Indication	Relapsed or refractory Mantle Cell Lymphoma First line treatment of Mantle Cell Lymphoma in less fit patients unsuitable for more intensive treatment.
Treatment Intent	Disease Modification. Curative if used as a bridge to allograft or CAR-T cell therapy. NB Funding approval required.
Frequency and number of cycles	Repeat every 28 days Maximum of 6 cycles
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. • Ensure irradiated blood products are used. • FBC, LFT, U&Es monitoring required before each cycle, or more frequently if clinically indicated. • Patients with previous cardiac disease require an ECG before each cycle. • Monitoring of potassium is required. • Proceed with treatment if neuts >/=1x10^9/L or platelets >/=100x10^9/L. • **Hepatic impairment:** o **Rituximab:** no recommended dose adjustment. o **Bendamustine:** no dose adjustment 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 **Cytarabine**:** If bilirubin >34µmol/l reduce dose by 50%, consider dose escalation in the absence of toxicity. • **Renal impairment:** o **Rituximab:** no recommended dose adjustment. o **Bendamustine:** no dose reduction is required if CrCl >10ml/min. o **Cytarabine**:** o CrCl 46-60ml/min give 60% dose; o CrCl 30-45ml/min give 50% dose; o CrCl < 30ml/min omit Cytarabine. **Note these recommendations are based on when cytarabine is being used in high doses >1g/m^2 • **Dose modifications:** 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. o **Rituximab:** no recommended dose reduction. • **<u>Infusion rates and Infusion-related reactions (IRRs):</u>** • Ensure pre-medication of rituximab with chlorphenamine, hydrocortisone & paracetamol. Monitor rituximab (complete monitoring form) infusions closely, watch for signs of dyspnoea, fever and rigors. If such symptoms occur stop infusion 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:** o Use rituximab infusion monitoring record. o 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. ○ 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. • **Bendamustine:** ○ 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). ○ **Skin reactions:** Bendamustine can induce severe skin reactions such as Stevens-Johnson syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms and Toxic Epidermal Necrolysis. Patients should be informed of the possibility of such reactions and informed to seek urgent medical advice should any symptoms of a severe skin reaction occur. Treatment should be permanently discontinued in affected patients. • **Cytarabine syndrome:** A cytarabine syndrome has been described. It is characterised by fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 - 12 hours following drug administration. Corticosteroids have been shown to be beneficial in treating or preventing this syndrome. If the symptoms of the syndrome are serious enough to warrant treatment, corticosteroids should be contemplated as well as continuation of therapy with cytarabine. • **<u>Common drug interactions (for comprehensive list refer to BNF/SPC)</u>:** ○ Bendamustine metabolism involves the cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine exists. ○ Caution with concomitant use of Allopurinol with bendamustine – risk of Stevens Johnson Syndrome and toxic epidermal necrolysis. ○ Patients should not receive live vaccines during treatment, and until B cell counts have normalised. • **Driving:** Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine, patients should be instructed that if they experience these symptoms they should avoid driving and using machines.
References	SPC accessed online 08.12.2023 Clatterbridge protocol REF: MPHARBACHA

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

Repeat every 28 days:

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Paracetamol	1gm	PO		stat
	Chlorphenamine	10mg	IV	1 min	By slow IV infusion
	Hydrocortisone	100mg	IV	stat	
	Commence Rituximab at least 30 mins after pre-medication.				
	RITUXIMAB	**375mg/m^2**	IV	**See notes**	Sodium Chloride 0.9% 500ml
2	Ondansetron	8mg	PO		Starting on day 2 take first dose 30mins before bendamustine. (supplied as the TTO)
	BENDAMUSTINE	**70mg/m^2**	IV	30-60 minutes	Sodium Chloride 0.9% 500ml
	Cytarabine must start 2 hours after completion of bendamustine.				
	CYTARABINE*	**500mg/m^2**	IV	2 hours	Sodium chloride 0.9% 250ml
3	Ondansetron	8mg	PO		Take 30mins before bendamustine. (supplied as the TTO)
	BENDAMUSTINE	**70mg/m^2**	IV	30-60 minutes	Sodium Chloride 0.9% 500ml
	Cytarabine must start 2 hours after completion of bendamustine.				
	CYTARABINE*	**500mg/m^2**	IV	2 hours	Sodium chloride 0.9% 250ml
4	Ondansetron	8mg	PO		Take 30mins before cytarabine treatment (supplied as the TTO).
	CYTARABINE*	**500mg/m^2**	IV	2 hours	Sodium chloride 0.9% 250ml
	***CYTARABINE dose can be increased to 800mg/m^2 from cycle 2 for patients <70yrs if tolerated 500mg/m^2 in cycle 1**				

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	10mg TDS PRN. Do not take for more than 5 days continuously.
	Ondansetron	8mg	PO	BD days 2 to 6. (take first dose 30 minutes before bendamustine)
	Allopurinol	300mg	PO	OD **Cycle 1 only** **Caution** with concomitant use of allopurinol and bendamustine – risk of SJS and TEN. Consider omitting allopurinol on bendamustine treatment days in patients at low risk of tumour lysis syndrome.
	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		BD for 2 weeks Dispense only if required.
	Prednisolone Eye drops 0.5%	1 drop	Both eyes	Four times a day starting before chemotherapy and for 5 days after cytarabine has stopped (day 9).
	Filgrastim	300 micrograms or consider dose of 480 micrograms if patient > 80kg	Sub cut	OD for 7 days starting on day 7.