Indication	Polatuzumab vedotin in combination with bendamustine and rituximab for previously treated adult patients with relapsed or refractory diffuse large B-cell lymphoma and who are not candidates for haematopoietic stem cell transplantation. NB No prior treatment with polatuzumab vedotin, or if continuing previous treatment with polatuzumab vedotin, this was either within the polatuzumab EAMS scheme and all other criteria in this form are fulfilled or within the Interim SACT treatment options allowed for polatuzumab as bridging treatment to CAR-T therapy during the Covid-19 pandemic. No prior treatment with bendamustine for DLBCL or if the patient has been treated previously with bendamustine for DLBCL, this application is to continue a previous registration for the polatuzumab EAMS scheme or the interim polatuzumab Covid-19 access or if treated with bendamustine outside either of these two schemes, then the response duration to that course of treatment with bendamustine for DLBCL exceeded 1 year. Please note that the use of bendamustine in this indication is unlicensed, and individual trust policy should be followed with regards to prescribing unlicensed treatment.
Treatment Intent	Disease modification
Frequency and number of cycles	Repeat every 21 days for a maximum of 6 cycles. A formal medical review must be scheduled to occur at least by the end of the first 6 weeks of treatment to determine whether treatment should continue or not.
Monitoring Parameters pre-treatment	• **Hepatitis B/C status checked and negative prior to cycle 1** • Ensure irradiated blood products are used. • If total lymphocyte count is >25 x 10^9/L d/w consultant. • FBC, LFT, U&Es monitoring required before each cycle, or more frequently if clinically indicated. • Proceed with treatment if neuts >/=1 or platelets >/=50. See below for dose modifications. • Patients with previous cardiac disease require an ECG before each cycle. • Monitoring of potassium is required. • Baseline neurological clinical examination. • **Renal Impairment:** o No dose reduction for bendamustine is required if CrCl >10ml/min. o No dose reduction for polatuzumab is required if CrCl >/=30ml/min. There is limited data available for patients with CrCl<30ml/min, clinical decision. • **Hepatic Impairment:** o No dose adjustment for bendamustine in mild hepatic impairment (Bilirubin < 21µmol/L). A 30% dose reduction is recommended for moderate hepatic impairment (Bilirubin 21-51µmol/L). Contraindicated in severe hepatic impairment (Bilirubin> 51µmol/L). o No dose adjustment for polatuzumab in mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5xULN or AST greater than ULN). Polatuzumab should be avoided in patients with moderate or severe hepatic impairment (bilirubin greater than 1.5 × ULN). • **Dose reductions:** o Bendamustine: If grade 3 or 4 non-haematological toxicity occur, with the exception of hypersensitivity reactions – delay treatment and reduce dose by 25% once resolved.

- Polatuzumab: If grade 2-3 peripheral neuropathy (PN) occurs hold until recovery to </= grade 1. If recovery is on or before day 14 restart at a permanently reduced dose of 1.4mg/kg, otherwise discontinue. If a prior dose reduction of 1.4mg/kg has previously been applied no further reduction is advised, discontinue polatuzumab. For any grade 4 PN reaction discontinue polatuzumab.
- Myelosuppression: NB rate of Grade 3 to 4 febrile neutropenia is 10%.
  Myelosuppression caused by treatment:
  If neuts <1, hold all treatment until ANC recovers to >1. If recovery of ANC to >1 occurs on or before day 7 resume all treatment without any dose reductions. If recovery of ANC to >1 occurs after day 7:
  - Restart all treatment with a dose reduction of bendamustine from 90mg/m² to 70mg/m² or 70mg/m² to 50mg/m²
  - If a bendamustine dose reduction to 50mg/m² has already occurred discontinue all treatment.

  If platelets < 50, hold all treatment until platelets recover to >75. If recovery to >75 occurs on or before day 7 resume all treatment without any dose reductions. If recovery of platelets to >75 occurs after day 7:
  - Restart all treatment with a dose reduction of bendamustine from 90mg/m² to 70mg/m² or 70mg/m² to 50mg/m²
  - If a bendamustine dose reduction to 50mg/m² has already occurred discontinue all treatment.

