LSCCN haematology protocols

IBRUTINIB + VENETOCLAX (I+V)
FLAIR trial Protocol Version 4

INDICATION: Patients with previously untreated chronic lymphocytic leukaemia

Prior to commencement

- See trial protocol version 4 for full eligibility and exclusion criteria. The list below is not complete.
- Patients must have a WHO performance status of 0, 1 or 2.
- Patients must have evidence of progressive CLL requiring therapy as defined by IWCLL criteria and not have received prior therapy
- Patients must have < 20% p53 deletion by FISH
- Check concomitant therapy prior to commencing ibrutinib and venetoclax. . Potential for multiple drug interactions
- Beware strong or moderate CYP3A inhibitors (e.g. ketoconazole). See protocol re moderate inhibitors such as itraconazole, voriconazole and clarithromycin. Beware QT prolonging agents. See protocol.
- Venetoclax can be associated with neutropenia, lymphopenia and tumour lysis syndrome
- Ibrutinib can be associated with bruising and bleeding. Patients requiring anticoagulation for greater than 6 months or requiring dual anti-platelet therapy are not eligible for trial entry. Ibrutinib should be held 3 – 7 days pre and post surgery. Ibrutinib can be associated with exacerbation of lymphocytosis at first but monitoring is all that is usually required. See protocol.
- Liaise with trial team re investigations which include FBC, HOP, coagulation screen, β2 microglobulin, HIV & hepatitis screen, immunoglobulins and serum electrophoresis, p53 deletion, bone marrow aspirate & biopsy and CT scan of thorax, abdomen and pelvis

Prior to each cycle

- Medical review of fitness for chemotherapy – exclude active infection, major changes in organ function
- Check tumour lysis bloods prior to commencing venetoclax
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Dosing for weeks 1 - 8 is as below:

Ibrutinib	420 mg	oral	daily

Dosing for weeks 9 - 12:

Ibrutinib	420mg	oral	daily
+			
Venetoclax	**week 9** 20mg oral daily, **week10** 50mg daily, **week 11** 100mg daily, **week 12** 200mg daily,		

Dosing from week 13 onwards:

Ibrutinib	420mg	oral	daily
+			
Venetoclax	400mg	oral	daily

Continue therapy until 6 years post randomisation, disease progression, or the MRD negative stopping criteria is reached. Always consult trial protocol. Take venetoclax on a full stomach. Venetoclax must be stored between 15 and 25 ^{o}C (i.e. not in a fridge).

Anti-emetic prophylaxis	Metoclopramide
Other medications	Consider allopurinol 300mg od for 28 days when starting ibrutinib if bulky disease Tumour lysis prophylaxis essential to start 3 days prior to venetoclax Allopurinol 300mg od and increase oral hydration to commence at least 72 hours prior to venetoclax, unless high tumour burden present when use rasburicase 200 ug/kg for up to 7 days as per local policy pus IV fluid support Co-trimoxazole 480mg daily

Venetoclax toxicities

Venetoclax (previously known as ABT-199) is a first in class BCL-2 inhibitor helping to induce apoptosis in CLL cells

- Venetoclax can lead to lymphopenia and neutropenia. GCSF support may be required.
- Tumour lysis has been seen in patients with CLL treated with venetoclax but so far has not been reported in phase 1 trials in patients with myeloma when combined with bortezomib and dexamethasone. Nevertheless consider TLS prophylaxis in myeloma patients in this study with high tumour burden, rapidly increasing M-protein, high proliferative activity, plasmablastic morphology, unfavourable karyotype or compromised renal function (CrCl < 50 ml/min. All subjects require oral hydration prior to therapy.

Ibrutinib Toxicities

Ibrutinib is a first in class Bruton's tyrosine kinase inhibitor helping to reduce proliferation of CLL cells via B cell receptor signaling pathway inhibition.

