Systemic Anti-Cancer Therapy Protocol

Obinutuzumab and Bendamustine Previously Untreated and Relapsed or Refractory Follicular Lymphoma

PROTOCOL REF: MPHAOBBEHA
(Version No: 1.0)

Approved for use in:

Obinutuzumab in combination with bendamustine is recommended as an option for **untreated advanced follicular lymphoma (FL)** in adults (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), only if the person has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more.

- The patient has a confirmed histological diagnosis of grade 1-3a CD20 –positive FL
- The patient has bulky stage II disease (>7cm) or stage III disease or stage IV disease.
- No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed
- ECOG PS 0-2

Obinutuzumab in combination with bendamustine is recommended as an option for **relapsed or refractory advanced follicular lymphoma (FL)** for adults who did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regime.

- Patients must not have previously received treatment with bendamustine unless completed more than 2 years previously.
- No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed.
- ECOG PS 0-2

Blueteq registration required: see blueteq for full eligibility criteria

Dosage:

Cycle 1:

Drug	Dosage	Route	Frequency
Obinutuzumab	1000mg	IV infusion	Day 1
Bendamustine	90mg/m^2	IV infusion	Day 1
Bendamustine	90mg/m^2	IV infusion	Day 2
Obinutuzumab	1000mg	IV infusion	Day 8
Obinutuzumab	1000mg	IV infusion	Day 15

Cycle 2-6

Drug	Dosage	Route	Frequency
Obinutuzumab	1000mg	IV infusion	Day 1
Bendamustine	90mg/m^2	IV infusion	Day 1
Bendamustine	90mg/m^2	IV infusion	Day 2

Each cycle is a 28 day cycle up to a maximum of 6 cycles

Patients may then be eligible or Obinutuzumab maintenance therapy – please refer to separate protocol.

Administration:

- Obinutuzumab is for intravenous use and should be given as an intravenous infusion through a dedicated line after dilution.
- If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose.
- Obinutuzumab should not be administered as an intravenous push or bolus.
- Obinutuzumab has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion, and patients experiencing infusion related symptoms should be advised not to drive or use machines until symptoms abate.
- Bendamustine has major influence on the ability to drive and use machines. Ataxia, peripheral neuropathy and somnolence have been reported during treatment with bendamustine. Patients should be instructed that if they experience these

symptoms such should avoid potentially hazardous tasks such as driving and using machines.

Emetogenic risk:

Mild to moderately emetogenic

Supportive Treatments:

Pre-medication: (see treatment schedule table below)

- Paracetamol orally 1g to be taken 30 minutes prior to the infusion
- Chlorphenamine intravenously 10mg to be taken 30 minutes prior to the infusion
- Patients with Grade 3 IRRs with the previous infusion OR those with a lymphocyte counts > 25 x 10^9/L prior to the next treatment should have intravenous dexamethasone 20mg 60 minutes prior to the infusion.

Take home medication:

- Ondansetron 8mg Twice a day for 5 days
- Metoclopramide 10mg Three times a day when required
- Docusate 100mg Twice a day when required
- Co- trimoxazole 480mg once daily
- Allopurinol 300mg (reduce dose if renal dysfunction) daily for first two cycles

Extravasation risk:

Obinutuzumab – neutral

Bendamustine - vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal	Obinutuzumab	No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance > 30mL/min). The safety of obinutuzumab has not been established in patients with severe renal impairment (patients with a creatinine clearance < 30mL/min).

	Bendamustine	No adjustment is necessary in patients with a creatinine clearance of > 10mL/min. Experience in patients with severe renal impairment is limited.

Hepatic	Obinutuzumab	The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established.
	Bendamustine	No adjustment is necessary in patients with mild hepatic impairment (bilirubin ≥20µmol/L). A 30% dose reduction is recommended in patients with moderate hepatic impairment (bilirubin >21-≤51 µmol/L. There is no data available for patients with severe hepatic impairment (bilirubin >52 µmol/L).

Interactions:

No formal drug-drug interaction studies have been performed with obinutuzumab; please consult the summary of product characteristics via https://www.medicines.org.uk/emc for the full list of interactions.

The safety of immunisation with live or attenuated viral vaccines following obinutuzumab has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.

Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine exists.

Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
CYCLE 1				
1	**Dexamethasone**	**20mg**	IV	Give as a slow IV bolus - 60 minutes prior to the infusion
	Paracetamol	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	Bolus – to be administered 30 minutes prior to the infusion
Day	**Drug**	**Dose**	**Route**	**Diluent and rate**
1	**Obinutuzumab**	**1000mg**	IV	In 250mL Sodium Chloride 0.9% (see below for rates)

	Bendamustine	**90mg/m^2**	IV	In 500mL Sodium Chloride 0.9% over 60 minutes.
2	**Bendamustine**	**90mg/m^2**	IV	In 500mL Sodium Chloride 0.9% over 60 minutes.
8	**Paracetamol**	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	Bolus – to be administered 30 minutes prior to the infusion
	Obinutuzumab	**1000mg**	IV	In 250ml Sodium Chloride 0.9% (see below for rates)
15	**Paracetamol**	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	Bolus – to be administered 30 minutes prior to the infusion
	Obinutuzumab	**1000mg**	IV	In 250ml Sodium Chloride 0.9% (see below for rates)
CYCLE 2-6				
1	**Paracetamol**	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	Bolus – to be administered 30 minutes prior to the infusion
	Obinutuzumab	**1000mg**	IV	In 250ml Sodium Chloride 0.9% (see below for rates)
	Bendamustine	**90mg/m^2**	IV	In 500mL Sodium Chloride 0.9% over 60 minutes.
2	**Bendamustine**	**90mg/m^2**	IV	In 500mL Sodium Chloride 0.9% over 60 minutes.

