Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

IBRUTINIB-VENETOCLAX

Regimen

CLL – Ibrutinib & Venetoclax

Indication

- Ibrutinib plus Venetoclax is recommended as an option for untreated chronic lymphocytic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in adults.
- All the criteria as described in the appropriate Blueteq form are met and an application for use has been approved.

Toxicity

Drug	Adverse Effect
Ibrutinib	Diarrhoea, fatigue, arthralgia, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea, pyrexia, neutropenia, thrombocytopenia, constipation, atrial fibrillation, ventricular tachycardia, hypertension, onycholclasis
Venetoclax	Upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, electrolyte disturbances, tumour lysis syndrome (TLS), gastrointestinal disturbance, raised blood creatinine, fatigue.

The adverse effects listed are no exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

- Confirm immunophenotype or histology prior to administration of therapy.
- Record: stage and TLS risk - CT scan (neck, chest, abdomen, and pelvis), B symptoms, cytopenias, clinical extent of disease.
- Blood tests - FBC, DAT, U&Es, LDH, G6PD (in at risk population), urate, calcium, magnesium, creatinine, phosphate, LFTs, glucose, IGs, β2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, HIV 1+2 after consent.
- FBC, U+Es, LFTs before each cycle, extending to 3 monthly from cycle 5 onward for clinically stable patients.
- Genetic tests for 17p deletion, TP53 mutation, and *IGHV* mutation status.
- Urine pregnancy test – required before first cycle of chemotherapy in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.

- ECG +/- ECHO and baseline BP in all patients with a cardiac history or at risk of cardiac complications (hypertension, smokers, diabetes).
- Record height and weight & performance status (ECOG).
- Consent and counselling - ensure patient has received adequate verbal and written information regarding their disease, treatment, and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
- Treatment should be agreed in the relevant MDT.
- Document baseline and pre cycle 4 tumour lysis syndrome (TLS) risk in Aria journal.
- Patients at high baseline TLS risk due to tumour bulk should be re-assessed with further CT imaging before cycle 4.
- Use caution initiating with severe thrombocytopenia and consider platelet support if needed.

Dose Modifications

Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only. Dose adjustment may be necessary for other toxicities as well.

If a patient discontinues either ibrutinib or venetoclax for reasons other than disease progression, the other drug should be continued, unless otherwise indicated by the treating consultant (up to max. 15 cycles of ibrutinib and max. 12 cycles of venetoclax).

Haematological

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if patient symptomatic of anaemia or has haemoglobin of less than 8g/dL (80g/L).

Haematological Toxicity	**Occurrence**	**Ibrutinib**	**Venetoclax**
Grade 3 neutropenia (ANC < 1 x 10^9 /L with infection or fever) **or Grade 4 haematologic toxicities** (ANC < 0.5 x 10^9 /L or plts <25 x 10^9 /L except lymphopenia (e.g., ANC < 25 x 10^9 /L)	1st occurrence	Interrupt ibrutinib. Once toxicity has resolved to grade 1 or baseline (recovery), reinitiate ibrutinib at the starting dose.	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose if stopped.
	2nd and subsequent occurrence	Reduce dose by 140mg. If toxicities persist or recur following two dose reductions, discontinue ibrutinib.	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Once the toxicity has resolved, resume treatment at next dose reduction level (see Table 1 below for dose reduction guideline)

[ANC = Absolute Neutrophil Count]

Hepatic Impairment

Liver Function	Ibrutinib	Venetoclax
Child Pugh A	280mg once a day	No dose adjustment required
Child Pugh B	140mg once a day	
Child Pugh C	Not recommended	At least 50% dose reduction

Patients with moderate or severe hepatic impairment (Child Pugh B or C) should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase.

Renal Impairment

Renal function	Ibrutinib	Venetoclax
CrCl < 80 mL/min but >30 mL/min	No dose adjustment necessary	Increased risk of TLS. More intensive TLS prophylaxis and increased TLS monitoring may be recommended.
CrCl < 30 mL/min	No data available. Use only if benefit outweighs risks. Monitor closely for signs of toxicity due to increased risk of TLS.	

Non-haematological toxicities

Non-haematological toxicities	Occurrence	Venetoclax
Other grade 3 or 4 non-haematological toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to Grade 1 or baseline level, it may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guideline in table 1 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the clinician.

