Indication	Treatment of patients with follicular lymphoma (FL) who have either not responded or who have progressed during or up to 6 months after treatment with rituximab or rituximab –containing regimen. The treatment of untreated advanced CD20-positive follicular lymphoma.
Treatment Intent	Disease Modification.
Frequency and number of cycles	**Induction every 28 days for 6 cycles** **Cycle 1** Obinutuzumab Day 1, 8 & 15. Bendamustine- Days 1 & 2 only **Cycles 2 to 6** Obinutuzumab Day 1 only. Bendamustine- Days 1 & 2. **Maintenance** Previously treated patients - For patients who respond to initial 6 treatment cycles or who have stable disease should have single agent Obinutuzumab once every 2 months for two years or until disease progression (whichever occurs first). Untreated patients - On completion of induction chemotherapy in combination with obinutuzumab, only patients having at least a documented partial response to treatment will commence maintenance therapy with single agent obinutuzumab once every 2 months for a maximum of 2 years or until disease progression (whichever occurs first) A formal medical review as to whether treatment with obinutuzumab in combination with chemotherapy should continue or not will be scheduled to occur at least by the end of the third cycle of treatment.
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. • **<u>Obinutuzumab</u>** • Monitor FBC, U&Es and LFTs Day 1 of each cycle plus Day 8 & Day 15 of cycle 1 • Monitor LDH at baseline then Day 1 of every other cycle. • **Haematological toxicity:** If neutrophils < 1.0 x 10^9/L and / or platelets < 75 x 10^9/L (at all cycles), delay until counts have recovered, then continue with full dose treatment. • Patients who experience neutropenia should be closely monitored; it is recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Late onset neutropenia (occurring > 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur. • Patients with renal impairment (CrCl < 50 mL/min) are more at risk of neutropenia. Patients should be closely monitored for thrombocytopenia, especially during the first cycle. • **Risk of 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 12-24 hours prior to start of infusion.

- **Antihypertensives:** Withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration.
- **Renal impairment:** No dose adjustment is required if CrCl > 30ml/min. There is no data for CrCl < 30ml/min.
- Patients with a history of cardiac disease should be monitored closely.
- Patients should not receive live vaccines during treatment, and until B cell counts have normalised.
- **Progressive multifocal leukoencephalopathy** (PML) has been reported in patients treated with obinutuzumab.
- **Missed dose:** If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose. During induction, the planned treatment interval for obinutuzumab should be maintained between doses. During maintenance, maintain the original dosing schedule for subsequent doses.
- **Management of Infusion related reactions (IRRs):**
  - **Standard rate infusion -** 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.
  - **Short duration infusion (from cycle 2 onwards) -** In the event of an infusion related reaction (IRR), the administration rate should be modified as follows:
    - **Grade 1-2 (mild to 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 (severe):** Infusion must be temporarily stopped and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred) and not greater than **400 mg/hr.**
    - If a grade 3 IRR occurs at re-challenge, stop infusion immediately and discontinue therapy permanently. If the patient is able to complete the infusion without further Grade 3 IRRs, the next infusion should be given at a rate not higher than the standard rate.
    - **Grade 4 IRR (life threatening): Stop infusion and discontinue therapy.**
- **<u>Bendamustine</u>**
- Ensure irradiated blood products are used.
- FBC, creatinine and electrolyte monitoring required before each cycle. Proceed with next cycle once ANC >/=1.0x 10^9/l and platelets >/=75 x 10^9/l

	• No dose reduction is required if CrCl >10ml/min. • 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). • Patients with previous cardiac disease require an ECG before each cycle. • Monitoring of potassium is required. • Caution with concomitant use of Allopurinol – risk of Stevens Johnson Syndrome and toxic epidermal necrolysis • If grade 4 haematological toxicity, or grade 3 or 4 non-haematological toxicity occur – delay treatment and reduce dose by 25% once resolved.
References	SPC bendamustine and obinutuzumab accessed online 22.7.22 KMCC protocol HAEM-NHL-079 V3

