Systemic Anti-Cancer Therapy Protocol

Obinutuzumab and Venetoclax Chronic Lymphocytic Leukaemia

PROTOCOL REF: MPHAOBVEHA
(Version No: 1.0)

Approved for use in:

Previously untreated CLL in patients with a 17p deletion or TP53 mutation

OR

Previously untreated CLL in patients *without* a 17p deletion or TP53 mutation where treatment with FCR (fludarabine/cyclophosphamide/rituximab) or BR (bendamustine/rituximab) *would not* be suitable

OR

Previously untreated CLL in patients *without* a 17p deletion or TP53 mutation where treatment with FCR (fludarabine/cyclophosphamide/rituximab) or BR (bendamustine/rituximab) *would* be suitable

Blueteq registration is required for all indications: see eligibility criteria. Note there are three different forms.

Dosage:

Cycle 1:

Drug	Dose	Route	Frequency
Obinutuzumab	**100mg**	IV infusion	Day 1
Obinutuzumab	**900mg**	IV infusion	Day 2
Obinutuzumab	**1000mg**	IV infusion	Day 8
Obinutuzumab	**1000mg**	IV infusion	Day 15
Venetoclax	**20mg OD**	Oral	Day 22 to 28

Cycle 2:

Drug	Dose	Route	Frequency
Obinutuzumab	**1000mg**	IV infusion	Day 1 only
Venetoclax	**50mg OD**	Oral	Days 1 to 7
Venetoclax	**100mg OD**	Oral	Days 8 to 14
Venetoclax	**200mg OD**	Oral	Days 15 to 21
Venetoclax	**400mg OD**	Oral	Days 22 to 28

Cycle 3 to 6:

Drug	Dose	Route	Frequency
Obinutuzumab	**1000mg**	IV infusion	Day 1 only
Venetoclax	**400mg OD**	Oral	Days 1 to 28

Cycle 7 to 12:

Drug	Dose	Route	Frequency
Venetoclax	**400mg OD**	Oral	Days 1 to 28

Maximum of 12 cycles (28 day cycle)

Administration:

Venetoclax

- Taken daily at approximately the same time each day.
- Take with or just after food or a meal (preferably morning to facilitate lab monitoring).
- Swallow whole. Do not crush or chew medication.
- Emphasize importance of gradual titration regimen.
- Food to avoid during treatment: Grapefruit products, Seville oranges and star fruit (may increase exposure to venetoclax).

Missed Doses

- If the patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible on the same day.

- If the patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the following day.
- If dose missed for more than two weeks restart titration.

Vomiting

If vomiting occurs following dose administration, no additional doses should be taken on that day and the next dose should be taken at the normal time.

Hydration

Patient should aim to drink 1.5–2 litres of water daily, starting 2 days before and throughout the dose-titration phase (due to risk of tumor lysis syndrome (TLS)), especially during days of dose titration.

Contraception

Ensure effective non-hormonal contraception during and for 30 days after treatment in women of child-bearing potential. It is unknown whether venetoclax affects the effectiveness of hormonal contraceptives.

Obinutuzumab

- 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.

Anti-emetic risk:

Mildly emetogenic.

Supportive treatments:

Pre-meds for obinutuzumab:

- Paracetamol orally 1g to be taken 30 minutes prior to the infusion
- Chlorphenamine intravenously 10mg to be taken 30 minutes prior to the infusion
- Intravenous dexamethasone should be administered at least 60 minutes prior to the first dose of obinutuzumab (cycle 1, day 1).
- 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.