Tumour Lysis Syndrome (TLS)

Tumour Lysis Syndrome	Venetoclax	
Blood chemistry changes or symptoms suggestive of TLS	Any occurrence	Withhold the next day's dose. If resolved within 24–48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose and discuss with consultant. If rapid dose escalation is required due to progressive disease, patients must be admitted for IV hydration and management of TLS.
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 1 below for dose reduction guideline).

Regimen

28-day cycle - 15 cycles will be set in Aria

TLS RISK ASSESSMENT – DOCUMENT in ARIA				
CYCLES 1–3				
Drug	**Days**	**Dose**	**Route**	**Administration details**
IBRUTINIB	1–28	420mg once daily (OD)	PO	Take at approximately the same time each day. Swallow tablets whole with water.

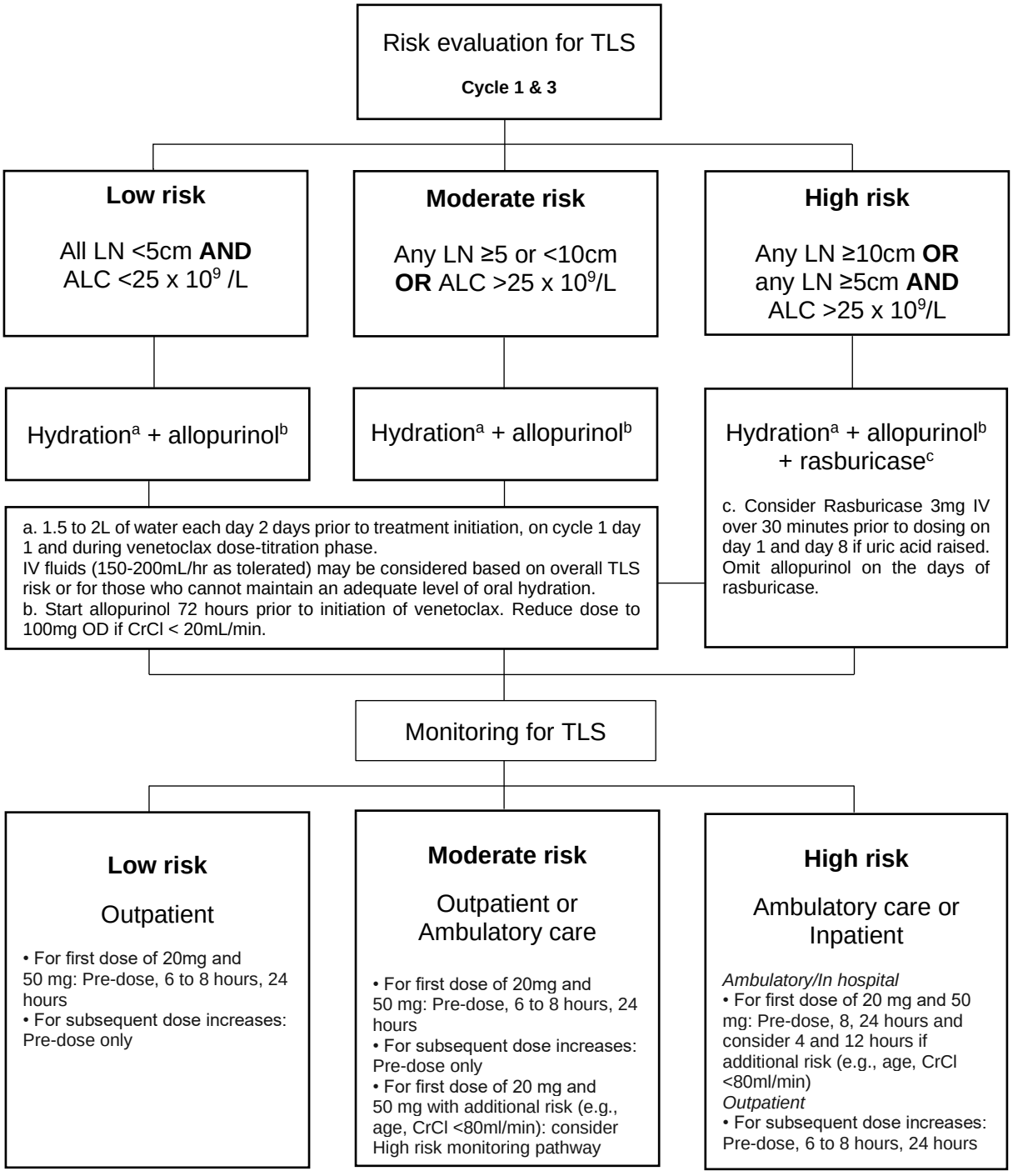
TLS RISK ASSESSMENT – DOCUMENT in ARIA				
CYCLE 4				
Drug	**Days**	**Dose**	**Route**	**Administration details**
IBRUTINIB	1–28	420mg OD	PO	Take at approximately the same time each day. Swallow whole with water.
VENETOCLAX	1-7	20mg OD	PO	Take in the morning, with food. Swallow tablets whole with water.
	8-14	50mg OD		
	15-21	100mg OD		
	22-28	200mg OD		

