Indication	The treatment of untreated advanced CD20-positive follicular lymphoma.
Treatment Intent	Disease Modification
Frequency and number of cycles	Induction: Obinutuzumab & CHOP21 every 21 days for 6 cycles followed by Obinutuzumab every 21 days for a further 2 cycles 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. Maintenance: 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).
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. • **ECG** prior to doxorubicin. • Maximum cumulative dose of Doxorubicin = 450-550mg/m^2. Check previous exposure to anthracyclines. • 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**: **CHOP & obinutuzumab**: If neutrophils < 1.0 x 10^9/L and / or platelets < 80 x 10^9/L, delay until counts have recovered, then continue with full dose obinutuzumab. After first neutropenic event, subsequent cycles should be given prophylactic GCSF. For continued neutropenia even with GCSF support dose reduce Cyclophosphamide and Doxorubicin. 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. **Maintenance obinutuzumab:** If neutrophil <1.5 x 10^9/L and / or platelets < 100 x 10^9/L, delay until counts have recovered, then continue with full dose obinutuzumab. • **Renal impairment:** o Obinutuzumab: no dose adjustment is required if CrCl >/= 30ml/min; there is no data for CrCl < 30ml/min. o Cyclophosphamide: CrCl 10-20 ml/min dose at 75%; CrCl < 10ml/min dose at 50%

- **Hepatic impairment:**
  - Vincristine: bilirubin 26-51µmol/L or AST/ALT 60-180 units give 50%; bilirubin > 51µmol/L and AST/ALT normal give 50%; bilirubin > 51µmol/L and AST/ALT > 180 units omit dose.
  - Doxorubicin: bilirubin 20-51µmol/L give 50%, bilirubin 52-85µmol/L give 25%, bilirubin > 85µmol/L omit.
  - The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.
- **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 12-24hours 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.
- **Neurotoxicity** – Grade 2 motor and Grade 3 sensory toxicity give Vincristine 50% dose or Vinblastine 4–6mg/m^2.
- Patients with a history of **cardiac disease** should be monitored closely.
- **Progressive multifocal leukoencephalopathy** (PML) has been reported in patients treated with obinutuzumab.
- **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.** • Patients should not receive live vaccines during treatment, and until B cell counts have normalised. • **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. • NB Complete Obinutuzumab monitoring/administration details.
Reference(s)	KMCC protocol HAEM-NHL-083 V2 SPC accessed online 01.09.2022

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

Cycle 1: 21-day cycle

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.				
	Ondansetron	<75yrs 16mg ≥75yrs 8mg	IV	15 min	Sodium chloride 0.9% 50ml
	VINCRISTINE	**1.4mg/m² (max 2mg)**	IV	5-10 mins	Sodium chloride 0.9% 50ml
	DOXORUBICIN	**50mg/m²**	IV	bolus	through the side of a fast running NaCl 0.9% infusion.
	CYCLOPHOSPHAMIDE	**750mg/m²**	IV	Bolus	If dose >1500mg, administer in 250ml NaCl over 30-60mins.
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	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	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.				

Day	Drug	Dose	Route	Infusion Duration	Administration Details
8 cont	**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 100 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 100 mg per hour every 30 minutes to a maximum rate of 400 mg 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 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.				
15	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	1g	PO	STAT	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	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: 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 100 mg/hr. In the absence of any infusion related reactions or hypersensitivity, the rate of infusion may be escalated in increments of 100 mg per hour every 30 minutes to a maximum rate of 400 mg 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 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.				

Cycle 1

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.
	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)
	Non-E/C PREDNISOLONE	100mg	PO	OM Days 2 – 5
	Omeprazole	20mg	PO	OD
	Allopurinol	300mg	PO	OD, starting 24hrs before first cycle and reviewed after 4 weeks. Prescribe continuing supply if required from cycle 2 onwards
	Chlorhexidine Mouthwash	10ml	Top	QDS. Use as mouthwash, rinsing mouth for at least 1 minute
	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.

Cycles 2 to 6 repeat every 21 days.

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 Omit if patient tolerated previous obinutuzumab infusion.	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: 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 900mg/hr for approximately 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
	VINCRISTINE	**1.4mg/m² (max 2mg)**	IV	5-10 mins	Sodium chloride 0.9% 50ml
	DOXORUBICIN	**50mg/m²**	IV	bolus	through the side of a fast running NaCl 0.9% infusion.
	CYCLOPHOSPHAMIDE	**750mg/m²**	IV	bolus	If dose >1500mg, administer in 250ml NaCl over 30-60mins.

Cycles 2 to 6:

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.
	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)
	Non E/C PREDNISOLONE	100mg	PO	OM Days 2 – 5
	Omeprazole	20mg	PO	OD
	Chlorhexidine Mouthwash	10ml	TOP	QDS. Use as mouthwash, rinsing mouth for at least 1 minute
	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.

<u>Cycles 7 and 8</u> – every 21 days followed where appropriate by

<u>Maintenance Obinutuzumab</u> - every 56 days (2 months) for two years or until disease progression (whichever occurs first).

Day	Drug	Dose	Route	Infusion Duration	Administration Details
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	1g	PO	stat	Given at least 30 minutes before the obinutuzumab infusion.
	Chlorphenamine Omit if patient tolerated previous obinutuzumab infusion.	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%
	<u>Obinutuzumab infusion rate notes</u>: If no infusion related reaction 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 900mg/hr for approximately 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						

Protocol No	HAEM-NHL-083	Kent and Medway SACT Protocol Disclaimer: No responsibility will be accepted for the accuracy of this information when used elsewhere.	
Version	3	Written by	M.Archer
Supersedes version	2	Checked by	C.Waters (V2) H.Paddock V3 B. Willis/O. Okuwa (V1) V2 updated as per SOP-005 V3 updated in line with SPC and commissioning criteria
Date	29.12.2022	Authorising consultant (usually NOG Chair)	C. Wykes/L.Banerjee/L.Chia (V1)