Glofitamab (DLBCL)

Indication

Relapsed or refractory diffuse large B-cell lymphoma after 2 or more systemic treatments. Indication includes primary mediastinal B cell lymphoma, double hit lymphoma, transformed follicular lymphoma. Patients must have performance status 0 or 1 to be eligible.

(NICE TA927)

ICD-10 codes

Codes prefixed with C83

Regimen details

Cycle 1 (NB. Includes single dose of Obinutuzumab to mitigate risk of cytokine release syndrome (CRS))

Day	Drug	Dose	Route
1	Obinutuzumab	1000mg	IV infusion
8	Glofitamab*	2.5mg	IV infusion
15	Glofitamab*	10mg	IV infusion

Cycle 2-12

Day	Drug	Dose	Route
1	Glofitamab*	30mg	IV infusion

*Note: Prior to cycle 1 and 2 glofitamab administration, at least 1 dose of tocilizumab must be available for immediate use in the event of CRS (see below for further details).

Cycle frequency

21 days

Number of cycles

Up to 12 cycles

Administration

Obinutuzumab is administered as an IV infusion in 250mL sodium chloride 0.9% at a rate of 50mg/hr. The rate can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.

Hypotension may occur during obinutuzumab infusion. Therefore, antihypertensive treatments should be withheld for 12 hours prior to, throughout and 1 hour after each infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

Glofitamab is administered as an IV infusion. The 2.5mg dose is administered in 25mL sodium chloride 0.9%, all other doses may be administered in 50-100mL sodium chloride 0.9%. The first three doses of glofitamab (cycle 1 day 8 and day 15 and cycle 2 day 1) should be administered over 4 hours. If patients experienced cytokine release syndrome (CRS) during a previous dose the infusion time may be extended from 4 hours to 8 hours. From cycle 3 onwards, if the previous infusions were well tolerated and patient did **not** experience CRS the infusion time may be reduced to 2 hours. If a patient has experienced CRS with a previous dose the infusion time should be maintained at 4 hours.

All patients must be monitored for signs and symptoms of potential CRS during the first infusion of glofitamab and for 24 hours after completion of the infusion. Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of subsequent infusions. See details below on management of CRS.

If doses are delayed or missed then the following actions should be followed:

- Following pre-treatment with Obinutuzumab if the 2.5mg glofitamab dose is delayed by more than 1 week then repeat the pre-treatment Obinutuzumab dose
- If there is a 2-6 week treatment free interval following a 2.5mg or 10mg glofitamab dose, then repeat the last tolerated dose and then resume the step up dosing schedule
- If there is a >6 week treatment free interval following a 2.5mg or 10mg glofitamab dose, then repeat pre-treatment with Obinutuzumab and restart step up dosing schedule
- If there is a >6 week gap in treatment from cycle 2 onwards (30mg dose) then repeat pre-treatment with Obinutuzumab and restart step up dosing schedule

Prior to cycle 1 and 2 glofitamab administration, at least 1 dose of tocilizumab must be available for immediate use in the event of CRS, and access to an additional dose within 8 hours of initial dose must be ensured. Use of tocilizumab for treating CRS is off-label and must be agreed via local trust's medicine prescribing policy. Tocilizumab is commissioned for up to 4 doses in total with retrospective blueteq submission required after all required doses have been administered.

Pre-medication

Patients should be well hydrated during treatment aiming for oral hydration of 3L/day, starting 48hours prior to Obinutuzumab administration and first dose of glofitamab. Consider IV hydration if patients cannot maintain adequate oral hydration.
Obinutuzumab premedication:

- Paracetamol 1g PO at least 30 minutes prior to obinutuzumab infusion
- Chlorphenamine 10mg IV bolus at least 30 minutes prior to obinutuzumab infusion
- Dexamethasone* 20mg IV bolus at least 60 minutes prior to obinutuzumab infusion

* Hydrocortisone should **not** be used as an alternative to dexamethasone as it has not been effective in reducing rates of infusion related reaction (IRR).

Glofitamab premedication:

Treatment day	**Premedication**
Cycles 1-3	Dexamethasone 20mg IV bolus at least 60 minutes prior to glofitamab Paracetamol 1g PO at least 30 minutes prior to glofitamab Chlorphenamine 10mg IV bolus at least 30 minutes prior to glofitamab
Cycle 4 onwards if ***no*** CRS with previous doses	Paracetamol 1g PO at least 30 minutes prior to glofitamab Chlorphenamine 10mg IV bolus at least 30 minutes prior to glofitamab
Cycle 4 onwards if CRS with previous doses	Dexamethasone 20mg IV bolus at least 60 minutes prior to glofitamab Paracetamol 1g PO at least 30 minutes prior to glofitamab Chlorphenamine 10mg IV bolus at least 30 minutes prior to glofitamab

Emetogenicity

This regimen has low emetic potential – refer to local policy

Additional supportive medication

Allopurinol 300mg (100mg if CrCl <20ml/min) OD for the first cycle starting 12-24 hours prior to cycle 1 day 1.
PJP, antiviral and antifungal prophylaxis advised, as per local policy.
Strongly consider GCSF if neutrophils <1.0, then as secondary prophylaxis in future cycles eg. for 5 days starting on day 5.
H2 antagonist or PPI unless contra-indicated

Extravasation

Glofitamab is neutral (group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days*
U&Es (including creatinine)	14 days
LFTs	14 days
Phosphate	14 days
Magnesium	14 days
Calcium	14 days
Potassium	14 days
Sodium	14 days
Virology (Hep B/C, HIV)	3 months or as per local policy

* FBC also required within 24 hours of cycle 1 day 8 and day 15.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U&Es (including creatinine)	7 days
LFTs	7 days
Phosphate	7 days
Magnesium	7 days
Calcium	7 days
Potassium	7 days
Sodium	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance (CrCl)	≥ 30ml/min
ALT/AST	< 3 x ULN
Bilirubin	< 1.5 x ULN

Dose modifications

No dose reductions are recommended. Adverse events should be managed with dose interruption, treatment discontinuation and reduction of infusion rate.