- In the event of an allergic reaction requiring discontinuation of one of the drugs, it is the clinician's decision whether to continue with the rest of the regimen.
- **Tumour lysis syndrome:** 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. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), starting 12-24hours prior to start of infusion.
- **Progressive multifocal leukoencephalopathy (PML):** PML has been reported in patients receiving polatuzumab. Patients should be monitored for new or worsening neurological, cognitive or behavioural changes. All treatment should be held if PML is suspected and permanently discontinued if PML is confirmed.
- **Infusion rates and Infusion-related reactions (IRRs):**
- Ensure pre-medication of rituximab and polatuzumab with chlorphenamine, hydrocortisone & paracetamol. Monitor rituximab (complete monitoring form), and polatuzumab infusions closely, watch for signs of dyspnoea, fever and rigors. If such symptoms occur stop infusion(s) and seek medical advice. Infusion may be recommenced at half the previous rate, once symptoms have subsided (see below for when to discontinue). Anaphylaxis drugs must be available.

- **Rituximab:**
  Consider withdrawing any anti-hypertensives 12 hours before treatment with rituximab.
  First infusion – Initiate at 50 mg/hr. Increase at 50mg/hr increments every 30mins to 400mg/hr max.
  Subsequent infusions – Initiate infusion at 100mg/hr. Increase rate at 100mg/hr increments every 30mins to 400mg/hr max.
  From cycle 2 onwards rapid infusion may be used if requested by prescriber (patient must not have had a grade 3 or 4 reaction to previous rituximab treatment). In this case infuse first 100ml over 20 minute, and if no reaction, infuse remaining 400ml over 60 minutes. Use rapid rituximab infusion chart.

	○ **Polatuzumab:** First infusion should be administered over 90 minutes and the patient monitored for 90 minutes after completion. Subsequent infusions, if no reaction occurred to prior infusion, can be administered over 30 minutes and the patient monitored for 30 minutes after completion. In the event of any grade IRR polatuzumab should be interrupted immediately and supportive treatment given. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue polatuzumab. Otherwise, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. For the next cycle, infuse polatuzumab over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles. For any Grade 4 reaction stop the infusion immediately, give supportive treatment and permanently discontinue polatuzumab. • IV antihistamine and steroid cover should be considered with subsequent doses of bendamustine for patients who experience even a mild hypersensitivity reaction to first infusion (when not already prescribed). • **<u>Drug Interactions</u>** ○ Caution with concomitant use of allopurinol with bendamustine – risk of Stevens Johnson Syndrome and toxic epidermal necrolysis. ○ Strong CYP3A4 and P-gp inhibitors (e.g. ketoconazole) should be used with caution with polatuzumab and patients monitored for toxicity. ○ Strong CYP3A inducers may decrease efficacy of polatuzumab. • Live or live-attenuated vaccines should not be given concurrently with polatuzumab. • Patients should be advised to avoid driving or operating machinery whilst on this treatment. • **<u>Delayed or Missed doses</u>** • Treatment breaks of up to 6 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow toxicities to settle. • If a planned dose is missed, the next dose should be administered as soon as possible. The administration schedule must be adjusted to maintain a 3 week interval between doses.
References	KMCC protocol HAEM-NHL-088 V3 SPC accessed online 08.06.2023

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

Cycle 1-6
Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Ondansetron	<75yrs 16mg ≥75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	Paracetamol	1gm	PO		Stat
	Chlorphenamine	10mg	IV	1 min	By slow injection
	Hydrocortisone	200mg	IV		Stat
	Commence Rituximab/Polatuzumab at least 30 mins – 1 hour after pre-medication.				
	RITUXIMAB	**375mg/m²**	IV	See notes above	Sodium chloride 0.9% 500ml
	POLATUZUMAB VEDOTIN	**1.8mg/kg Maximum dose 240mg**	IV	See notes above	Glucose 5% 100ml or Sodium chloride 0.9% 100ml (final concentration of 0.72-2.7mg/ml) Via in-line 0.22micron filter. Flush line with sodium chloride 0.9%.
	BENDAMUSTINE	**90mg/ m²**	IV	30-60 minutes	Sodium Chloride 0.9% 500ml
2	Ondansetron	<75yrs 16mg ≥75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	BENDAMUSTINE	**90mg/ m²**	IV	30-60 minutes	Sodium Chloride 0.9% 500ml

TTOs

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg TDS starting on day 2 for 4 days, then 10mg TDS PRN. Do not take for more than 5 days continuously.
	Dexamethasone	6mg	PO	OM from day 2 for 3 days. (day 2 dose to be taken prior to bendamustine infusion)
	Allopurinol	300mg	PO	OD **Cycle 1 only**
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday. (Continue for at least 3 months after treatment).
	Aciclovir	400mg	PO	BD (Continue for at least 3 months after treatment).
	Chlorhexidine mouthwash	10ml	Use as mouth wash	BD for 2 weeks
	Filgrastim to be considered if clinical need arises.			