Indication	For previously untreated CD20 positive diffuse large B-cell lymphoma or CD20 positive follicular lymphoma grade 3B, **with an IPI score of 2 to 5.** NB the use of polatuzumab vedotin in combination with rituximab, cyclophosphamide, doxorubicin and prednisolone is unlicensed for CD20 positive follicular lymphoma grade 3B 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 second cycle of treatment to determine whether treatment should continue or not.
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. • If total lymphocyte count is >25 x 10^9/L d/w consultant. • ECG baseline. Baseline MUGA/ECHO where clinically indicated. • FBC, U&E and LFTs at baseline and before each cycle. Monitor between cycles as clinically indicated. • Maximum cumulative dose of Doxorubicin = 450-550mg/m². Check previous exposure to anthracyclines. • **Haematological Toxicity:** • Neutrophils < 1.0 x 10^9/L and / or platelets < 75 x 10^9/L, delay chemotherapy by up to 1 week. See table 1. • **Renal Impairment:** o **Doxorubicin:** no dose adjustment required. o **Cyclophosphamide:** CrCl 10-29ml/min consider 75% dose; CrCl <10ml/min give 50% dose. o **Polatuzumab:** No dose reduction for polatuzumab is required if CrCl >/=30ml/min. There is limited data available for patients with CrCl <30ml/min, clinical decision. o **Rituximab:** no recommended dose adjustment. • **Hepatic Impairment:** o **Doxorubicin:** bilirubin 20-51umol/L give 50% dose; bilirubin 52-85umol/L give 25% dose; bilirubin > 85umol/L omit. Doxorubicin is contraindicated in patients with severe liver impairment (Child-Pugh C). o **Cyclophosphamide:** No dose adjustment for mild or moderate impairment. Severe d/w consultant. o **Polatuzumab:** 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). o **Rituximab:** no recommended dose adjustment. • **<u>Infusion rates and Infusion-related reactions (IRRs):</u>** • Ensure pre-medication of rituximab and polatuzumab with chlorphenamine, prednisolone & 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:**
  Use rituximab infusion monitoring record.
  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 clinician (patient must not have had a grade 3 or 4 reaction to previous rituximab treatment). In this case infuse first 100ml over 20 minutes, and if no reaction, infuse remaining 400ml over 60 minutes. Use rapid rituximab infusion chart.
  Consider reduction of cell load by other means prior to rituximab infusion if high tumour load and consider decreasing infusion speed.
  Patients with a high tumour burden or with a high number of lymphocytes (>25 x 10^9/l) who may be at higher risk of especially severe cytokine release syndrome, should only be treated with extreme caution. These patients should be very closely monitored throughout the first infusion. Consideration should be given to the use of a reduced infusion rate for the first infusion in these patients or a split dosing over two days during the first cycle.
- **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.

- **Dose reductions:**
- For guidance in the event of myelosuppression see table 1.
  - **Polatuzumab:**
    If Grade 2 sensory neuropathy (SN) occurs reduce dose to 1.4mg/kg, if Grade 2 SN persists or recurs at day 1 of a future cycle dose reduce to 1.0mg/kg, if already dose reduced to 1.0mg/kg discontinue. If grade 3 SN occurs withhold until recovery to </= Grade 2, restart at a reduced dose of 1.4mg/kg, if already receiving 1.4mg/kg reduce to 1.0mg/kg if already dose reduced to 1.0mg/kg discontinue. Grade 4 SN discontinue polatuzumab.
    If Grade 2 motor neuropathy (MN) occurs withhold until recovery to </= Grade 1, restart at next cycle at a dose of 1.4mg/kg. If already dose reduced to 1.4mg/kg and Grade 2 MN occurs at day 1 of future cycle withhold until improves to </= Grade 1 and restart at 1.0mg/kg. if already dose reduced to 1.0mg/kg and Grade 2 MN occurs at day 1 of future cycles discontinue. Grade 3 MN occurs withhold until recovery to </= Grade 1, restart at

	the next cycle at 1.4mg/kg, if already dose reduced to 1.4mg/kg and Grade 2-3 MN occurs withhold until recovery to </=Grade 1, restart at 1.0mg/kg. if already dose reduced to 1.0mg/kg and Grade 2-3 MN occurs discontinue polatuzumab. Grade 4 MN discontinue polatuzumab. If concurrent SN and MN occurs follow the most severe restrictions recommended. • 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. • **Drug Interactions:** o Doxorubicin: ciclosporin o Polatuzumab: 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. • **Driving:** Patients may experience undesirable effects which could affect the ability to drive or use machines. • **Delayed or Missed doses:** 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-092 V1 SPC accessed online 08.06.2023

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

Table 1 Dose modifications to manage myelosuppression in previously untreated DLBCL

Severity of myelosuppression on Day 1 of any cycle	**Dose Modification**
Grade 3–4 Neutropenia	Withhold all treatment until ANC* recovers to >1000/µL. If ANC recovers to >1000/µL on or before Day7, resume all treatment without any dose reductions. If ANC recovers to >1000/µL after Day7: · resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25-50%. · if cyclophosphamide and/or doxorubicin are already reduced by 25%, consider reducing one or both agents to 50%.
Grade 3–4 Thrombocytopenia	Withhold all treatment until platelets recover to >75,000/µL. If platelets recover to >75,000/µL on or before Day7, resume all treatment without any dose reductions. If platelets recover to >75,000/µL after Day7: · resume all treatment; consider a dose reduction of cyclophosphamide and/or doxorubicin by 25-50%. · if cyclophosphamide and/or doxorubicin are already reduced by 25%, consider reducing one or both agents to 50%.

Cycle1-6 Repeat every 21 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15min	In 50ml Sodium chloride 0.9%
	Paracetamol	1000mg	PO		Stat
	Chlorphenamine	10mg	IV	1 min	By slow IV infusion
	PREDNISOLONE	**100mg**	**PO**	STAT	
	Commence Rituximab/Polatuzumab at least 30 mins – 1 hour after pre-medication.				
	RITUXIMAB	**375mg/m²**	IV	**See notes**	Sodium Chloride 0.9% 500ml
	POLATUZUMAB VEDOTIN	**1.8mg/kg**	IV	**See notes**	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%.
	DOXORUBICIN	**50mg/m²**	IV	bolus	Through the side of a fast running NaCl 0.9% infusion.
	CYCLOPHOSPHAMIDE	**750mg/m²**	IV	bolus	Doses </=1500mg give through the side of a fast running Sodium Chloride 0.9% infusion For doses >1500mg give in 250-500ml NaCl over 30-60mins.

TTO	Drug	Dose	Route	Directions
1	**NON E.C. PREDNISOLONE**	**100MG**	PO	OM days 2-5 Take with or after food.
	Omeprazole	20mg	PO	OD
	Metoclopramide	10mg	PO	TDS PRN 3 days. Do not take for more than 5 days continuously.
	Allopurinol	300mg	PO	OD for first cycle only
	Chlorhexidine mouthwash	10ml	TOP	QDS for 2 weeks - rinse mouth for at least one minute
	Aciclovir	400mg	PO	BD continue for duration of chemotherapy and for 6 weeks after.
	Co-trimoxazole	480mg	PO	BD Monday, Wednesday and Friday. Continue for duration of chemotherapy and for 6 weeks after.
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	Sub cut	OD for 5 days starting on day 6.