Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

Venetoclax- Obinutuzumab (including rapid infusion pathway)

Regimen

- CLL – Venetoclax & Obinutuzumab

Indication

- Chronic lymphatic leukaemia (CLL) or small lymphocytic lymphoma (SLL) in adult patients where;
    - There is 17p deletion or TP53 mutation
    - There is no 17p deletion or TP53 mutation, and fludarabine, cyclophosphamide and rituximab (FCR) or bendamustine and rituximab (BR) is unsuitable
    - There is no 17p deletion or TP53 mutation and FCR or BR is suitable
- All the criteria as described in the appropriate Blueteq form are met and an application for use has been approved.

Toxicity

Drug	Adverse Effect
Obinutuzumab	Infusion related reactions, progressive multifocal leukoencephalopathy, cardiac toxicity, thrombocytopenia, neutropenia, tumour lysis syndrome (TLS).
Venetoclax	Upper respiratory tract infection, neutropenia, anaemia, hyperphosphataemia, electrolyte disturbances, TLS, gastrointestinal disturbance, raised blood creatinine, fatigue.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Pre-assessment and monitoring

- Confirm immunophenotype or histology prior to administration of therapy.
- Record stage of disease, TLS risk - CT scan (neck, chest, abdomen, and pelvis), hepatitis B symptoms, cytopenias and clinical extent of disease.
- Blood tests - FBC, U&Es and LFTs before each cycle. DAT, LDH, G6PD (in at risk population), urate, calcium, magnesium, creatinine, phosphate, glucose, IGs, β2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, HIV 1+2 after consent.
- Refer to TLS risk assessment flowchart for frequency of monitoring bloods when initiating venetoclax.
- Genetic tests for 17p deletion, TP53 mutation, and *IGHV* mutation status.
- Urine pregnancy test is 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 blood pressure in all patients with a cardiac history or at risk of cardiac complications (i.e. hypertension, smoking, diabetes).
- Record height and weight & ECOG performance status.
- 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.
- For patients whose obinutuzumab can be administered as a short duration infusion (approximately 90 minutes) from cycle 2 onwards, risk of infusion-related reactions should be discussed and documented in the consent form. Note short duration infusion is off licence for CLL.
- Treatment should be agreed in the relevant MDT.
- Document tumour lysis syndrome (TLS) risk at baseline and before initiation of venetoclax in Aria journal.
- Patients at high baseline TLS risk due to tumour bulk should be re-assessed with further CT imaging before cycle 2.
- Use caution initiating with severe thrombocytopenia and consider platelet support if needed.

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well. Please discuss all dose reductions/delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

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

Haematological Toxicity	Obinutuzumab	Venetoclax
Grade 3 or 4 neutropenia (Absolute neutrophil count (ANC) < 1 x 10^9 /L with infection or fever), **or Grade 4 haematological toxicities** (ANC < 0.5 x 10^9 /L or PLTS <25 x 10^9 /L, except lymphopenia (e.g., ANC < 25 x 109 /L)) or thrombocytopenic bleeding that delays treatment by less than 4 weeks	Hold until the above parameters are met then restart at usual dose.	*1st occurrence* - Interrupt venetoclax. Consider using *G-CSF (including pegylated G-CSF) as clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax may be resumed at the same dose if stopped. *2nd and subsequent occurrence* - Interrupt venetoclax. Consider using *G-CSF (including pegylated G-CSF) as clinically indicated. Follow dose modification guide in Table 1 below when resuming venetoclax after resolution.
Grade 3 or 4 haematological toxicity that delays treatment by more than 4 weeks	Discontinue	

[ANC = Absolute Neutrophil Count]
**If asymptomatic, use G-CSF to support moderate or severe neutropenia - i) GSCF once weekly and titrate up as needed or ii) pegylated GCSF once monthly.*

Hepatic Impairment

Liver Function	Obinutuzumab	Venetoclax
Child-Pugh A	The safety and efficacy have not been established; no specific dose recommendations can be made	No dose adjustment required
Child-Pugh B		
Child-Pugh C		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 venetoclax dose titration phase.