Supportive meds

- Allopurinol 300mg daily (depending on renal function) from day 0 until the venetoclax has been titrated to the full dose (first 2 cycles)
- Metoclopramide 10mg three times a day when required
- Co-trimoxazole 480mg daily
- Aciclovir 400mg twice daily at the discretion of the consultant

Tumour Lysis Risk (TLS) with Venetoclax:

- TLS risk must be assessed prior to starting treatment with venetoclax, and appropriate action taken.
- Patients at high/medium risk of TLS must be admitted for their first dose of venetoclax for monitoring purposes.
- TLS can occur rapidly, within 6-8 hours of initiation and/or dose increases.
- Pre-dose/ titration: Tumour lysis bloods (urea and electrolytes (U&Es), uric acid, calcium profile (including phosphate and creatinine) should be performed prior to initiation and before each dose titration (correct any abnormalities prior to commencing treatment/ titrating dose).
- For those at medium or high risk of TLS, tumour lysis bloods should be monitored at 6 to 8 hours and 24hours after the 1st dose. The same monitoring schedule should be followed at the start of the 50mg dose at clinicians discretion and then for patients that continue to be at risk, at subsequent dose increases (patients will need admitting for monitoring in these circumstances, if blood monitoring can't be done in the day case setting for logistical reasons)

Risk Category	Clinical Features	Treatment Location	TLS Management
High	Lymph node ≥10cm OR lymphocyte count ≥25x 10^9/L AND Lymph nodes ≥5cm	Inpatient only for at least the first dose	Rasburicase (dose as per local guidance) on day 1 with further doses as required. Consider further doses prior to each dose escalation as clinically indicated AND Allopurinol 300mg once daily starting 3 days before the first dose of venetoclax and continue until day 7 of venetoclax 400mg. Omit allopurinol on the days of rasburicase. (reduce to allopurinol 100mg OD if CrCl <20ml/min)
Medium	Lymph Node 5-10cm OR CrCl <80mL/min OR lymphocyte count ≥25x 10^9/L	Consultant decision	Allopurinol 300mg starting 3 days before the first dose of venetoclax and continue until day 7 of venetoclax 400mg. Rasburicase at consultant discretion.
Low	Lymph Node <5cm AND CrCl >80mL/min AND lymphocyte count <25x 10^9/L	Day Case	Allopurinol 300mg once daily starting 3 days before the first dose of venetoclax and continue until day 7 of venetoclax 400mg. No rasburicase is required.

Extravasation risk:

Obinutuzumab: neutral

Refer to the Trust guidance for the prevention and management of extravasation

Interactions:

Obinutuzumab

No formal drug-drug interaction studies have been performed

Venetoclax

Concomitant use of venetoclax with strong CYP3A inhibitors (e.g., itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin, ritonavir) at initiation and during the dose-titration phase is contraindicated due to increased risk for TLS.

At initiation and during the dose-titration phase, concomitant use of venetoclax with moderate CYP3A inhibitors (e.g., ciprofloxacin, diltiazem, erythromycin, fluconazole, verapamil) should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation dose of venetoclax and the doses for the titration phase should be reduced by at least 50%. Patients should be monitored more closely for signs and symptoms of TLS.

For patients who have completed the dose-titration phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2 to 3 days after discontinuation of the inhibitor.

Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax as they contain inhibitors of CYP3A.

Concomitant use of venetoclax with P-gp and BCRP inhibitors (e.g. rifampicin) at initiation and during the dose-titration phase should be avoided; if a P-gp and BCRP inhibitor must be used, patients should be monitored closely for signs of toxicities.

Concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, or rifampin) or moderate CYP3A inducers (e.g., bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided. Alternative treatments with less CYP3A induction should be considered. Preparations containing St. John's wort are contraindicated during treatment with venetoclax, as efficacy may be reduced.

Co-administration of narrow therapeutic index P-gp, or BCRP substrates (e.g., digoxin, dabigatran, everolimus, sirolimus) with venetoclax should be avoided.

If a narrow therapeutic index P-gp or BCRP substrate must be used, it should be used with caution. For an orally administered P-gp or BCRP substrate sensitive to inhibition in the

gastrointestinal tract (e.g., dabigatran exetilate), its administration should be separated from venetoclax administration as much as possible to minimise a potential interaction.

