Systemic Anti-Cancer Therapy Protocol

Obinutuzumab Maintenance Follicular Lymphoma

PROTOCOL REF: MPHAOBMAHA
(Version No: 1.0)

Approved for use in:

Obinutuzumab is recommended as an option for **untreated advanced follicular lymphoma (FL)** in adults (that is, first as induction treatment with chemotherapy (see obinutuzumab in combination with bendamustine, CHOP and CVP protocols), then alone as maintenance therapy), only if:

- 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.
- The patient has a FL International Prognostic Index (FLIPI) score of 2 or more.
- 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 (see obinutuzumab in combination with bendamustine) followed by obinutuzumab maintenance is recommended as an option for treating adults with **follicular lymphoma that did not respond or progressed** during or up to 6 months after treatment with rituximab or a rituximab containing regimen.

- The patient 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:

Patients who achieve a complete or partial response to induction treatment with obinutuzumab in combination with chemotherapy (CHOP or CVP or bendamustine) should continue to receive obinutuzumab 1,000 mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever is sooner).

Drug	Dosage	Route	Frequency
Obinutuzumab	1000mg	IV infusion	Every 2 months for 2 years or until disease progression (whichever occurs first).

For patients with follicular lymphoma who did not respond to or who progressed during 6 months after treatment with rituximab or a rituximab containing regimen. Patients who achieved a complete or partial response to induction treatment (i.e. the initial 6 treatment cycles) with obinutuzumab in combination with bendamustine or have stable disease should continue to receive obinutuzumab 1000mg as single agent maintenance therapy once every 2 months for 2 years or until disease progression (whichever occurs first).

Drug	Dosage	Route	Frequency
Obinutuzumab	1000mg	IV infusion	Every 2 months for 2 years or until disease progression (whichever occurs first).

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.

Emetogenic risk:

Mildly 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.

Extravasation risk:

Obinutuzumab – neutral

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

Dosing in renal and hepatic impairment:

Renal	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).

Hepatic	The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established.

Interactions:

No formal drug-drug interaction studies have been performed; 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.

Treatment Schedule:

Day	Drug	Dose	Route	Diluent and rate
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%

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:

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. Incremental escalation of the infusion rate should be considered only in the absence of Infusion Related Reactions (IRRs).

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:

Maintenance Obinutuzumab
During the maintenance period in the study the most common adverse reactions were cough, upper respiratory infections, neutropenia, sinusitis, diarrhoea, IRRs, nausea, fatigue, bronchitis, arthralgia, pyrexia, nasopharyngitis and urinary tract infections. The most common Grade 3-5 adverse reactions were neutropenia, anaemia, febrile neutropenia, thrombocytopenia, upper respiratory tract infection and urinary tract infection.

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 maintenance treatment	Cycle 1	Cycle 2	Cycle 3 onwards	Ongoing
Informed Consent	x				
Clinical Assessment		x	x	x	Prior to each cycle as clinically indicated
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
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	Continuous monitoring required if on Obinutuzumab
Temp, respiratory rate, pulse		x	x	x	Continuous monitoring required if on Obinutuzumab
Bone marrow assessment					If clinically indicated at the end of treatment
Radiological imaging					If clinically indicated at the end of treatment

Dose Modifications and Toxicity Management:

During maintenance, maintain the original dosing schedule for subsequent doses.

Haematological toxicity

Proceed on day 1 of next cycle;

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.

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. NICE TA 472 - Obinutuzumab with bendamustine for treating follicular lymphoma refractory to rituximab – published 30 August 2017
3. NICE TA 513 Obinutuzumab for untreated advanced follicular lymphoma – Published 21 March 2018
4. Sehn LH et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol. 2016 Aug;17 (8):1081-93.