VENETOCLAX

Treatment of CLL in the presence of 17p deletion or TP53 mutation in adult patients who have progressed on either a BTKI or a PI3ki (e.g. ibrutinib or idelalisib), ***or*** who have a contra-indication to both ibrutinib and idelalisib

Treatment of CLL in the absence of 17p deletion or TP53 mutation in adult patients who have progressed on or after chemo-immunotherapy, **and**
who have progressed on either a BTKI or a PI3ki (e.g. ibrutinib or idelalisib) *or* who have a contra-indication to both ibrutinib and idelalisib

Blueteq registration is required before treatment may start

Drugs/Dosage: **Venetoclax** start at 20mg po once daily for 7 days, then gradually increase over a period of 5 weeks, as below, until the recommended dose of 400mg once daily is reached.

Week	Venetoclax dose
1	20mg once daily
2	50mg once daily
3	100mg once daily
4	200mg once daily
5	400mg once daily

Frequency: once daily dosing continuously, until disease progression or unacceptable toxicity

Administration: Venetoclax is available as 10mg, 50mg and 100mg tablets.
The tablets should be swallowed whole with a meal at approximately the same time each day, ideally in the morning.
If a patient misses a dose by more than 8 hours, do not take the missed dose but resume the usual dosing schedule the following day.
If a patient vomits after a dose, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time the following day.
Grapefruit and its juice, Seville oranges and starfruit should be avoided while on venetoclax

Other Drugs: Ensure patient has a supply of loperamide for prn use, for diarrhoea
Allopurinol and hydration, as discussed below, for prevention of tumour lysis syndrome

Prevention of tumour lysis syndrome:

Tumour lysis syndrome (TLS) can occur rapidly; within 6-8 hours after the first dose, and at each dose increase.
Patients with any lymph node of diameter ≥5 cm or lymphocyte count ≥ 25 x 10^9/L are at greater risk of TLS when initiating venetoclax. CrCl < 80 ml/min further increases the risk.

Adequate hydration and an anti-hyperuricaemic agent are essential throughout the 5 week dose titration phase:

- **Allopurinol** should be started at least 48 - 72 hours before starting venetoclax, and should continue throughout the titration phase.
- Patients should be encouraged to drink plenty of water;
  specifically, **all** patients must have oral hydration of at least 1.5 - 2 litres of water per

day, starting 2 days before and on the days of dosing at initiation, and also starting 2 days before each subsequent dose increase.

N.B. Pre-existing hyperuricemia, hyperkalemia, hyperphosphatemia or hypocalcemia should be corrected before treatment starts.

Recommended TLS prophylaxis and monitoring, based on risk

Tumour Burden	Prophylaxis	TLS screen*
Low risk All lymph nodes < 5cm and lymphocyte count < 25 x 10^9/l	Oral hydration** (1.5 – 2 litres/day, as discussed above) *and* Allopurinol	***Outpatient*** Pre-dose, and also at +6 hours and +24 hours**** after first dose of 20mg and 50mg. Pre-dose only at subsequent dose escalations.
Medium risk Any lymph node 5cm to < 10 cm **or** lymphocyte count ≥ 25 x 10^9/l (If CrCl < 80ml/min, consider treating as high risk)	Oral hydration (1.5 – 2 litres/day, as discussed above) *and* consider additional IV hydration *and* Allopurinol	***Outpatient*** Pre-dose, and also at +6 hours and +24 hours**** after first dose of 20mg and 50mg. Pre-dose only at subsequent dose escalations. Consider hospitalisation if CrCl < 80ml/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High risk Any lymph node ≥ 10 cm **or** lymphocyte count ≥ 25 x 10^9/l, with any lymph node ≥ 5cm*** **or** lymphocyte count > 100 x 10^9/l	Oral hydration (1.5 – 2 litres as discussed above) *and* IV hydration (150-200ml/hr as tolerated) *and* Allopurinol (but consider rasburicase if baseline urate is elevated)	***In hospital at first dose of 20 mg and 50 mg*** TLS pre-dose, and then at +4 hrs, +8 hrs,+12 hrs and +24 hrs ***Outpatient at subsequent dose escalations*** TLS pre-dose, and also at +6 hours

* TLS screen = Urea, Creatinine, Uric acid / Urate, Phosphate, Potassium, Calcium
(see also Alliance TLS guidelines)
If TLS diagnosed at any time, see advice below, on page 4.

** Administer IV hydration if a patient cannot tolerate oral hydration

***These patients may have their tumour burden re-evaluated – and downgraded to medium risk - if most recent lymphocyte count falls to < 25, for dose increases above 50mg

****The next venetoclax dose should not be administered until the 24-hour blood chemistry results have been evaluated.

Main Toxicities: tumour lysis syndrome and electrolyte abnormalities; neutropenia, including febrile neutropenia; anaemia; diarrhoea or constipation;

Anti - emetics: mildly emetogenic

Regular Investigations:	FBC	weekly during titration, then every 4 weeks for 3 months, increasing to 3 monthly in stable, responding patients
	LFTs	every 4 weeks initially, then as clinically indicated
	U&Es	as part of TLS screen during initiation and titration, then every 4 weeks for 3 months, then every 3 months in stable, responding patients
	TLS screen	within 72 hrs before starting, and before each dose increase in the titration period. Also, after each dose escalation, as specified in the table above.