CYCLE 5 onwards				
Drug	**Days**	**Dose**	**Route**	**Administration details**
IBRUTINIB	1–28	420mg OD	PO	Take at approximately the same time each day. Swallow whole with water.
VENETOCLAX	1-28	400mg OD	PO	Take in the morning, with food. Swallow tablets whole with water.

Dose information

- Ibrutinib tablets are available as 140mg, 280mg and 420mg film-coated tablets.
- Missed doses for ibrutinib should be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra tablets to make up the missed dose.
- Venetoclax is available as 10mg, 50mg and 100mg film-coated tablets.
- Missed doses of venetoclax should be taken within 8 hours of the usual taking time, otherwise it should be omitted, and the usual dosing schedule resumed the following day. For patients who have had a dosing interruption lasting more than 1 week during the first 5 weeks of dose-titration or more than 2 weeks after completing the dose-titration phase, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose-titration; see table 1 below).
- Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

TLS Risk assessment



[TLS=Tumour Lysis Syndrome, LN=Lymph Node, ALC=Absolute Lymphocyte Count]

- **Cycle 1**: Low, moderate and high-risk TLS patients: TLS management usually only requires oral hydration and allopurinol - **TLS bloods monitoring is not required for the majority of patients**, unless specifically indicated otherwise by treating clinician.

- TLS risk reduces following initial 3 cycles of ibrutinib lead-in therapy. Based on the current clinical data, <2% patients remain in high-risk category at the start of cycle 4.

Table 1: Venetoclax dose modifications for TLS and other toxicities

Dose at interruption	Restarting dose[a]
400mg	300mg
300mg	200mg
200mg	100mg
100mg	50mg
50mg	20mg
20mg	10mg

[a]The modified dose should be continued for 1 week before increasing the dose.

Additional Information

- The National Patient Safety Alert on Oral Systemic Anti-Cancer Therapy (NPSA/2008/RRR001) must be followed in relation to ibrutinib and venetoclax.
- It must be made clear to all staff, including those in the community, that venetoclax and ibrutinib should only be prescribed under the supervision of a consultant haematologist or oncologist.
- Cases of ventricular tachyarrhythmia have been reported. Temporarily discontinue ibrutinib in patients who develop symptoms suggestive of ventricular arrhythmia, including palpitations, chest pain, dyspnoea, dizziness, or fainting, and assess benefit-risk before restarting therapy.
- Consider change of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blocker (ARBs) to alternative treatments given possible risk of sudden death.
- Ibrutinib should be withheld at least 3 to 7 days pre- and post-surgery, depending upon the type of surgery and the risk of bleeding. There is little data around venetoclax and surgery. It may be reasonable to stop venetoclax with ibrutinib.
- Ibrutinib and venetoclax are primarily metabolized by Cytochrome P450 3A4 (CYP3A). Please refer to Summary of Product Characteristics (SmPC) to check relevant drug interactions (i.e., CYP3A inhibitors/inducers and P-gp/BCRP substrates and inhibitors) and recommended dose modifications.
- Co-administration of grapefruit and grapefruit juice, Seville oranges and starfruit (carambola), should be avoided during treatment with ibrutinib and venetoclax.

Additional Therapy

- Antiemetics

  As take-home medication

  - metoclopramide 10mg three times a day when required oral for Cycle 1 only

- Patients should be adequately hydrated during the venetoclax dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L of water daily, 2 days prior to and the days of dosing at initiation and each subsequent dose

increase. Intravenous fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration.

- Allopurinol 300mg once a day oral for 7 days (ibrutinib initiation in Cycle 1). Then it should start 72 hours prior to the initiation of venetoclax in Cycle 4 and for 5 weeks continuously including the first week of Cycle 5 unless otherwise indicated in TLS risk assessment.

