PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

# Ibrutinib and Venetoclax Chronic Lymphocytic Leukaemia (CLL)

PROTOCOL REF: MPHAIVCLL
(Version No. 1.0)

## Approved for use in:

- Untreated CLL or SLL (first line treatment) in patients who have symptomatic disease that requires systemic treatment. Note that patients must have been tested for 17p and TP53 mutations.

**Blueteq registration must be completed prior to initiation.**

## Dosage:

| Drug | Dose | | Route | Frequency |
|---|---|---|---|---|
| **Ibrutinib** | **420mg** | | Oral | Once daily from cycle 1 to cycle 15 |
| **Venetoclax** | **Week 1** | **20mg days 1 to 7*** | Oral | Once daily in **cycle 4 only** |
| | **Week 2** | **50mg days 8 to 14*** | | |
| | **Week 3** | **100mg days 15 to 21*** | | |
| | **Week 4** | **200mg days 22 to 28*** | | |
| **Venetoclax** | **400mg** | | Oral | Once daily from cycle 5 to 15 |

* If dose escalation is delayed, patients should continue their current dose of venetoclax 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 venetoclax until cycle 5.

**Cycle length: 28 days. Maximum 15 cycles (12 cycles of venetoclax only)**

## Administration:

- Ibrutinib and venetoclax should be taken at the same time every day with a glass of water. Venetoclax should be taken in the morning to facilitate laboratory monitoring.
- Venetoclax should be taken with a meal
- Ibrutinib and venetoclax tablets should be swallowed whole and not crushed, broken or chewed
- Ibrutinib must not be taken with grapefruit juice or Seville oranges. Venetoclax should not be taken with grapefruit juice, Seville oranges or starfruit (carambola).
- Ibrutinib should be held at least 3 to 7 days pre- and post-surgery depending upon the type of surgery and the risk of bleeding.
- Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take ibrutinib.
- 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.
- 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 of venetoclax should be taken on that day and the next dose should be taken at the normal time.

## Emetogenic risk:

Mildly emetogenic.

## Supportive treatments:

- Allopurinol 300mg once daily (first cycle and then start 2 to 3 days before venetoclax titration until titration is complete). Consider rasburicase 3mg IV prior to venetoclax titration if high risk of tumour lysis.
- Aciclovir 400mg twice daily (at clinician discretion)
- Co-trimoxazole 480mg daily
- Metoclopramide 10mg three times daily when required

## Interactions:

For more detailed interactions please refer to the SPC

### Venetoclax

**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 the table below. The venetoclax dose that was used prior to initiating the CYP3A inhibitor should be resumed 2-3 days after discontinuation of the inhibitor.

| Agent | 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 |

### Ibrutinib

| Agent | Dose Modification |
|---|---|
| **Warfarin / anticoagulants / antithrombotic agents** (aspirin / clopidogrel) | Warfarin is contraindicated due to bleeding risk. Other agents may be used with caution, but only be started under specialist supervision |
| **Strong / moderate CYP3A4 inducers** (St John's Wort, phenytoin, carbamazepine, rifampicin, phenobarbital) | Avoid concomitant use due to reduced exposure to ibrutinib. If the benefit outweighs the risk and a strong/moderate inducer must be used, monitor closely for lack of efficacy. Monitor when used with mild inducers. |
| **Strong / moderate CYP3A4 inhibitors** | Avoid concomitant use where possible<br>**Mild:** Monitor for toxicity<br>**Moderate:** Reduce ibrutinib to 280mg daily and monitor closely (fluconazole, erythromycin, aprepitant, ciprofloxacin, diltiazem, verapamil, amiodarone)<br>**Strong:** If used short term (7 day or less) consider interrupting ibrutinib therapy during duration of inhibitor use or reducing dose to 140mg daily and monitoring closely (ketoconazole, ritonavir, clarithromycin, itraconzole, voriconazole, posaconazole) |
| **Grapefruit / Sevile Oranges** | Avoid concomitant use |
| **Oral P-gp or BCRP substrates** with a narrow therapeutic range such as digoxin or methotrexate | Take at least 6 hours before or after ibrutinib. |
| **Rosuvastatin** | Monitor due to increased exposure to rosuvastatin |

## Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

| **Ibrutinib** |
|---|
| Atrial fibrillation, haemorrhage, leukostasis, splenic rupture, hepatotoxicity, hepatitis B, reactivation, hepatitis E, interstitial lung disease, cardiac failure, cerebrovascular accidents, tumour lysis syndrome, non-melanoma skin cancer, hypertension, haemophagocytic lymphohistiocytosis (HLH) |
| **Venetoclax** |
| Tumour lysis syndrome, neutropenia, thrombocytopenia, anaemia, lymphopenia, diarrhoea, respiratory tract infection, urinary tract infection, fatigue, electrolyte disturbance (hyperkalaemia, hyperphosphataemia, hypocalcaemia, hyperuricaemia – TLS), vomiting, nausea, constipation, raised creatinine. |

## 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<br><br>**OR**<br><br>lymphocyte count ≥25x $10^9$/L AND Lymph nodes ≥5cm | Inpatient only for the first 2 doses | Allopurinol 300mg once daily starting 3 days before the first dose of venetoclax and continue until day 7 of venetoclax 400mg (reduce to allopurinol 100mg OD if CrCl <20ml/min).<br><br>Consider 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. Omit allopurinol on the days of rasburicase |

| | | | |
|---|---|---|---|
| **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 |