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L, discuss with consultant, consider holding glofitamab and administer GCSF.

Platelets should be >75 x 10^9/L to commence glofitamab following Obinutuzumab pre-treatment.

- **Renal impairment**

No dose adjustment is required in mild or moderate renal impairment (CrCl ≥ 30ml/min). Glofitamab has not been studied in severe renal impairment.

- **Hepatic impairment**

No dose adjustment is required in mild hepatic impairment (Bilirubin < 1.5 x ULN or ALT/AST < 3 x ULN). Glofitamab has not been studied in moderate or severe hepatic impairment.

- **Other toxicities**

Cytokine Release Syndrome (CRS)

Symptoms/Grade	Management	Action for subsequent infusion
Grade 1 Fever ≥ 38°C	If CRS occurs during infusion: • Interrupt infusion and treat symptoms • Restart infusion at slower rate when symptoms resolve • If symptoms recur, discontinue current infusion If CRS occurs post-infusion: • Treat symptoms If CRS lasts more than 48h after symptomatic management: • Consider corticosteroids • Consider tocilizumab	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate
Grade 2 Fever ≥ 38°C and: - hypotension not requiring vasopressors - and/or hypoxia requiring low-flow oxygen by nasal canula or blow-by	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids • Consider tocilizumab If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids • Consider tocilizumab	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate Monitor patients post-infusion (median time to onset from start of infusion: 10mg dose: 26.2hrs, 30mg dose: 15hrs)

Symptoms/Grade	Management	Action for subsequent infusion
Grade 3 Fever ≥ 38 °C and: - hypotension requiring a vasopressor (+/- vasopressin) - and/or hypoxia requiring high-flow oxygen by nasal cannula, face mask, non-rebreather mask, or Venturi mask	If CRS occurs during infusion: • Discontinue current infusion and treat symptoms • Administer corticosteroids • Administer tocilizumab If CRS occurs post-infusion: • Treat symptoms • Administer corticosteroids • Administer tocilizumab	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate Monitor patients post-infusion (median time to onset from start of infusion: 10mg dose: 26.2hrs, 30mg dose: 15hrs). If Grade ≥ 3 CRS recurs at subsequent infusion, stop infusion immediately and permanently discontinue Glofitamab
Grade 4 Fever ≥ 38 °C and: - hypotension requiring multiple vasopressors (excluding vasopressin) - and/or hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	If CRS occurs during or post-infusion: • Permanently discontinue Glofitamab and treat symptoms • Administer corticosteroids • Administer tocilizumab	

CRS Management

Corticosteroids
Grade 1–2 CRS: dexamethasone IV 10-20 mg/day
Grade 3–4 CRS: dexamethasone IV 10-20 mg 6-hourly OR methylprednisolone IV 1-2 mg/kg/day. If no response, methylprednisolone IV 1000 mg/day.

Tocilizumab administration
Do not exceed 3 doses of tocilizumab in a period of 6 weeks
If no prior use of tocilizumab or 1 dose of tocilizumab within last 6 weeks:

- Administer first dose of IV tocilizumab 8mg/kg (max 800mg)
- If grade 2 toxicity and no improvement within 8 hours administer second dose of tocilizumab
- If grade 3 or 4 toxicity and no improvement within 8 hours or rapid progression of CRS, administer second dose of tocilizumab
- After 2 doses of tocilizumab, consider alternative anti-cytokine therapy and/or immunosuppressant therapy

If 2 doses of tocilizumab within last 6 weeks:

- Administer only one dose of tocilizumab
- If no improvement within 8 hours or rapid progression of CRS, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy

Tumour flare
Tumour flare due to T-cell infiltration has been reported in patients treated with glofitamab, including symptoms such as localised pain and swelling. Consider use of corticosteroids and analgesics as needed.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Cytokine release syndrome
Sepsis
Febrile neutropenia
Myelosuppression
Pleural effusion
Tumour lysis syndrome
GI haemorrhage

- **Frequently occurring side effects**

Cytokine release syndrome
Myelosuppression
Rash
Infections
Tumour flare
Electrolyte abnormalities
Headache
Somnolence
Tremor
Constipation, diarrhoea
Nausea, vomiting
Pyrexia
Deranged LFTs

Significant drug interactions – for full details consult product literature/ reference texts

CYP450 substrates with narrow therapeutic index e.g. warfarin, ciclosporin: initial cytokine release during Glofitamab treatment could suppress CYP450 enzymes, with higher risk during the first 2 weeks of glofitamab treatment. Monitor for toxicity/loss of effect of substrate.

Additional comments

Patients should be provided with the patient card and advised to carry it with them at all times. The card describes symptoms of CRS which, if experienced, should prompt the patient to seek immediate medical attention.

Female patients of childbearing potential must use highly effective contraception methods during treatment and for 2 months following the last dose.

References

- National Institute for Health and Care Excellence TA927. Accessed 18 March 2024 via www.nice.org.uk
- Summary of Product Characteristics Glofitamab (Roche) accessed 18 March 2024 via www.medicines.org.uk
- Dickinson, M.J. et al. Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med 2022;387:2220-2231

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