- Anti-infective prophylaxis for duration of treatment:

    - Aciclovir 400mg twice a day oral
    - Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday only

- Oral loperamide 4mg at the onset of diarrhoea followed by 2-4mg after each each loose stool (maximum 16mg/24 hours).

- Consider growth factors at the discretion of treating clinician, when clinically indicated according to local formulary choice. For example:

    - Filgrastim or bioequivalent 30 million units once a day subcutaneous
    - Lenograstim or bioequivalent 33.6 million units once a day subcutaneous
    - Pegfilgrastim or bioequivalent 6mg once only subcutaneous

References

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3. MHRA. Ibrutinib (Imbruvica▼): reports of ventricular tachyarrhythmia; risk of hepatitis B reactivation and of opportunistic infections. Drug Safety Update volume 11 issue 1, August 2017: 1. Published 15/08/2017
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6. Kater AP, Owen C, Moreno C, et al. Fixed-duration ibrutinib-venetoclax in patients with chronic lymphocytic leukemia and comorbidities. N Engl J Med. Published online May 13, 2022. doi:10.1056/EVIDoa2200006 7.
7. Tam S, et al. Fixed-duration ibrutinib plus venetoclax for first-line treatment of CLL: primary analysis of the CAPTIVATE FD cohort. Blood. 2022;139(22), 3278–3289. 8.
8. Moreno C, et al. Fixed-duration (FD) Ibrutinib + Venetoclax For First-line Treatment of Chronic Lymphocytic Leukemia(CLL)/Small Lymphocytic Lymphoma (SLL): 3-year Follow-up From The Phase 2 Captivate Study FD Cohort. 2022; EHA2022 357531; P669.
9. Munir T, et al. Sudden or cardiac deaths on ibrutinib-based therapy were associated with a prior history or hypertension or cardiac disease and the use of ACE-inhibitors at study entry: analysis from the Phase lll NCRI FLAIR trial. Blood. 2021; 138(1), P2636.
10. NSSG Chemotherapy Protocol (oxford-haematology.org.uk) With thanks to Dr Toby Eyre and OUH pharmacy team; used and altered with permission.

REGIMEN SUMMARY

Ibrutinib – Venetoclax

Take Home Medicines

Cycle 1

Day 1

1. Warning – TLS Assessment and Prevention
   Administration Instructions
   There is a risk of tumour lysis syndrome in CLL patients having this regimen. Ensure the patient has been assessed for TLS risk and documented in Journal on Aria. Please ensure the appropriate prophylaxis are prescribed and arrangements are in place to monitor the patient.

   For patients with high TLS risk, please prescribe rasburicase 3mg intravenous infusion in 50mL sodium chloride 0.9% over 30 minutes.

2. Warning – Check hydration status
   Administration Instructions
   Patient should be adequately hydrated prior to starting treatment with ibrutinib and venetoclax and venetoclax dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before, on the day of the first dose, and every time the dose is increased. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

3. Ibrutinib 420mg once a day for 28 days oral
   Administration instructions
   Oral Systemic Anti-Cancer Therapy

   Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

   Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

4. Allopurinol 300mg once a day for 7 days oral

5. Aciclovir 400mg twice a day for 28 days oral

6. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
   Administration instructions
   Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

7. Metoclopramide 10mg three times a day when required for the relief of nausea oral
   Administration instructions
   Please supply 28 tablets or nearest equivalent original pack size

8. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24hours)

Cycle 2

Day 1

9. Ibrutinib 420mg once a day for 28 days oral
   Administration instructions
   Oral Systemic Anti-Cancer Therapy

   Ibrutinib tablets should be swallowed whole with water at approximately the same time each day

   Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

10. Aciclovir 400mg twice a day for 28 days oral

11. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
    Administration instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

12. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24 hours)

Cycle 3

Day 1

13. Ibrutinib 420mg once a day for 28 days oral
    Administration instructions
    Oral Systemic Anti-Cancer Therapy

    Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

    Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

14. Allopurinol 300mg once a day for 3 days oral
    Administration instruction
    Start 72 hours prior to the first dose of venetoclax.

15. Aciclovir 400mg twice a day for 28 days oral

16. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
    Administration instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

17. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24 hours)

Cycle 4

Day 1

18. Warning – TLS Assessment and Prevention
    Administration Instructions
    There is a risk of tumour lysis syndrome in CLL patients having this regimen. Ensure the patient has been assessed for TLS risk and documented in Journal on Aria. Please ensure the appropriate prophylaxis are prescribed and arrangements are in place to monitor the patient.

