Indication	Monotherapy for the treatment of relapsed or refractory diffuse large B-cell lymphoma (DLBCL) or transformed follicular lymphoma (TFL), after two or more lines of systemic therapy and that these 2 lines of therapy have included an anti-CD20 regimen and an anthracycline-containing regimen. Patients must have not received prior treatment with glofitamab unless either glofitamab monotherapy needs to be continued following EAMS access/a Roche compassionate access scheme or the patient received and responded to no more than 3 cycles of glofitamab monotherapy used specifically as bridging treatment prior to **3rd or more** line of CAR T therapy. NB: patients with TFL must have received 2 or more lines of systemic therapy given specifically for the transformed follicular lymphoma.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 21 days. For a maximum of 12 cycles, unless a patient experiences unmanageable toxicity, disease progression or patient choice to stop. A formal medical review should be scheduled to occur by the end of the first 6 weeks of treatment to establish if treatment should continue.
Monitoring Parameters pre-treatment	• **Virology screening:** All new patients referred for systemic anti-cancer treatment should be screened for hepatitis B and C and the result reviewed prior to the start of treatment. Patients not previously tested who are starting a new line of treatment, should also be screened for hepatitis B and C. Further virology screening will be performed following individual risk assessment and clinician discretion. • Patients must be admitted overnight for cycle 1 day 8 administration of glofitamab and potentially for further glofitamab infusions if >/= grade 2 cytokine release syndrome occurs with the previous infusion. • Monitor FBC, U&Es and LFTs Day 1 of each cycle plus Day 8 & Day 15 of cycle 1. • **Haematological toxicity/parameters:** • **Cycle 1:** If haematological toxicity occurs following obinutuzumab, toxicity must have resolved to </=grade 1 prior to glofitamab administration on day 8. Proceed with glofitamab if PLT >/= $75x10^9$ and NEUTS >/= 1.5. • **Cycle 1 day 15 and Cycle 2 onwards:** Glofitamab administration should be delayed to allow for resolution of haematological toxicity to </= Grade 2. See table 1 for further detail for the management of neutropenia. • **Hepatic impairment:** o **Obinutuzumab:** The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made. o **Glofitamab:** No dose adjustment required in mild hepatic impairment (total bilirubin >ULN to </= 1.5 x ULN or AST >ULN). No data available in moderate or severe impairment, clinician's decision. • **Renal impairment:** o **Obinutuzumab:** Obinutuzumab: no dose adjustment is required if CrCl >/= 30ml/min; there is no data for CrCl < 30ml/min. o **Glofitamab:** No dose adjustment in mild or moderate impairment (CrCl 30 to <90ml/min). No data available in severe impairment, clinician's decision. • **Infusion-related reactions:** **Obinutuzumab:**

- In the event of an infusion related reaction (IRR), the administration rate should be modified as follows:
  - **Grade 1-2 IRR (mild-moderate):** Reduce infusion rate and treat symptoms. Upon resolution of symptoms, continue infusion and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.
  - **Grade 3 IRR (severe):** Temporarily interrupt infusion and treat symptoms. Upon resolution of symptoms, restart infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred) and, if participant does not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose. If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently.
  - Grade 4 IRR (life threatening): Stop infusion and discontinue therapy.
  - Complete obinutuzumab monitoring/administration form

Glofitamab: Infusion-related reactions may be clinically indistinguishable from manifestations of CRS see CRS guidance see table 2.

- **Management of adverse reactions:**
  - **Tumour lysis syndrome (TLS)** has been reported in patients receiving **glofitamab** and **obinutuzumab.**
    Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 10^9/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis prior to obinutuzumab and glofitamab. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), starting 12-24hours prior to start of infusion.
  - **Obinutuzumab:**
    Antihypertensives: Withholding of antihypertensive treatments should be considered for 12 hours prior to infusion and for the first hour after administration.
  - Patients with a history of **cardiac disease** should be monitored closely.
  - **Glofitamab:**
    Cytokine release syndrome.
    - At least 1 dose of tocilizumab, at a dose of 8mg/kg IV (dose not to exceed 800 mg), for use in the event of Cytokine release syndrome (CRS) must be available prior to glofitamab infusion, at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.
    - All patients must be counselled on the risk, signs and symptoms of CRS and advised to contact their healthcare team immediately if they experience signs and symptoms of CRS.
    - All patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 24 hours after completion of the infusion of the first glofitamab dose (2.5mg on cycle 1 day 8). The prescriber should use the information on CRS times to onset and, grade after each dose, provided in table 2, when determining the appropriate monitoring strategy, according to local guidelines and refer to SPC.
    - Patients who experienced grade >/= grade 2 CRS with their previous infusion should be monitored after the completion of the infusion (see table 2).