Comments: Live vaccines should not be administered during treatment and until B-cell recovery.

Interactions: Venetoclax is predominantly metabolized by CYP3A.

CYP3A inhibitors: Use of strong CYP3A4 inhibitors (e.g. clarithromycin, itraconazole, posaconazole, voriconazole) is contra-indicated during the first 5 weeks (i.e. the initiation and titration phase), due to increased risk of TLS.

Use of moderate CYP3A4 inhibitors (e.g. erythromycin, aprepitant, ciprofloxacin, diltiazem, fluconazole, verapamil, amiodarone) should also be avoided during the first 5 weeks.
If this is not possible, reduce the initiation and titration doses of venetoclax by at least 50% and monitor closely for TLS.

Once the dose-titration phase is completed and the patient is on a steady daily dose of venetoclax, the venetoclax dose should be reduced by 50% if a moderate CYP3A inhibitor is initiated, and by 75% when used concomitantly with strong CYP3A inhibitor. Patients should be monitored more closely for signs of toxicities and the dose may need to be further adjusted. Once the CYP3A inhibitor is discontinued, the venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed after 2 to 3 days.

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

CYP3A inducers: Concomitant use of venetoclax with strong CYP3A inducers (e.g. carbamazepine, phenytoin, rifampicin) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin) should be avoided, as this may result in lack of efficacy. Alternative treatments with less CYP3A induction should be considered. St. John's wort is also contraindicated.

Warfarin: Monitor INR closely in patients also on warfarin

Statins: If a patient is also on a statin, monitor closely for statin-related toxicity, as venetoclax may increase plasma levels of the statin.

Bile acid sequestrants: Venetoclax should be administered at least 4-6 hours after any bile acid sequestrant (e.g. cholestyramine)

Dose Modifications Dose modifications table for TLS and all other toxicities:

Dose at interruption	Restart dose (to continue for 1 week before increasing the dose)
400mg	300mg
300mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	10mg

- For patients who require a dosing interruption of > 1 week during the first 5 weeks of dose titration **or** > 2 weeks when at 400 mg od, TLS risk should be reassessed before re-starting, to determine if restarting at a reduced dose is necessary (e.g. all or some levels of the dose titration)
- For patients who require dose reduction to < 100 mg od for more than 2 weeks, consider discontinuing venetoclax.

Haematological Toxicity:	Neutrophils < 1.0 x 10^9/l with infection or fever, or Neutrophils < 0.5 x10^9/l or Platelets < 25 x 10^9/l	Withhold venetoclax. Once toxicity resolved to Grade 1 or baseline, venetoclax may be re-started at the same dose. If the toxicity recurs, and for any subsequent occurrences, follow the dose reduction guidelines in the table above, when restarting venetoclax. (A larger dose reduction may occur at prescriber's discretion)

Tumour lysis syndrome: If a +24-hour TLS screen is considered required, the next venetoclax dose should not be administered until the 24-hour blood chemistry results have been evaluated.
If a patient experiences blood chemistry changes suggestive of TLS, the following day's venetoclax dose should be withheld.
Electrolyte abnormalities should be corrected promptly - see Alliance TLS guidelines for treatment of established TLS.
If TLS resolves within 24-48 hours of last dose, venetoclax can be resumed at the same dose.
For clinical or laboratory TLS requiring > 48 hours to resolve, resume venetoclax at a reduced dose as the table above.
When resuming treatment after interruption due to TLS, the instructions above for prevention of TLS should again be followed.

Other Toxicities: Venetoclax should be withheld for any Grade 3 or 4 non-haematological toxicity.
Once resolved to Grade 1 or baseline, venetoclax may be re-started at the same dose.
If the toxicity recurs, and for any subsequent occurrences, follow the dose reduction guidelines in the table above when restarting venetoclax. (A larger dose reduction may occur at prescriber's discretion)

Renal Impairment: No venetoclax dose adjustment is required for CrCl ≥ 30ml/minute.
If CrCl < 80ml/minute, more intensive prophylaxis and monitoring may be required, to reduce the risk of TLS at initiation and during the dose-titration phase.
There are no data in patients with CrCl < 30ml/min or patients on dialysis; administer venetoclax to these patients only if the benefit outweighs the risk, and monitor patients closely for signs of toxicity, especially increased risk of TLS.

Hepatic Impairment: No dose adjustment required with mild or moderate hepatic impairment, but as a trend for increased adverse events was observed in patients with moderate hepatic impairment, these patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase.
Venetoclax is not recommended with severe hepatic impairment, as safety in this patient group has not been established.

Patient Information: No Macmillan/CRUK leaflet currently available.

References: Roberts, A et al; NEJM 2016; 374; 311 - 322

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