    For patients with high TLS risk, please prescribe rasburicase 3mg intravenous infusion in 50mL sodium chloride 0.9% over 30 minutes.

19. Warning – Check hydration status
    Administration Instructions
    Patient should be adequately hydrated prior to starting treatment with ibrutinib and venetoclax and venetoclax dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before, on the day of the first day, and every time dose is increased. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

20. Ibrutinib 420mg once daily for 28 days oral

Administration instructions
Oral Systemic Anti-Cancer Therapy

Ibrutinib tablets should be swallowed whole with water at approximately the same day each day.

Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

21. Venetoclax 20mg once a day for 7 days oral
    Administration instructions
    Take in the morning with or just after food, or a meal. Swallow whole with a full glass of water.

    Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

22. Aciclovir 400mg twice a day for 28 days oral

23. Allopurinol 300mg once a day for 28 days oral

24. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
    Administration instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

25. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24 hours)

Day 8

26. Warning – Dose escalation and hydration
    Administration instructions
    Please note this dose has been automatically escalated by ARIA. Please check the dose is appropriate for the patient.

    Patient should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before, on the day of the first dose, and each subsequent dose increases. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

27. Venetoclax 50mg once a day for 7 days oral
    Administration instructions
    Take in the morning with or after food. Swallow whole with a full glass of water.

    Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

Day 15

28. Warning – Dose escalation and hydration
    Administration instructions
    Please note this dose has been automatically escalated by ARIA. Please check the dose is appropriate for the patient.

    Patient should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before, on the day of the first dose, and each subsequent dose increases. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

29. Venetoclax 100mg once a day for 7 days oral
    Administration instructions
    Take in the morning with or after food. Swallow whole with a full glass of water.

    Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

Day 22

30. Warning – Dose escalation and hydration

Administration instructions
Please note this dose has been automatically escalated by ARIA. Please check the dose is appropriate for the patient.

Patient should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before, on the day of the first dose, and each subsequent dose increases. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

31. Venetoclax 200mg once a day for 7 days oral
    Administration instructions
    Take in the morning with or after food. Swallow whole with a full glass of water.

    Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

Cycle 5

Day 1

32. Warning - Dose escalation and hydration
    Administration instructions
    Please note this dose has been automatically escalated by ARIA. Please check the dose is appropriate for the patient.

    Patient should be adequately hydrated during the dose-titration phase to reduce the risk of TLS. Patients should be instructed to drink 1.5 to 2L (approximately 6-8 glasses) of water daily 2 days before and on the day of the first dose, and each subsequent dose increases. Intravenous fluid (150-200ml/hr as tolerated) should be administered as indicated based on overall risk of TLS of for those who cannot maintain an adequate level of oral hydration.

33. Ibrutinib 420mg once a day for 28 days oral
    Administration instructions
    Oral Systemic Anti-Cancer Therapy

    Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

    Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

34. Venetoclax 400mg once a day for 28 days oral
    Administration instructions
    Take in the morning with or after food. Swallow whole with a full glass of water.

    Venetoclax should be dispensed 24 hours prior to the administration date of each dose escalation.

35. Aciclovir 400mg twice a day for 28 days oral

36. Allopurinol 300mg once a day for 7 days oral

37. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
    Administration instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

38. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24 hours).

Cycle 6 onwards

Day 1

39. Ibrutinib 420mg once a day for 28 days oral
    Administration instructions
    Oral Systemic Anti-Cancer Therapy

Ibrutinib tablets should be swallowed whole with water at approximately the same time each day.

Avoid grapefruit and grapefruit juice, and Seville oranges while on ibrutinib. Always check for drug interactions.

40. Venetoclax 400mg once a day for 28 days oral
    Administration instructions
    Take in the morning with or after food. Swallow whole with a full glass of water.

41. Aciclovir 400mg twice a day for 28 days oral

42. Co-trimoxazole 960mg once a day on Monday, Wednesday, and Friday for 28 days oral
    Administration instructions
    Co-trimoxazole 960mg once a day on Mondays, Wednesdays, and Fridays. This may be dispensed as 480mg twice a day on Mondays, Wednesdays, and Fridays according to local practice.

43. Loperamide 4mg at the onset of diarrhoea followed by 2mg after each loose stool oral (maximum 16mg/ 24 hours)

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	September 2023	None	Alexandre Guedes Pharmacist Aram Shortland Pharmacist	Dr David Dutton Consultant haematologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
Isle of Wight NHS Trust
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.