Renal Impairment

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression.

Safety in patients with severe renal impairment or on dialysis has not been established for venetoclax, and a recommended dose for these patients has not been determined.

Renal impairment	Obinutuzumab	Venetoclax
Mild to moderate	No dose adjustment necessary for CrCl 30-89 mL/min	Increased risk of TLS if CrCl < 80m/min. More intensive TLS prophylaxis and monitoring at initiation and during the dose titration phase.
Severe	No safety and efficacy data available for CrCl < 30mL/min	Use only if benefit outweighs risks for CrCl 15-29 mL/min. Monitor closely for signs of toxicity due to increased risk of TLS.

Other 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.

Non-haematological toxicity	Obinutuzumab
Grade 2 or 3 related organ/non- haematological toxicity	Hold until less than or equal to grade 1
Grade 2 non-haematological toxicity that delays treatment by more than 4 weeks	Discontinue
Grade 4 related organ/non- haematological toxicity, severe haemorrhage, severe skin reaction, pneumonitis, severe arrhythmias or other severe cardiovascular events	Discontinue
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue

- *Progressive Multifocal Leukoencephalopathy*

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre-existing neurologic manifestations. The patient should be referred to a neurologist for the evaluation and treatment of PML.

- *Infusion related reactions (IRRs)*

Obinutuzumab administration is associated with infusion related reactions, particularly during the first cycle.

Most frequently reported symptoms associated with an infusion related reaction were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation have also been reported.

Anaphylaxis has been reported during administration of obinutuzumab. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued.

Infusion related reactions should be treated as described in the table below.

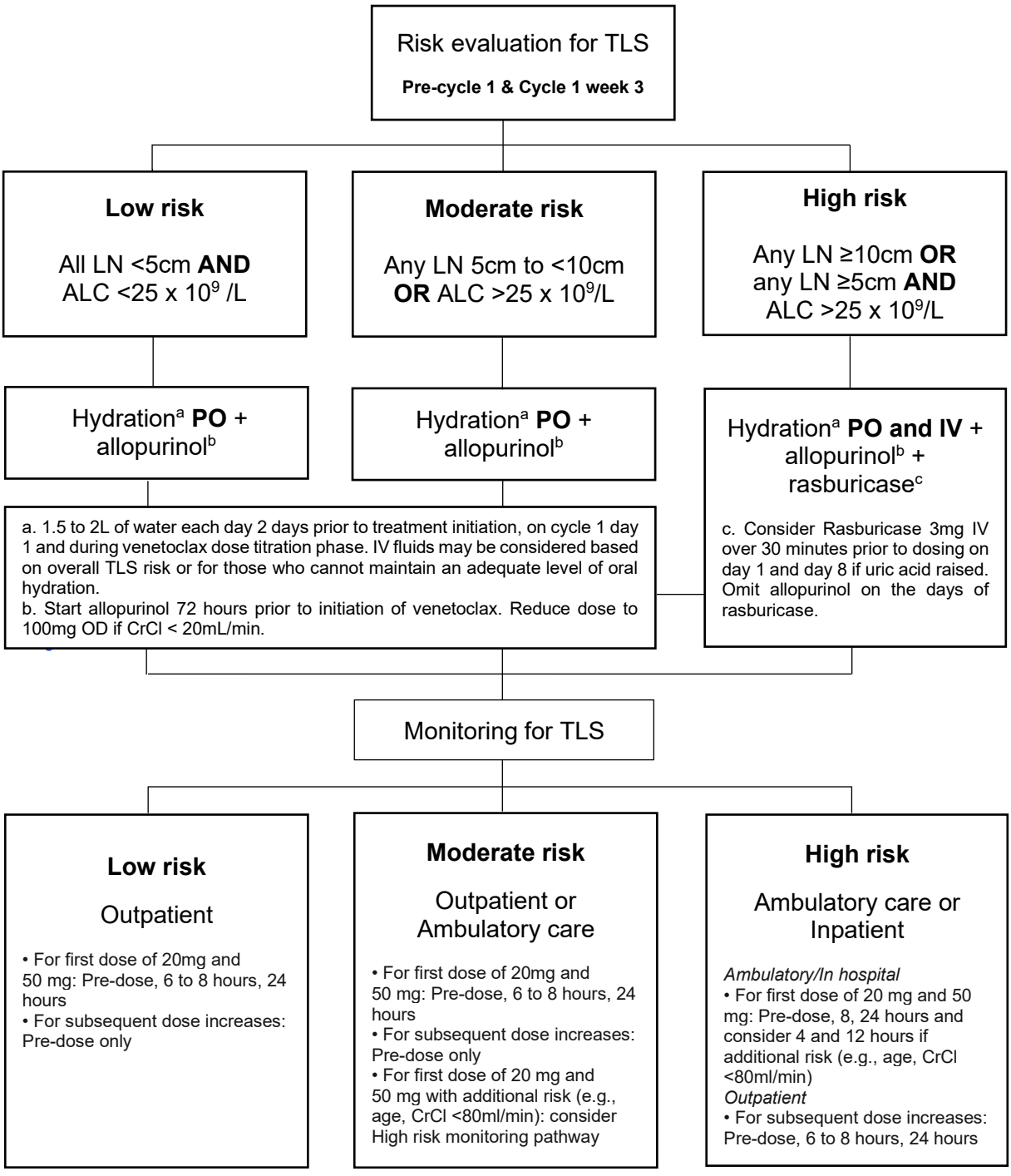
Toxicity Grade	**Obinutuzumab**
Grade 1 or 2 (mild and moderate)	Reduce the infusion rate by half or stop and treat symptoms, Restart the infusion once symptoms have resolved. Escalated infusion rate as tolerated at increments appropriate for treatment
Grade 3 (severe prolonged or recurrent symptoms that require hospitalisation)	Infusion must be stopped temporarily, and symptoms treated. Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred). If the patient dose not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose. The infusion must be stopped, and therapy permanently discontinued if the patient experiences a second occurrence of a severe (Grade 3) IRR.
Grade 4 (life-threatening)	Infusion must be stopped, and therapy must be permanently discontinued.

