OBINUTUZUMAB + BENDAMUSTINE, followed by OBINUTUZUMAB MAINTENANCE

An option for treating follicular lymphoma that did not respond or progressed, during or up to 6 months after, treatment with rituximab or a rituximab-containing regimen

Blueteq registration is required before treatment may start

All patients should be screened for hepatitis B virus before starting treatment

Drugs/Dosage:

Obinutuzumab 1000mg		IV	Day 1, Day 8 and Day 15 of Cycle 1, then Day 1 only of Cycles 2 - 6
then			
Bendamustine 90mg/m^2		IV	once daily on Day 1 and Day 2 of Cycles 1 – 6
then, for non-progressing patients, maintenance as follows;			
Obinutuzumab 1000mg		IV	every 2 months for up to 2 years.

Pre-medication for obinutuzumab:

Paracetamol	1000 mg	po	at least 30 minutes before infusion starts
Chlorphenamine**	10 mg	IV	at least 30 minutes before infusion starts
Dexamethasone*	20 mg	IV	at least 60 minutes before infusion starts

*Once WBC < 25 x 10^9/l **and** if the previous obinutuzumab dose was administered without a serious reaction, the dexamethasone dose may be reduced or omitted for the remaining infusions, according to clinician preference.
** If the patient tolerated the previous obinutuzumab dose without any adverse reactions, the chlorphenamine dose may be omitted for the remaining infusions.

Frequency:
Obinutuzumab + bendamustine: 28 day cycle for 6 cycles
Obinutuzumab maintenance: every 2 months for up to 2 years

Other Drugs:
Allopurinol 300mg po od, ideally starting 24 hours before treatment – review after 4 weeks
For patients with high initial counts (WBC > 25) or CrCl < 70ml/min, it is suggested that at least 1 litre of IV N/saline is administered before starting treatment.
Consider advising patient to omit any antihypertensive medicines on the morning of treatment, particularly on the first cycle.
Co-trimoxazole 480mg od throughout treatment and until lymphocyte count > 1 x 10^9/l
Aciclovir 400mg bd throughout treatment
Consider fluconazole as antifungal prophylaxis

Anti- emetics:
highly emetogenic on Days 1 and 2

Main Toxicities:
obinutuzumab infusion-related reactions +/- cytokine release syndrome (in majority of patients during the 1st infusion);
tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration)
hypersensitivity reactions to bendamustine (e.g. rash, urticaria);
myelosuppression; increased infection risk; diarrhoea; alopecia;
worsening of pre-existing cardiac conditions (e.g. AF, heart failure); ovarian failure/infertility

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Extravasation: obinutuzumab and bendamustine are non-vesicants

Administration: Bendamustine in 500ml sodium chloride 0.9% and infused over 30 – 60 minutes.
Obinutuzumab in 250ml sodium chloride 0.9%, and infused as follows, in the absence of any infusion related reactions:

Cycle & Day of treatment	Rate of infusion
Cycle 1, Day 1	Administer at 50 **mg**/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. **For 1000mg in 250ml volume only,** this means that the infusion may be administered as follows: Give 6ml at 12.5ml/hour; then 12.5ml at 25ml/hour; then 19ml at 37.5ml/hour; then 25ml at 50ml/hour; then 32ml at 62.5ml/hour; then 38ml at 75ml/hour; then remainder (approx 120ml) at 100ml/hour. Total time approx 4¼ hours
Cycle 1, Days 8 & 15 and Cycle 2 – 6, Day 1 and Maintenance doses	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. **For 1000mg in 250ml volume only,** this means that the infusion may be administered as follows: Give 12.5ml at 25ml/hour; then 25ml at 50ml/hour; then 37.5ml at 75ml/hour; then remainder (approx 175ml) at 100ml/hour Total time approx 3 hours

For Day 1 of Cycle 1, monitor patient's vital signs at baseline and then every **15** minutes (including before each increase in infusion rate).
For all subsequent doses, monitor patient's vital signs at baseline and then every 30 minutes (including before each increase in infusion rate).

Infusion-related reactions:

Obinutuzumab:
In the event of a Grade 1-2 (mild or moderate) infusion-related reaction, the infusion rate must be slowed down and symptoms treated. Once the symptoms have resolved, the infusion rate can be escalated according to standard procedure for the dose.

In the event of a Grade 3 (severe) infusion-related reaction, the infusion should be interrupted and, when the patient is stable, re-started at no more than half the previous rate at the time the reaction occurred. The infusion rate can then be increased according to standard procedure for that dose.

In the event of a Grade 4 (life-threatening) infusion-related reaction, or a second occurrence of a Grade 3 (severe) infusion-related reaction, the infusion must be stopped and obinutuzumab permanently discontinued.

Bendamustine:
IV antihistamine and steroid cover should be considered with subsequent doses of bendamustine for patients who experience even a mild hypersensitivity reaction on Cycle 1. It is suggested that bendamustine-related reactions ≥ Grade 3 should not be re-challenged.

Regular Investigations:	FBC	Day 1 of each cycle, **plus** Day 8 and Day 15 of Cycle 1, and before each maintenance dose
	U&Es and LFTs	Day 1 of each cycle
	LDH	every other cycle

Comments: Patients should not receive live vaccines during treatment, and until B cell counts have normalised. The shingles vaccine is also contra-indicated in follicular lymphoma patients at any time, even if not on treatment.

Dose Modifications

Haematological Toxicity: If neutrophil count is < 1.0 x 10^9/L or platelet count is < 75 x 10^9/L, defer treatment until FBC recovered, then proceed with dose reductions as follows:
Patients with neutrophils < 0.5 x 10^9/l or platelets < 25 x 10^9/l to continue treatment once recovered, but reduce the bendamustine dose to 60mg/m^2 on Day 1 and Day 2; patients with counts above these levels can proceed with full dose.
There are no dose reductions for obinutuzumab.

Non-haematological Toxicities: For any Grade 3 non-haematological toxicity, defer treatment until resolved to Grade 1 – 0, and then give bendamustine 60mg/m^2 for further cycles.

Renal Impairment: If CrCl < 50ml/minute, the patient is more at risk of myelosuppression.
No obinutuzumab dose adjustment is required if CrCl > 30ml/min. There is no data for CrCl < 30ml/min.
No bendamustine dose adjustment required if CrCl > 10ml/min.

Hepatic Impairment: Obinutuzumab in hepatic impairment has not been studied. No specific dose recommendations can be made.

Bilirubin (µmol/l)	Bendamustine dose
21 – 51	Give 70% dose
> 51	No data available

Patient Information: Macmillan leaflet for Bendamustine; no Macmillan/CRUK leaflet currently available for obinutuzumab.
Patients may be guided to website http://www.gazyva.com/ for patient information

Reference: Sehn, L et al; Lancet 2016; 17 (8): 1081 – 1093 (Gadolin trial)
Dose modifications advice for haem and non-haem toxicities in line with the Alliance R-Bendamustine-90 protocol