SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

VENETOCLAX +/- RITUXIMAB CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL)

PROTOCOL REF: MPHAVRHA
(Version No.3.0)

Approved for use in:

Venetoclax monotherapy is indicated for the treatment of chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) when the following criteria are met:

- They are **negative** for **both** 17q deletion and TP53 mutations and have progressive disease after a B cell receptor pathway inhibitor: bruton kinase inhibitor (ibrutinib / acalabrutinib) and/or PI3K inhibitor (idelalisib), or these were unsuitable.
- They are **positive** for 17q deletion and/or TP53 mutations and have progressive disease on or after treatment with a B cell receptor pathway inhibitor: bruton kinase inhibitor (ibrutinib / acalabrutinib) and/or PI3K inhibitor (idelalisib) or these were unsuitable.

Venetoclax plus rituximab is indicated for the treatment of chronic lymphocytic leukaemia (CLL) / small lymphocytic lymphoma (SLL) when the following criteria are met:

- They have received at least 1 previous line of treatment such as anti-CD20 containing chemo-immunotherapy and/or B-Cell receptor pathway inhibitor (ibrutinib, acalabrutinib, idelalisib). **NB** they must not have had progressive disease whilst receiving venetoclax based therapy.

Blueteq request must be completed prior to initiation

Dosage:

Venetoclax Monotherapy

Drug	Dose		Route	Frequency
Cycle 1 (28 day cycle)	**Week 1**	**Venetoclax** 20mg (days 1-7) *	Oral	Once daily
	Week 2	**Venetoclax** 50mg (days 8-14)*	Oral	
	Week 3	**Venetoclax** 100mg (days 15-21)*	Oral	
	Week 4	**Venetoclax** 200mg (days 22-28)*	Oral	
Cycle 2 + (28 day cycle)	**Week 5 +**	**Venetoclax** 400mg	Oral	Once daily

* If dose escalation is delayed, patients should continue their current dose until the next dose increase can be arranged. Patients will need weekly review during the dose titration and should only get one weeks supply of medications until week 5.

Treatment should be continued until disease progression or unacceptable toxicity.

Venetoclax plus Rituximab

Drug	Dose		Route	Frequency
Cycle 1 (28 day cycle)	**Week 1**	**Venetoclax** 20mg (days 1-7) *	Oral	Once daily
	Week 2	**Venetoclax** 50mg (days 8-14)*	Oral	
	Week 3	**Venetoclax** 100mg (days 15-21)*	Oral	
	Week 4	**Venetoclax** 200mg (days 22-28)*	Oral	
Cycle 2 (35 day cycle)	**Venetoclax 400mg**		Oral	Once daily
	****Rituximab 375mg/m^2**		IV	Day 8
Cycle 3 to 7 (28 day cycle)	**Rituximab 500mg/m^2**		IV	Day 1
	Venetoclax 400mg		Oral	Once daily
Cycle 8 to 25 (28 day cycle)	**Venetoclax 400mg**		Oral	Once daily

* If dose escalation is delayed, patients should continue their current dose until the next dose increase can be arranged. Patients will need weekly review during the dose titration and should only get one weeks supply of medications until week 5.

******Commenced once venetoclax titration has completed and patient has received 400mg daily for 7 days (i.e. at day 35). If lymphocyte count >25 x 10^9/L consider splitting first dose of rituximab, giving 100mg as a flat dose over 2 hours on day 8 and the remainder of the dose on day 9.

Maximum treatment duration of 2 years when used in combination with rituximab. Venetoclax is taken for 24 months from Cycle 1 Day 1 of rituximab (max. cycle no. 25)

Administration:

- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
- Patients should be counselled on the importance of the titration regimen and attending for blood monitoring during this phase. Patients will need admitting for monitoring if they are at high risk of developing tumour lysis syndrome (TLS) or if blood monitoring can't be done in the day case setting for logistical reasons
- Due to risk of TLS associated with venetoclax titration, the patient should be encouraged to drink 1.5-2 litres of water per day to maintain hydration, especially during titration phase.
- Venetoclax should be taken daily at approximately the same time each day with or just after food (preferably morning to facilitate blood monitoring). Swallow whole, do not crush or chew.
- 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 consider restarting titration.
- 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.
- Avoid grapefruit products, Seville oranges and star fruit during as they may increase exposure to venetoclax.