If a statin (OATP substrate) is used concomitantly with venetoclax, close monitoring of statin-related toxicity is recommended

Treatment schedule Cycle 1:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**20mg**	**IV**	60 mins before chemotherapy
	Paracetamol	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**100mg**	**IV**	In 100mls NaCl 0.9% over 4 hours
2	**Dexamethasone**	**20mg**	**IV**	60 mins before chemotherapy
	Paracetamol	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**900mg**	**IV**	In 250mL Sodium Chloride 0.9% (see rate below)
8	**Paracetamol**	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**1000mg**	**IV**	In 250mL Sodium Chloride 0.9% (see rate below)
15	**Paracetamol**	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**1000mg**	**IV**	In 250mL Sodium Chloride 0.9% (see rate below) .
22 to 28	**Venetoclax**	**20mg**	**PO**	Post dose tumour lysis bloods depending on risk factor after first dose (see above)

Treatment schedule Cycle 2:

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**1000mg**	**IV**	In 250mL Sodium Chloride 0.9% (see rate below)
1 to 7	**Venetoclax**	**50mg**	**PO**	Post dose tumour lysis bloods depending on risk factor after first dose (see above)
8 to 14	**Venetoclax**	**100mg**	**PO**	Post dose tumour lysis bloods depending on risk factor after first dose (see above)
15 to 21	**Venetoclax**	**200mg**	**PO**	Post dose tumour lysis bloods depending on risk factor after first dose (see above)
22 to 28	**Venetoclax**	**400mg**	**PO**	Post dose tumour lysis bloods depending on risk factor after first dose (see above)

Treatment schedule Cycle 3 to 6:

Day	Drug	Dose	Route	Diluent and rate
1	**Paracetamol**	**1g**	**PO**	30 mins before chemotherapy
	Chlorphenamine	**10mg**	**IV**	Bolus 30 mins before chemotherapy
	Obinutuzumab	**1000mg**	**IV**	In 250mL Sodium Chloride 0.9% (see rate below).
	Venetoclax	**400mg**	**PO**	For 28 days

Treatment schedule Cycle 7 to 12:

Day	Drug	Dose	Route	Diluent and rate
1	**Venetoclax**	**400mg**	**PO**	For 28 days

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:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, tumour lysis syndrome and IRRs.

Investigations and treatment plan:

Cycle 1:

	Pre	Cycle 1 D1	Cycle 1 D2	Cycle 1 D8	Cycle 1 D15	Cycle 1 D22	Ongoing
Informed Consent	x						
Clinical Assessment	x	x				x	Every cycle
SACT Assessment (including toxicity assessment and PS)		x	x	x	x	x	Prior to every dose
Weight	x	x					Every cycle
Height	x						
FBC	x	x				x	
U&E, LFT and Bone profile	x	x				x	Patients at medium/high risk of TLS need these bloods repeating at 6-8 hours post dose and again 24 hours post dose on day 22
Uric acid and magnesium						x	
Creatinine Clearance (Cockcroft and Gault)	x						
Blood pressure	x	x	x	x	x		Continuous monitoring required if on Obinutuzumab
Temp, respiratory rate, pulse		x	x	x	x		Continuous monitoring required if on Obinutuzumab
Pregnancy test	x						Where appropriate
Bone marrow assessment							Where clinically indicated
Radiological imaging	x						If clinically indicated, repeat scans at the discretion of MDT
ECHO +/- ECG							If clinically indicated
Hepatitis B core	x						

antibody and surface antigens & Hep C & HIV 1+2							

Cycle 2:

	Cycle 2 D1	Cycle 2 D8	Cycle 2 D15	Cycle 2 D22	Ongoing
Clinical Assessment	x			x	Every cycle
SACT Assessment (including toxicity assessment and PS)	x	x	x	x	Prior to every dose escalation
Weight	x				Every cycle
FBC	x				
U&E, LFT and Bone profile	x	x	x	x	Patients at medium/high risk of TLS need these bloods repeating at 6-8 hours post dose and again 24 hours post dose on day 1, and again on days 8, 15 and 22 at the discretion of the prescriber depending on TLS risk
Uric acid and magnesium	x	x	x	x	
Blood pressure	x				Continuous monitoring required if on Obinutuzumab
Temp, respiratory rate, pulse	x				Continuous monitoring required if on Obinutuzumab