    Tumour flare has been reported in patients, monitoring and evaluation for tumour flare is recommended.
- **Dose Modification:**
  Obinutuzumab: No dose reductions are recommended.
  Glofitamab: No dose reductions are recommended, treatment should be interrupted or discontinued or infusion rate reduced to treat adverse events. Glofitamab administration should be delayed to allow resolution of non-haematological toxicities to Grade </=1.

	• **Missed dose:** **Glofitamab:** ○ **During escalation** (weekly dosing): Following pre-treatment with obinutuzumab, if the glofitamab 2.5 mg dose is delayed by more than 1 week, then repeat pre-treatment with obinutuzumab. Following glofitamab 2.5 mg dose or 10 mg dose, if there is a glofitamab treatment-free interval of 2 to 6 weeks, then repeat the last tolerated glofitamab dose and resume the planned step-up dosing. Following glofitamab 2.5 mg dose or 10 mg dose, if there is a glofitamab treatment-free interval of more than 6 weeks, then repeat pre-treatment with obinutuzumab and glofitamab step-up dosing. ○ **After Cycle 2** (30 mg dose): If there is a glofitamab treatment-free interval of more than 6 weeks between cycles, then repeat pre-treatment with obinutuzumab and glofitamab dose escalation and then resume the planned treatment cycle (30 mg dose). • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** ○ No formal drug interaction studies have been performed for **obinutuzumab** or **glofitamab.** Due to the cytokine release at the start of treatment concomitant use with CYP450 substrates may lead to fluctuations in concentration, patient receiving substrates with a narrow therapeutic range (e.g. warfarin, cyclosporin) should be monitored closely. ○ Patients should not receive live vaccines during treatment, and until B cell counts have normalised. • **Driving and machinery:** patients should be aware that glofitamab may affect their ability to drive or operate machinery due to the possibility of neurological effects/CRS. • Patients should carry the glofitamab patient card at all times.
References	BlueTeq form accessed online 07.11.2023 CDF list V1.279 accessed online 07.11.2023SPC accessed online 07.11.2023

NB For funding information, refer to CDF and NICE Drugs Funding List

Table 1: Management of glofitamab induced neutropenia

Event	Initial management recommendation	Action
Grade 1 (mild)	Monitor blood counts weekly. Consider growth factor support	Continue glofitamab treatment
Grade 2 (moderate)	Monitor blood counts weekly. Administer growth factor support.	Consider holding glofitamab treatment in the presence of comorbidities or complications.
Grade 3-4 (severe-life threatening)	Monitor blood counts at least twice weekly until an increase of neutrophils is noticed. Administer growth factor support.	Hold glofitamab until resolution to </=grade 2

Table 2 American Society for Transplantation and Cellular Therapy (ASTCT) grading and CRS management guidance for glofitamib

Grade[1]	CRS management	For next scheduled glofitamab infusion
GRADE 1 Fever >/=38°C	If CRS occurs during infusion: Interrupt and treat symptoms Restart infusion at slower rate once symptoms resolve If symptoms recur, discontinue current infusion If CRS occurs post infusion: Treat symptoms If CRS last >48hrs after symptom management: Consider corticosteroids[3] Consider tocilizumab[4]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate[2]
GRADE 2 Fever >/= 38 °C and/or hypotension not requiring vasopressors and/or hypoxia requiring low-flow oxygen by nasal cannula	If CRS occurs during infusion: Discontinue current infusion and treat symptoms Administer corticosteroids[3] Consider tocilizumab[4] If CRS occurs post infusion: Treat symptoms Administer corticosteroids[3] Consider tocilizumab[4]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate[2] Monitor patients post infusion[5,6]
For Grade2: Tocilizumab use: Do not exceed 3 doses in a 6-week period If no prior use of tocilizumab or if 1 dose was used within the last 6 weeks: administer first dose If no improvement within 8 hours administer second dose. After 2 doses consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy. If 2 doses were used within the last 6 weeks: Administer 1 dose only If no improvement within 8 hours consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy.		
Grade 3 Fever >/= 38°C and/or 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	If CRS occurs during infusion: Discontinue current infusion and treat symptoms Administer corticosteroids[3] Administer tocilizumab[4] If CRS occurs post infusion: Treat symptoms Administer corticosteroids[3] Administer tocilizumab[4]	Ensure symptoms are resolved for at least 72 hours prior to next infusion Consider slower infusion rate[2] Monitor patients post infusion[5,6] If >/=grade 3CRS recurs at subsequent infusion, stop infusion and permanently discontinue glofitamab.
Grade 4 Fever >/=38°C and/or 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 infusion or post infusion: Permanently discontinue glofitamab and treat symptoms Administer corticosteroids[3] Administer tocilizumab[4]	
For Grade 3 and 4: tocilizumab use: Do not exceed 3 doses in a 6-week period. If no prior use of tocilizumab or if 1 dose was used within the last 6 weeks: Administer first dose If no improvement within 8 hours or rapid progression of CRS, administer second dose. After 2 doses consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy. If 2 doses were used within the last 6 weeks: Administer 1 dose only If no improvement within 8 hours or rapid progression of CRS, consider alternative anti-cytokine therapy and/or alternative immunosuppressant therapy.		