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Rituximab pre-infusion medications:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone 100mg IV

Supportive Medication:

- Allopurinol 300mg once daily (first cycle only, continued at clinician discretion). Consider rasburicase 3mg IV if high risk of tumour lysis
- Aciclovir 400mg twice daily (at clinician discretion)
- Co-trimoxazole 480mg daily
- Metoclopramide 10mg three times daily when required

Tumour Lysis Risk (TLS) Risk:

- TLS risk must be assessed prior to treatment (see table 1 below).
- TLS can occur rapidly, within 6-8 hours of initiation and/or dose increases. Therefore it is crucial that the TLS blood monitoring schedule in the table 2 below is followed.
- Tumour lysis blood monitoring includes: urea and electrolytes (U&Es), uric acid, calcium profile (including phosphate and creatinine) - correct any abnormalities prior to commencing treatment/ titrating dose.

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 the first 2 doses	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)

Intermediate	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	Outpatient	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.

Table 1: TLS Risk Stratification

Risk of TLS	Titration Dose	Timing of TLS blood monitoring
High	20mg or 50mg	Pre dose, +4hrs, +8hrs, +12hrs, +24hrs
	Subsequent	Pre dose, +6-8hrs, +24 hrs
Intermediate or Low	20mg or 50mg	Pre dose, +6-8hrs, +24 hrs
	Subsequent	Pre-dose only

Table 2: TLS blood monitoring based on TLS risk

Extravasation risk:

Rituximab - Non-vesicant

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

Dosing in renal and hepatic impairment:

Renal Dose Modifications		
	Creatinine Clearance (mL/min)	**Dose Modification**
Venetoclax	<80	Monitor closely for TLS. Nos dose adjustment required
	<30 or haemodialysis	Safety not established. Administer only if benefit outweighs risk.
Rituximab	No adjustment required	

Hepatic Dose Modifications		
Venetoclax	Moderate	Monitor more closely for toxicity
	Severe	50% dose. Monitor closely
Rituximab	No dose adjustment necessary	

Interactions:

CYP3A Inhibitors (increased venetoclax exposure)

Concomitant use of strong CYP3A inhibitors (e.g. itraconazole, ketoconazole, posaconazole, voriconazole, clarithromycin and ritonavir) is contraindicated during titration. Avoid concomitant use with moderate CYP3A inhibitors (e.g. ciprofloxacin, diltiazem, erythromycin, fluconazole and verapamil) at initiation and during the dose-titration phase. Consider alternative medications or reduce the venetoclax dose as described in **table 3** below. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2-3 days after discontinuation of the inhibitor.

Inhibitor	Dose Modification
Strong CYP3A inhibitor	Initiation and dose-titration phase: Contraindicated
	Steady daily dose (After dose-titration phase): Reduce the venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons). Monitor closely.
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%. Monitor closely.
Strong or moderate CYP3A inducers (St. John's Wort, sulphonylureas, carbamazepine, rifampicin, phenytoin, griseofluvin, phenobarbital)	Contraindicated due to reduced venetoclax efficacy
Grapefruit/grapefruit products, Seville oranges or star fruit (including marmalade containing Seville oranges)	Avoid within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed
Inhibitors of P-gp or BCRP (rifampicin)	Avoid during dose titration or monitor closely for toxicity
P-gp and BCRP substrates (digoxin, everolimus, sirolimus, dabigatran)	Avoid if possible. If must be used, use with caution
Bile acid sequestrants	Administer at least 4-6 hours after the sequestrant
Warfarin	Monitor INR closely
Statins	Monitor for statin related toxicity

Table 3: Dose Modifications due to interactions

Treatment schedule (Rituximab):

Rituximab should be only be administered **after** the patient has completed the venetoclax dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for **7 days**.

If lymphocyte count ≥25 x 10^9/L the first dose of rituximab may be split to give 100mg in 500mL sodium chloride over 2 hours followed by the rest of the dose in 500mL sodium chloride at standard infusion rate.

Cycle	Drug	Dose	Route	Diluent and rate
Cycle 2 (Day 8)	**Paracetamol**	**1g**	PO	30 mins before chemotherapy
	Chlorphenamine	**10mg**	IV	30 mins before chemotherapy
	Hydrocortisone	**100mg**	IV	30 mins before chemotherapy
	Rituximab**	**375mg/m^2**	IV	Sodium Chloride 0.9% 500mL
Cycles 3-7	**Paracetamol**	**1g**	PO	30 mins before chemotherapy
	Chlorphenamine	**10mg**	IV	30 mins before chemotherapy
	Hydrocortisone	**100mg**	IV	30 mins before chemotherapy
	Rituximab**	**500mg/m^2**	IV	Sodium Chloride 0.9% 500mL

**** Please refer to CCC Rituximab Administration Guideline. Observe patient for 15 minutes after rituximab.**

Main toxicities:

Rituximab
Infusion reactions, cytokine release syndrome, hepatitis B reactivation
Venetoclax
Tumour lysis syndrome, neutropenia, thrombocytopenia, anaemia, lymphopenia, diarrhoea, respiratory tract infection, urinary tract infection, fatigue, electrolyte disturbance (hyperkalaemia, hyperphosphataemia, hypocalcaemia, hyperuricaemia – TLS), vomitting, nausea, constipation, raised creatinine.