## Investigations and treatment plan:

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 D1 | Cycle 4 D8 | Cycle 4 D15 | Cycle 4 D22 | Cycle 5 (ongoing) | Ongoing |
|---|---|---|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | | | | |
| Clinical Assessment | x | x | x | x | x | X | x | x | x | Every cycle |
| FBC | x | x | x | x | x | | | | x | Every cycle |
| U&E & LFTs & Magnesium | x | x | x | x | x | X | x | x | x | Every Cycle and as per TLS prevention |
| CrCl (Cockcroft and Gault) | x | x | x | X | x | X | x | x | x | Every cycle and as per TLS prevention |
| Hepatitis B screen | x | | | | | | | | | |
| CT scan** | x | | | | | | | | | At the end of treatment and if clinically indicated |
| ECG | | | | | | | | | | If clinically indicated |
| Blood pressure measurement | x | | | | | | | | | Repeat if clinically indicated |
| Respiratory Rate | | | | | | | | | | If clinically indicated |
| Weight recorded | x | | | | | | | | | Every cycle |
| Blood glucose | x | | | | | | | | | Repeat if clinically indicated |

## Dose Modifications and Toxicity Management:

## Haematological toxicity:

| Event | Occurrence | Action |
|---|---|---|
| ANC ≤ 0.5 x $10^9$/L<br><br>or<br><br>ANC is between 0.5 and 1.0 x $10^9$/L with infection or fever | 1st occurrence | The recommended advice is to interrupt venetoclax and ibrutinib HOWEVER at clinician discretion treatment can be continued with the addition of granulocyte-colony stimulating factor (G-CSF).<br><br>If treatment is interrupted then once the ANC has returned to > 1.5 x $10^9$/L or baseline venetoclax and ibrutinib therapy may be resumed at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax and ibrutinib.<br><br>Consider using G-CSF as clinically indicated.<br><br>Once the ANC has returned to > 1.5 x $10^9$/L or baseline follow dose reduction guidelines in table 2 when resuming treatment with venetoclax and in table 3 with ibrutinib.<br><br>A larger dose reduction may occur at the discretion of the physician |
| Platelets ≤ 25 x $10^9$/L | 1st occurrence | Interrupt venetoclax and ibrutinib<br><br>Once the platelets have returned to > 75 x $10^9$/L or baseline venetoclax and ibrutinib therapy may be resumed at the same dose. |
| | 2nd and subsequent occurrences | Interrupt venetoclax and ibrutinib<br><br>Once the platelets have returned to > 75 x $10^9$/L or baseline follow dose reduction guidelines in table 2 when resuming treatment with venetoclax and table 3 with ibrutinib.<br><br>A larger dose reduction may occur at the discretion of the physician |

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.

**Dose modification steps for venetoclax**

| 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 1 week before increasing the dose. | |

**Dose modification steps for ibrutinib**

| Toxicity occurrence | Dose modification after recovery |
|---|---|
| First | restart at 420 mg daily |
| Second | restart at 280 mg daily |
| Third | restart at 140 mg daily |
| Fourth | discontinue ibrutinib |

## Non- Haematological toxicity:

## Dosing in renal and hepatic impairment:

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

| Hepatic Dose Modifications | | |
|---|---|---|
| **Venetoclax** | Moderate | Monitor more closely for toxicity |
| | Severe | 50% dose. Monitor closely |
| **Ibrutinib** | For patients with mild liver impairment (Child-Pugh class A), the recommended dose is 280 mg daily. For patients with moderate liver impairment (Child-Pugh class B), the recommended dose is 140 mg daily. It is not recommended to administer ibrutinib to patients with severe hepatic impairment (Child-Pugh class C) | |

| **Venetoclax** | | |
|---|---|---|
| Any grade 3 or 4 non-haematological toxicities | 1st occurrence | Interrupt venetoclax.<br>Once the toxicity has resolved to Grade 1 or baseline level, resume venetoclax at the same dose. |
| | 2nd and subsequent occurrence | Interrupt venetoclax.<br>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.<br>If resolved within 24-48hours of the last dose, treatment can be resumed at the same dose.<br>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).<br>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' | |
| **Ibrutinib** | | |
| Ventricular tachyarrhythmia and sudden cardiac death. | Periodically monitor all patients for cardiac complications, including cardiac arrhythmia and failure. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an electrocardiogram (ECG) performed.<br>In patients with pre-existing atrial fibrillation requiring anticoagulant therapy, alternative treatment options to ibrutinib should be considered.<br>In patients who develop atrial fibrillation on therapy with ibrutinib a thorough assessment of the risk for thromboembolic disease should be undertaken. In patients at high risk and where alternatives to ibrutinib are non-suitable, tightly controlled treatment with anticoagulants should be considered.<br>Hypertension can occur with treatment – monitor blood pressure prior to each cycle and if blood pressure becomes raised above 140/90 refer to GP | |

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|---|---|
| | for blood pressure management and discuss with consultants as may also need ECHO. Patients with pre-existing hypertension should be referred to their GP prior to commencing therapy to ensure control is optimised. Patients with pre-existing hypertension should have an ECHO prior to starting treatment and if a reduced ejection fraction identified ibrutinib should be used with caution. |

## References:

1. https://www.medicines.org.uk/emc venetoclax. Accessed 09/05/23. Updated 23/01/23
2. https://www.medicines.org.uk/emc ibrutinib. Accessed 09/05/23. Updated 03/04/23.
3. NICE TA 10746 Ibrutinib with venetoclax for untreated chronic lymphocytic leukaemia [ID3860] May 2023

## Circulation/Dissemination

| | |
|---|---|
| Date added into Q-Pulse | For completion by DCM |
| Date document posted on the Intranet | For completion by DCM |

## Version History

| | | Author name and designation | Summary of main changes |
|---|---|---|---|
| | | | |
| June 2023 | V1.0 | **Aileen McCaughey HO Pharmacist** | New protocol |
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