Cycles 3-12:

	Cycle 3-6 D1	Cycle 7 onwards D1	Ongoing
Clinical Assessment	x		Every cycle
SACT Assessment (including toxicity assessment and PS)	x	x	Prior to every dose escalation
Weight	x	x	Every cycle
FBC	x	x	
U&E, LFT and Bone profile	x	x	
Blood pressure	x		Continuous monitoring required if on Obinutuzumab
Temp, respiratory rate, pulse	x		Continuous monitoring required if on Obinutuzumab

Dose Modifications and Toxicity Management:

Non-Haematological toxicity:

Venetoclax	
Tumor Lysis Syndrome	If suspected withhold the following days dose of venetoclax. If resolved within 24-48hours of the last dose, treatment can be resumed at the same dose. For events of clinical TLS or blood chemistry changes requiring more than 48 hours to resolve, treatment should be resumed at a reduced dose (see dose modification table). When resuming treatment after interruption due to TLS, the instructions for prevention of TLS should be followed (see “Tumour Lysis Risk” above).
Use with CYP3A inhibitors	**Initiation and titration phase:** Concomitant use of venetoclax with strong CYP3A inhibitors at initiation and during the dose-titration phase is contraindicated. Concomitant use of venetoclax with moderate CYP3A inhibitors at initiation and during the dose-titration phase should be avoided. Alternative treatments should be considered. If a moderate CYP3A inhibitor must be used, the initiation and titration doses of venetoclax should be reduced by at least 50%. Patients should be monitored more closely for signs of toxicity. **After completion of titration phase:** For patients who are on a steady daily dose of venetoclax dose should be reduced by 50% when used concomitantly with moderate CYP3A inhibitors and by 75% when used concomitantly with strong CYP3A inhibitors. Patiens should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. The venetoclax dose should be resumed 2 to 3 days after discontinuation of the inhibitor.

Venetoclax		
Grade 3 or 4 toxicity	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in table 2 when

		resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the treating physician.

Haematological toxicity:

Venetoclax		
Grade 3 or 4 neutropenia (ANC < 1 x10^9/L) with infection or fever; or Grade 4 hematologic toxicities except lymphopenia (e.g. ANC <0.5 x10^9/L or Plt < 25 x109/L)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Dose reduce as per dose modification table- when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the treating physician.

Venetoclax Dose Modification Table

Dose at interruption (mg)	Restart dose (mg)*
400	300
300	200
200	100
100	50
50	20
20	10
*The modified dose should be continued for one week before increasing the dose	

If dosing is interrupted for >1 week during initial titration phase, or for >2 weeks after completion of titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

Dosing in renal and hepatic impairment:

Venetoclax

Renal	Obinutuzumab	No dose adjustment is required in patients with mild to moderate renal impairment (CrCl 30-89 ml/min). The safety and efficacy of obinutuzumab has not been established in patients with severe renal impairment (CrCl < 30 ml/min), use with caution
	Venetoclax	No dose adjustment is needed for patients with mild or moderate renal impairment (CrCl ≥30 ml/min and <90 ml/min). Patients with reduced renal function (CrCl <80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of TLS at initiation and during the dose-titration phase. Safety in patients with severe renal impairment (CrCl <30 ml/min) or on dialysis has not been established, and a recommended dose for these patients has not been determined. Venetoclax should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS.

Hepatic	Obinutuzumab	The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.
	Venetoclax	No dose adjustment is recommended in patients with mild or moderate hepatic impairment. Patients with moderate hepatic impairment (bilirubin between 1.5 and 3.0 times the ULN) should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase. A dose reduction of at least 50% throughout treatment is recommended for patients with severe hepatic impairment (i.e. bilirubin >3 times the ULN). These patients should be monitored more closely for signs of toxicity.

References:

1. https://www.medicines.org.uk/emc obinutuzumab (accessed 31/12/20)
2. https://www.medicines.org.uk/emc venetoclax (accessed 31/12/20)
3. NICE TA 663 Venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia (published 09/12/2020)