- *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 guidelines).

Both obinutuzumab and venetoclax carry the risk of TLS. Debulking with obinutuzumab before starting venetoclax is likely to reduce the TLS risk, therefore it is recommended to assess TLS risk before the first obinutuzumab dose and re-assess after 3 weeks, before the initiation of venetoclax, to adjust TLS monitoring and management accordingly.

TLS risk assessment



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

- **Cycle 1**: Low, moderated 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.

Regimen

28-day cycle for 6 cycles for treatment and 6 cycles for maintenance (12 cycles in total)

TLS RISK ASSESSMENT – DOCUMENT on ARIA			
CYCLE 1			
Drug	**Days**	**Dose**	**Administration**
OBINUTUZUMAB	1	100mg	Intravenous infusion in 100ml sodium chloride 0.9% at a rate of 25mg/hour (over 240 minutes)*
OBINUTUZUMAB	2	900mg	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 50mg/hour*
OBINUTUZUMAB	8 & 15	1000mg	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
VENETOCLAX	22-28	20mg	Take in the morning, with food. Swallow tablets whole with water.

ELIGIBILITY FOR RAPID INFUSION – DOCUMENT on ARIA			
CYCLE 2			
Drug	**Days**	**Dose**	**Administration**
OBINUTUZUMAB	1	1000mg	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
VENETOCLAX	1-7	50mg	Take in the morning, with food. Swallow tablets whole with water.
VENETOCLAX	8-14	100mg	
VENETOCLAX	15-21	200mg	
VENETOCLAX	22-28	400mg	

CYCLES 3 – 6			
Drug	**Days**	**Dose**	**Administration**
OBINUTUZUMAB	1	1000mg	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
VENETOCLAX	1-28	400mg	Take in the morning, with food. Swallow tablets whole with water.