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

CYCLE 1: 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Methylprednisolone	80mg	IV	Over 15mins	In 100ml Sodium Chloride 0.9%. Infusion **must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1gm	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine	10mg	IV	Slow bolus over 1min	
	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.				
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 mins	Sodium chloride 0.9% 50ml
	BENDAMUSTINE	**90mg/m^2**	IV	30-60 mins	Sodium chloride 0.9% 500ml
2	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 mins	Sodium chloride 0.9% 50ml
	BENDAMUSTINE	**90mg/m^2**	IV	30-60 mins	Sodium chloride 0.9% 500ml
8	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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	1gm	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1min	
	Ensure adequate hydration is given 12-24 hours prior to starting obinutuzumab infusion to patients with lymphocyte counts > 25 x 109/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: If no infusion related reaction or an IRR of grade 1 occurred during the prior infusion when the final infusion rate was 100mg/hr or faster, then infusions can be started at 100mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 100mg per hour every 30 minutes to a maximum rate of 400mg per hour. If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.				

Cycle 1 continued

Day	Drug	Dose	Route	Infusion Duration	Administration
15	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	80mg	IV	Over 15min	In 100ml Sodium Chloride 0.9%. Infusion **must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1gm	PO	Stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1 min	
	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: If no infusion related reaction or an IRR of grade 1 occurred during the prior infusion when the final infusion rate was 100mg/hr or faster, then infusions can be started at 100mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 100mg per hour every 30 minutes to a maximum rate of 400mg per hour. If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50 mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.				

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	Take 10mg up to TDS for three days, then take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Dexamethasone	6mg	PO	OM for 4 days starting on day 2. Day 2 dose to be taken before bendamustine.
	Chlorhexidine Mouthwash	10ml	Use as a mouthwash	BD for 2 weeks.
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose).
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last obinutuzumab treatment dose).

Cycle 2 to 6: repeat every 28 days

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	80mg	IV	Over 15min	In 100ml Sodium Chloride 0.9%. **Infusion must be completed at least 1 hour prior to the obinutuzumab infusion.**
	Paracetamol	1gm	PO	Stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus over 1min	
	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: If no infusion related reaction of >/= grade 3 occurred during cycle 1 the infusion can be started at 100mg/hr for 30 min and then administered as a short duration infusion (SDI) at approximately 900mg/hr for 60 minutes. If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 IRR occurred during the previous SDI infusion, administer the next obinutuzumab infusion at the standard rate see cycle 1 for administration details.				
	Ondansetron	<75yrs 16mg >/=75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	BENDAMUSTINE	**90mg/m²**	IV	30-60 mins	In 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 mins	In Sodium Chloride 0.9% 500ml

TTO	Drug	Dose	Route	Directions
Day 1	Metoclopramide	10mg	PO	Take 10mg up to TDS for three days, then take 10mg up to TDS when required. Do not take for more than 5 days continuously.
	Dexamethasone	6mg	PO	OM for 4 days starting on day 2. Day 2 dose to be taken before bendamustine.
	Chlorhexidine Mouthwash	10ml	Use as a mouthwash	BD for 2 weeks.
	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose).
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last obinutuzumab treatment dose).

Maintenance Obinutuzumab Every 56 days (2 months) for two years or until disease progression (whichever occurs first).
Cycle…….

Day	Drug	Dose	Route	Infusion Duration	Administration
1	Methylprednisolone Omit or reduce dose if patient tolerated previous obinutuzumab infusion and lymphocyte count <25 x 10^9/L	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	1gm	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	10mg	IV	Slow bolus Over 1 min	
	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 If no infusion related reaction of >/= grade 3 occurred during cycle 1 the infusion can be started at 100mg/hr for 30 min and then administered as a short duration infusion (SDI) at approximately 900mg/hr for 60 minutes If an IRR of Grade 1-2 with ongoing symptoms or a Grade 3 IRR occurred during the previous SDI infusion, administer the next obinutuzumab infusion at the standard infusion rate see cycle 1 for administration detail.				

TTO	Drug	Dose	Route	Directions
Day 1	Aciclovir	400mg	PO	BD continuously (plus 3 more months after completion of last obinutuzumab treatment dose).
	Co-trimoxazole	480mg	PO	TWICE daily on Mondays, Wednesdays and Fridays (plus 3 more months after completion of last obinutuzumab treatment dose).
	Fluconazole	100mg	PO	OD (plus 3 more months after completion of last obinutuzumab treatment dose)

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						