasone 15mg once a day oral on the morning of epcoritamab treatment and then for 3 days after.
    Administration Instructions
    Please supply 15 doses for days 2, 3, 4, 8, 9, 10, 11, 15, 16, 17, 18, 22, 23, 24 and 25.
    Please dispense all days on day 1 of the cycle. **
    Take with or after food.

13. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral
    Administration Instructions
    This may be administered as 480mg twice a day according to local practice. Please supply 28 days or the nearest original pack size.

14. Aciclovir 400mg twice a day oral for 28 days

15. Gastric Protection
    Administration Instructions: The choice of gastric protection is dependent on local formulary choice and may include;
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral
    Please supply 28 days or the nearest original pack size.

16. Allopurinol 300mg oral once a day for 28 days.

In accordance with patient assessment.

Cycle 1 Day EIGHT

17. Warning – Ensure TLS assessment completed.
    - TLS prophylaxis allopurinol supplied as pick-up internal on day 1.
    - Rasburicase if required will need prescribing on Aria internal prescription

18. Warning - Ensure patient has been issued with treatment alert card
19. Chlorphenamine 10mg oral
    Administration Instructions
    Administer 30 minutes prior to epcoritamab

20. Warning – Check patient has taken the dexamethasone dose*

21. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account.
    Administer 30 minutes prior to epcoritamab

22. Epcoritamab 0.8mg subcutaneous injection
    Administration Instructions
    Epcoritamab should be administered by subcutaneous injection, preferably in the lower part of abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3)

23. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

24. Hydrocortisone sodium succinate 100mg intravenous when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

25. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

26. Salbutamol 2.5mg nebule once only when required for the relief of infusion related bronchospasm

27. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly if required in the event of CRS. Maximum 3 doses.
    Administration Instructions
    See Trust Protocol for CRS management post epcoritamab.
    One dose of tocilizumab must be available on the ward or pre-specified location prior to infusion of epcoritamab. Follow local procedures for administration.

Cycle 1 Day FIFTEEN

28. Warning – Ensure TLS assessment completed.
    - TLS prophylaxis allopurinol supplied as pick-up internal from Day 1.
    - Rasburicase if required will need prescribing on in-patient prescribing system

29. Warning - Ensure patient has been issued with treatment alert card
30. Warning – Check supportive medication prescribed
    Administration instructions
    1. Dexamethasone 15mg once a day in the morning days 16 to 18 oral
    2. TLS prophylaxis as per TLS assessment.
    3. Chlorphenamine 10mg when required for infusion related reactions.
    4. Hydrocortisone sodium succinate 100mg when required for infusion related reactions.
    5. Paracetamol 1000mg oral when required for pyrexia.
    6. Salbutamol 2.5mg nebulised when required for the relief of infusion related bronchospasm.
    7. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly if required in the event of CRS. Maximum 3 doses. See Trust protocol for CRS Management post epcoritamab. One dose of tocilizumab must be available on the ward or pre-specified location prior to infusion of epcoritamab. Follow local procedures for administration.

31. Chlorphenamine 10mg oral
    Administration Instructions
    Administer 30 minutes prior to epcoritamab

32. Warning – Check patient has taken the dexamethasone dose*

33. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account.
    Administer 30 minutes prior to epcoritamab

34. Epcoritamab 48mg subcutaneous injection
    Administration Instructions
    Epcoritamab should be administered by subcutaneous injection, preferably in the lower part of abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3)

Cycle 1 Day TWENTY TWO

35. Warning – Ensure TLS assessment completed.
    - TLS prophylaxis allopurinol supplied as pick-up internal on day 1.
    - Rasburicase if required will need prescribing on Aria internal prescription.

36. Warning - Ensure patient has been issued with treatment alert card.

37. Chlorphenamine 10mg oral
    Administration Instructions
    Administer 30 minutes prior to epcoritamab

38. Warning – Check patient has taken the dexamethasone dose*

39. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account.
    Administer 30 minutes prior to epcoritamab

40. Epcoritamab 48mg subcutaneous injection
    Administration Instructions
    Epcoritamab should be administered by subcutaneous injection, preferably in the lower part of abdomen or the thigh. Change of injection site from left to right side or vice versa is recommended especially during the weekly administration schedule (i.e., Cycles 1-3)

41. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

42. Hydrocortisone sodium succinate 100mg intravenous when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

43. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

44. Salbutamol 2.5mg nebule once only when required for the relief of infusion related bronchospasm

45. Tocilizumab 8mg/kg (maximum 800mg) intravenous 8-hourly if required in the event of CRS. Maximum 3 doses.
    Administration Instructions
    See Trust Protocol for CRS management post epcoritamab.
    One dose of tocilizumab must be available on the ward or pre-specified location prior to infusion of epcoritamab. Follow local procedures for administration.

Administration information

* Please check the patient has taken dexamethasone 15mg oral on the morning of epcoritamab administration. On occasions where individuals attend for treatment and have forgotten to take the dexamethasone dose please administer dexamethasone 15mg oral 30 minutes prior to epcoritamab administration.

**The dexamethasone may be dispensed as a single supply in one container or as two containers depending on local preference. All doses for cycle one will be supplied on day 1.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	January 2025	New Document	Madeleine Norbury Pharmacist	Hwai Jing Hiew Consultant

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur because of following these guidelines.