CYCLES 7 – 12			
Drug	**Days**	**Dose**	**Administration**
VENETOCLAX	1-28	400mg	Take in the morning, with food. Swallow tablets whole with water.

*Please see administration information below for infusion rates

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.

Dose Information

- Venetoclax is available as 10mg, 50mg and 100mg film-coated tablets.
- 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 above).

Administration Information

- Obinutuzumab infusion rates, in the absence of reactions are as follows;

Cycle	Day of Treatment	Rate of Infusion
1	Day 1 (100mg in 100ml)	Administer at 25mg/hour (over 4 hours). Do not increase the rate. Consider slower rate in higher risk of IRRs.
1	Day 2 (900mg in 250ml)	Start the infusion at 50mg/hour for 30 minutes. The rate can be escalated in increments of 50mg/hour every 30 minutes to a maximum rate of 400mg/hour. Infusion may be administered as follows; *Give 7ml at 14ml/hour for 30 minutes* *then 14ml at 28ml/hour for 30 minutes* *then 21ml at 42ml/hour for 30 minutes* *then 28ml at 56ml/hour for 30 minutes* *then 35ml at 70ml/hour for 30 minutes* *then 42ml at 84ml/hour for 30 minutes* *then the remainder (approx.105ml) at 100ml/hour* Total infusion time minimum 4 hours
1	Day 8, 15 (1000mg in 250ml)	Start the infusion at 100mg/hour for 30 minutes. The rate can be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400mg/hour. Infusion may be administered as follows; *Give 12.5ml at 25ml/hour for 30 minutes* *then 25ml at 50ml/hour for 30 minutes* *then 37.5ml at 75ml/hour for 30 minutes* *then the remainder (approx. 175ml) at 100ml/hour* Total time minimum 3 hours 15 minutes
2-6	Day 1 (1000mg in 250ml)	If there has been no significant adverse events or reactions (≥ Grade 3) with previous 3 obinutuzumab infusions (Cycle 1 Day 2, 8, and 15) ***then from cycle 2 onwards obinutuzumab can be given over 90 minutes as a rapid infusion (666mg/hour).*** Please ensure lymphocyte counts are less than $5x10^9$/L. If > $5x10^9$/L, discuss with the consultant before proceeding with rapid infusion. If an IRR Grade 1 or 2 with ongoing symptoms or a ≥ Grade 3 occurred during the previous rapid infusion, administer the next

		obinutuzumab infusion at the standard rate (see Cycle 1 Day 8 and 15)

- Hypertension may occur during obinutuzumab infusion. Withhold antihypertensive treatments 12 hours prior to, during and 1 hour after the obinutuzumab infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medicines.

- The recommended dose of obinutuzumab is 1000 mg administered over Day 1 and Day 2, and on Day 8 and Day 15 of the first treatment cycle. Two infusion bags should be prepared for the infusion Days 1 and 2 (100mg for Day 1 and 900mg for Day 2).

- If the first infusion (100mg) is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg the second infusion (900mg) must be administered the following day.

- Venetoclax film-coated tablets are for oral use. Patients should be instructed to swallow the tablets whole with a meal and water at approximately the same time each day. The tablets should not be chewed, crushed, or broken before swallowing.

- Missed doses of venetoclax should be taken within 8 hours of the usual time, otherwise it should be omitted, and the usual dosing schedule resumed the following day.

Additional Therapy

- Antiemetics 15-30 minutes

    - Metoclopramide 10mg three times a day when required (supplied on Cycle 1 and 2 only)

- Premedication for Obinutuzumab infusion reactions

    - Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

    then as follows;

Pre-medication (60 minutes prior to Obinutuzumab)	**Cycle 1 Days 1 & 2**	**Cycle 1 Days 8 and 15 Cycles 2, 3, 4, 5, 6**		
	All patients	Patients without IRRs	Patients with Grade 1 or 2 IRRs	Patients with Grade 3 IRRs or lymphocyte count >25x10^9/L
Dexamethasone 20mg intravenous	✓			✓
Chlorphenamine 10mg intravenous	✓		✓	✓
Paracetamol 1000mg oral	✓	✓	✓	✓