Cycle frequency is every 28 days up to a maximum of 6 cycles

Patients may then be eligible or Obinutuzumab maintenance therapy – please refer to separate protocol.

Patients with a Grade 3 IRRs with the previous infusion should have intravenous corticosteroid at least 1 hour prior to the next obinutuzumab infusion.

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations or obinutuzumab as outlined below.

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.

- 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, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.
- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated. Infusion can be continued upon resolution of symptoms and, if the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.

Obinutuzumab rate:

First dose: Administer at 50mg/hour – the rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr. Incremental escalation of the infusion rate should be considered only in the absence of Infusion Related Reactions (IRRs).

Subsequent doses: If no IRR or if an IRR Grade 1 occurred during the previous infusion when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. 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 400mg/hr.

Monitor observations as routine including 30 minutes after each dose increment to identify infusion reactions. Incremental escalation of the infusion rate should be considered only in the absence of Infusion Related Reactions (IRRs).

Main Toxicities:

Induction treatment with Obinutuzumab
Upper respiratory tract infection, sinusitis, urinary tract infection, pneumonia, herpes zoster, oral herpes, rhinitis, pharyngitis, lung infection, influenza nasopharyngitis, squamous cell carcinoma of the skin, neutropenia, thrombocytopenia, anaemia, leukopenia, tumour lysis syndrome, hyperuricaemia, hypokalaemia, insomnia, depression, anxiety, headache, ocular hyperaemia, atrial fibrillation and cardiac failure, hypertension, cough, nasal congestion, rhinorrhoea, diarrhoea, constipation, alopecia, pruritus, dysuria, urinary incontinence, pyrexia, asthenia, chest pain, reduction in WCCs and neutropenia, weight increase and infusion related reactions.

Tumour lysis syndrome (TLS) prophylaxis: Patients with a high tumour burden and/or renal impairment (CrCl < 70mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or suitable alternative treatment such as urate oxidase (e.g. rasburicase), starting 12-24 hours prior to start of obinutuzumab infusion as per standard practice. Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

Hypotension: it is important to note that hypotension is a symptom of the potential infusion related reaction (IRR), which may occur during obinutuzumab intravenous infusions. **Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration.**

Investigations and treatment plan

	Pre	Cycle 1 D1	Cycle 1 D2	Cycle 1 D8	Cycle 1 D15	Cycle 2 D1	Cycle 2 D2	Cycle 3 D1 onwards	Cycle 3 D2 onwards	Ongoing
Informed Consent	x									
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	x									
Clinical Assessment	x	x				x		x		Every cycle as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	x	x	x	x	x	Prior to every dose
Weight	x	x				x		x		Every cycle
Height	x									
FBC	x	x				x		x		Every cycle
U&E, LFT and Bone profile	x	x				x		x		Every cycle
Creatinine Clearance (Cockcroft and Gault)	x									
Blood pressure	x	x		x	x	x		x		Continuous monitoring required if on Obinutuzumab
Temp, respiratory rate, pulse		x		x	x	x		x		Continuous monitoring required if on Obinutuzumab

Pregnancy test	x									Where appropriate
Bone marrow assessment										End of treatment or as clinically indicated
Radiological imaging	x									End of treatment or as clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed with treatment when;

Platelets ≥ 100	ANC ≥ 1.0

Neutropenia: Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. It treatment is necessary it should be administered in accordance with local guidelines and the administration G-CSF should be considered. Any signs of concomitant infection should be treated appropriately. Dose delays should be considered in case of severe or life threatening neutropenia. It is strongly 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. Antiviral and antifungal prophylaxis should be considered. 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 < 50mL/min) are more at risk of neutropenia.

Thrombocytopenia: Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with obinutuzumab. Patients should be closely monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia.

Skin reactions: A number of skin reactions have been reported, these include a rash to severe cases of Stevens-Johnson and Toxic Epidermal Necrolysis reactions. Patients should be advised of the signs and symptoms of these reactions and should be told to seek medical attention immediately if they develop these symptoms. Where skin reactions occur, they may be progressive and increase in severity with further treatment. When skin reactions are progressive, bendamustine hydrochloride should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine, treatment should be discontinued.

References:

1. Summary of Product Characteristics, Gazyvaro 1000mg concentrate for solution for infusion, Roche, available from https://www.medicines.org.uk/emc [accessed on the 26th June 2019]
2. Summary of Product Characteristics, Bendamustine hydrochloride 2.5mg/ml powder for concentrate for solution, Dr. Reddy's Laboratories Ltd., available from https://www.medicines.org.uk/emc [accessed on the 26th June 2019]
3. NICE TA 513 Obinutuzumab for untreated advanced follicular lymphoma – Published 21 March 2018
4. Marcus R., Davies A., Obinutuzumab for the First Line Treatment of Follicular Lymphoma. The New England Journal of Medicine, 2017; 377: 1331-1344