Investigations and treatment plan:

	Pre-treatment	Cycle 1* Week 1	Week 2	Week 3	Week 4	Cycle 2 D1*	Cycle 2 D8*	Cycle 3 onwards	Ongoing
Clinical Assessment	X						X	X	As clinically indicated or at the end of treatment
SACT Assessment		X	X	X	X	X	X	X	Patients must have their bloods reviewed prior to each dose titration. See TLS risk section
Viral screening (inc Hep B)	X								
LDH	X								Repeat if clinically indicated
Electrophoresis	X								Repeat if clinically indicated
FBC	X	X	X	X	X	X		X	Every cycle initially. Extended to every three cycles once patients stable on treatment
U&E & LFTs & calcium profile	X	X	X	X	X	X		X	Weekly during cycle one. U+Es, LFTs and calcium profile every cycle thereafter initially. Extended to every three cycles once patients stable on treatment. See TLS risk section.
Uric Acid, magnesium, bone profile	X	X	X	X	X	X		X	
CrCl (Cockcroft and Gault)	X					X		X	
CT scan	X								At the end of treatment and if clinically indicated
Informed Consent	X								
ECG	X								If clinically indicated
Blood pressure	X						X	X	Continuous monitoring required if on rituximab
Temperature, respiratory rate, pulse	X						X	X	Continuous monitoring required if on rituximab
PS recorded	X					X		X	Every Cycle
Pregnancy test	X								Where appropriate

Height Recorded	X								
Weight recorded	X	X				X		X	Every cycle
Blood glucose	X								Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Subsequent cycles to proceed when-

ANC ≥ 0.5 x 10^9/L (if no fever)	Platelets ≥ 25 x 10^9/L

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

Consider splitting the first dose of rituximab if lymphocyte count ≥25 x10^9/L

Venetoclax		
Grade 3 neutropenia (ANC < 1 x10^9/L) with infection or fever; **Or** Grade 4 haematologic toxicities except lymphopenia (e.g. ANC <0.5 x10^9/L or Platelets < 25 x10^9/L)	1st occurrence	Interrupt venetoclax or consider continuing with GSCF support at clinician discretion. Once the toxicity has resolved to Grade 1 or baseline level, resume venetoclax at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider G-CSF if appropriate. Once toxicity has resolved resume at a reduced dose as per dose reduction table below. Larger dose reductions may occur at consultant discretion.
Rituximab		
Although rituximab is not myelosuppressive in monotherapy, caution should be exercised when considering treatment of patients with neutrophils < 1.5 x 10^9/L and/or platelet counts < 75 x 10^9/L as clinical experience in this population is limited.		

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non-haematological toxicities:

Venetoclax		
Any grade 3 or 4 non-haematological toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, resume venetoclax at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Once toxicity has resolved resume at a reduced dose as per dose reduction table below. Larger dose reductions may occur at consultant discretion.
Tumour 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 blood monitoring should be followed as per Table 2	
Drug Interactions	Dose modifications may be required due to drug interactions – see separate section 'Interactions'	
Rituximab		
Cytokine release syndrome	Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.	

Venetoclax Dose Reduction Steps

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 >2 weeks after completion of titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary.

References:

1. eMC UK Summary of Product Characteristics for Venetoclax, AbbVie Ltd, 31st Jan 2023 (last accessed 24/4/2023)
2. eMC UK Summary of Product Characteristics for Rituximab, Napp Pharmaceuticals, 02-July-2019 (last accessed 24/4/2023)
3. BNF available via: https://bnf.nice.org.uk/
4. Clatterbridge Cancer Centre, Rituximab Administration Guideline (V1.0)
5. NICE: TA561 Venetoclax with Rituximab for previously treated chronic lymphocytic leukaemia: Published date: Feb 2019
6. NICE: TA796 Venetoclax for treating chronic lymphocytic leukaemia: Published date: June 2022
7. Seymour J et al. Venetoclax-Rituximab in Relapsed or Refractory Chronic Lymphocytic Leukaemia. *New England Journal of Medicine* 2018; 378: 1107-120.

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
		RLUH protocol	
	2.1	**Aileen McCaughey**	New protocol
May 2023	3.0	**Jennifer Gibson**	**Transferred to new template. Updated indication criteria. Re-formatted information.**