[1]American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading criteria (Lee DW et al ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant. 2019;25:625-38).
[2] Duration of infusion may be extended up to 8 hours, as appropriate for that cycle.
[3]Corticosteroids (e.g., 10 mg intravenous dexamethasone, 100 mg intravenous prednisolone, 1-2 mg/kg intravenous methylprednisolone per day, or equivalent).
[4] Tocilizumab 8 mg/kg intravenously (not to exceed 800 mg).
[5] In Study NP30179, Grade ≥ 2 CRS following glofitamab 10 mg dose at Cycle 1 Day 15 occurred in 5.2% of patients, with a median time to onset of 26.2 hours from the start of infusion (range: 6.7 to 144.2 hours).
[6]In Study NP30179, Grade ≥ 2 CRS following glofitamab 30 mg dose at Cycle 2 Day 1 occurred in one patient (0.8%), with a time to onset of 15.0 hours from the start of infusion.

Cycle 1: 21 days (pre-treatment and dose escalation schedule)

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Methylprednisolone	80mg	IV	Over 15 min	In 100ml Sodium Chloride 0.9%. Infusion **must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine	4mg	PO	stat	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 10^9/L to reduce the risk of TLS.				
	OBINUTUZUMAB	1000mg	IV inf	See below	In 250ml Sodium Chloride 0.9%. Flush line pre and post infusion with Sodium Chloride 0.9%
	Obinutuzumab infusion rate notes: Administer at 50 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 50 mg per hour every 30 minutes to a maximum rate of 400 mg per hour.				
8	Dexamethasone	20mg	IV	Bolus	**Given at least 1 hour prior to the glofitamab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the glofitamab infusion.
	Chlorphenamine	4mg	PO	stat	
	Ensure adequate hydration is given 12-24 hours prior to starting glofitamab infusion				
	GLOFITAMAB	**2.5mg**	IV	4 hours**	In 25ml Sodium Chloride 0.9% Final concentration must be between 0.1mg/ml and 0.6mg/ml
15	Dexamethasone	20mg	IV	Bolus	**Given at least 1 hour prior to the glofitamab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the glofitamab infusion.
	Chlorphenamine	4mg	PO	stat	
	Ensure adequate hydration is given 12-24 hours prior to starting glofitamab infusion				
	GLOFITAMAB	**10mg**	IV	4 hours**	In 50ml Sodium Chloride 0.9% Final concentration must be between 0.1mg/ml and 0.6mg/ml

** For patients who experience CRS with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours

Cycle 2: 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Dexamethasone	20mg	IV	Bolus	**Given at least 1 hour prior to the glofitamab infusion.**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the glofitamab infusion.
	Chlorphenamine	4mg	PO	stat	
	Ensure adequate hydration is given 12-24 hours prior to starting glofitamab infusion				
	GLOFITAMAB	**30mg**	IV	4 hours**	In 100ml Sodium Chloride 0.9% Final concentration must be between 0.1mg/ml and 0.6mg/ml

** For patients who experience CRS with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours

Cycles 3 to 12: 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration Details
1	Dexamethasone	20mg	IV	Bolus	**CYCLE 3: Given at least 1 hour prior to the glofitamab infusion.** **CYCLE 4 onwards:** only required by patients who experienced CRS with previous dose. **Given at least 1 hour prior to glofitamab infusion**
	Paracetamol	1g	PO	stat	Given at least 30 minutes before the glofitamab infusion.
	Chlorphenamine	4mg	PO	stat	
	Ensure adequate hydration is given 12-24 hours prior to starting glofitamab infusion				
	GLOFITAMAB	**30mg**	IV	2 hours***	In 100ml Sodium Chloride 0.9% Final concentration must be between 0.1mg/ml and 0.6mg/ml

***if the previous infusion was well tolerated. If the patient experienced CRS with a previous dose, the duration of infusion should be maintained at 4 hours.

TTO Cycle 1 to 12

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	Take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last glofitamab treatment dose)
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last glofitamab treatment dose)
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient >80kg	Sub cut	OD – only if required Prescriber to specify start day and duration.
	Consider antifungal prophylaxis			

Obinutuzumab Monitoring Record : Day…. Cycle….

Time after start of administration	**Actual time**	**Rate of infusion (ml/hr)** [Calculations based on 250ml reconstitution volume]	**B.P. (mmHg)**	**Pulse rate (beats/min)**	**Respiration rate (beats/min)**	**Temp (°C)**
0 – 15 mins						
16 – 30 mins						
31 – 45 mins						
46 – 60 mins						