- Diarrhoea
- Fatigue
- Bruising and bleeding
- Cytopenias
- Exacerbation of lymphocytosis during initial therapy
- Other GI toxicity - Nausea, vomiting, constipation, abdominal pain, anorexia

Dose modifications or Delays for Venetoclax Toxicities (*<u>Consult protocol – below is a guide only</u>)

Venetoclax Dose Levels

Starting dose level	400 mg daily
Dose level -1	300 mg daily
Dose level -2	200 mg daily
Dose level -3	100 mg daily

If venetoclax at dose level -3 is still not tolerable then no further reductions will be allowed and venetoclax / placebo should be discontinued.	

Haematological and non-haematological toxicities related to venetoclax

Grade 3 or grade 4 neutropenia with infection or fever, or grade 4 haematological toxicities (except for lymphopenia) or grade 3 or 4 non-haematological events:	• GCSF may be given for neutropenia • Interrupt venetoclax / placebo for the first episode and resume at same dose once toxicity resolved to grade 1 or less • For subsequent episodes interrupt venetoclax / placebo, consider using GCSF and dose reduce as per dose level guidance above
Blood chemistry changes or symptoms or TLS:	• Withhold the next day's dose. If resolved within 24-48 hours of last dose then resume at the same dose • For any blood chemistry changes requiring more than 48 hours to resolve then resume at reduced dose as per dose level guidance above • For any events of clinical TLS resume at reduced dose following resolution

Dose modifications or Delays for IbrutinibToxicities (*<u>Consult protocol – below is a guide only</u>)

Ibrutinib Dose Levels

Starting dose level	420 mg daily
Dose level -1	Restart 420 mg daily
Dose level -2	Restart at 280 mg daily
Dose level -3	Restart at 140 mg daily
If ibrutinib at dose level -3 is still not tolerable then no further reductions will be allowed and ibrutinib should be discontinued.	

Dose Modification for Thrombocytopenia (unless due to marrow infiltration)

Grade 4 thrombocytopenia (less than 25) withhold Ibrutinib. Once the thrombocytopenia has resolved to grade 1(>75) or baseline (recovery) Ibrutinib treatment can be reinitiated at the starting dose. If toxicity recurs, reduce dose by one capsule (140mg per day). A second dose reduction by 140mg per day may be considered as needed. If toxicity persists or recurs following two dose reductions, discontinue Ibrutinib.

Recommended Dose Modifications for thrombocytopenia are described below:

Toxicity Occurrence	CLL Dose Modification After recovery Starting dose = 420mg daily
First	Restart at 420mg daily
Second	Restart at 280mg daily
Third	Restart at 140mg daily
Fourth	Discontinue Ibrutinib

Consideration can be given to the use of GCSF, erythropoietin and blood transfusions.

Dose Modifications for Hepatic Impairment

Mild Liver Impairment (Child-Pugh Class A)	280mg od
Moderate Liver Impairment (Child-Pugh Class B)	140mg od
Severe Liver Impairment (Child-Pugh Class C)	Not recommended

Special Considerations:

1. Lymphocytosis compartmental shift well recognised with Ibrutinib therapy.
   Upon initiation of treatment with ibrutinib, a transient phase of increase in lymphocyte counts (i.e., ≥50% increase from baseline and above absolute count 5,000/μL) often associated with reduction of lymphadenopathy was observed in most patients (75%) with relapsed/refractory CLL/SLL. This effect has also been observed in 33% of patients in the MCL study. This observed lymphocytosis is a pharmacodynamic effect and should not be considered progressive disease in the absence of other clinical findings, occurs during the first few weeks (median time 1.1 weeks) of ibrutinib therapy and typically resolves within a median of 18.7 weeks, while on treatment.
2 Patients with lymphocyte count greater than 400,000 with CLL should be very closely monitored for signs of leukostasis
3 Administer supportive care including hydration and/or leukopheresis as indicated.

Pregnancy

Ibrutinib should not be used in pregnancy. It is not known whether ibrutinib or its metabolites are excreted in human milk. A risk assessment should be made whether to discontinue breast feeding or discontinue Ibrutinib, taking into account the importance of the Ibrutinib to the mother.

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References: FLAIR trial Protocol version 4

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