On an as required basis:

- Chlorphenamine 10mg intravenous for infusion reactions
- Lorazepam 1mg oral for rigors
- Dexamethasone 20mg intravenous for infusion reactions
- Paracetamol 1000mg oral for pyrexia
- Pethidine 25mg intravenous in 10ml sodium chloride 0.9% over 5 minutes for rigors following a verbal confirmation to administer from a doctor

- Tumour Lysis Syndrome
  - Allopurinol 300mg daily oral, starting three days prior to Cycle 1 Day 1
  - Rasburicase 3mg intravenous infusion may be required for high-risk individuals

- Anti-infective prophylaxis
  - Aciclovir 400mg twice a day oral (consultant discretion, included in regimen)
  - Co-trimoxazole 480mg once daily on Monday, Wednesday and Friday (consultant discretion, included in regimen)

- IRR prevention
  - Consider dexamethasone 10mg daily for 2 days, starting 3 days prior to first obinutuzumab infusion

- Mouthwashes as per local formulary. For example;
  - Nystatin 1ml four times daily (consultant discretion, not included in regimen)
  - Chlorhexidine 10ml four times daily (consultant discretion, not included in regimen)

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients at high risk of GI ulceration or bleed

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to venetoclax.

- It must be made clear to all staff, including those in the community, that venetoclax should only be prescribed under the supervision of a consultant haematologist.

- Venetoclax interacts with many other medications. Always check for drug interactions.

- Grapefruit products, Seville oranges, and starfruit (carambola) should be avoided during treatment with venetoclax.

References
1. Dawson K, Moran M, Guindon K et al. Managing infusion related reactions for patients with chronic lymphocytic leukemia receiving obinutuzumab. Clin J Oncol Nursing 2016; 20 (2): 41-48
2. National Institute for Health and Care Excellence. Technology Appraisal Guidance 663 (2020). Venetoclax and obinutuzumab for untreated chronic lymphocytic leukemia. DOH:London
3. Norwich and Norfolk Treatment Protocol for Obinutuzumab and venetoclax for CLL/SLL Doc ref H.T.C001.27 v2

REGIMEN SUMMARY

Obinutuzumab-Venetoclax

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. TLS risk should be assessed and documented in Journal on ARIA. Please ensure the appropriate prophylaxis are prescribed and arrangements are in place to monitor the patient.

2. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

3. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 60 minutes prior to Obinutuzumab.

4. Dexamethasone 20mg intravenous
   Administration Instructions
   Administer 60 minutes prior to Obinutuzumab.

5. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient takes regular paracetamol for pain control and take dose into account. Maximum dose is 4g in 24 hours. There should be 4 hours between doses.
   Administer 60 minutes prior to Obinutuzumab.

6. Obinutuzumab 100mg intravenous infusion in 100ml sodium chloride 0.9% over 240 minutes
   Administration Instructions
   Administer at 25mg/hour (over 4 hours). Do not increase the rate. Consider slower rate in higher risk of IRRs.

7. Chlorphenamine 10mg when required for infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions.

8. Lorazepam 1mg oral when required for rigors
   Administration Instructions
   For the relief of rigors

9. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

10. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account.

11. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 2

12. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

13. Chlorphenamine 10mg intravenous
    Administration Instructions
    Administer 60 minutes prior to obinutuzumab

14. Dexamethasone 20mg intravenous
    Administration Instructions
    Administer 60 minutes prior to obinutuzumab

15. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account
    Administer 60 minutes prior to obinutuzumab

16. Obinutuzumab 900mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions

    WARNING – the rates described below are only appropriate in the absence of infusion related reactions. Please refer to the protocol for information regarding infusion rates and infusion related reactions. Rates may be adjusted as tolerated.

    For obinutuzumab 900mg in NaCl 250ml start the infusion at 50mg/hr and escalate in increments of 50mg/hr every 30minutes to a maximum rate of 400mg/hr. This means the infusion may be administered as follows:
    Give 7ml at 14ml/hour for 30 minutes
    then 14ml at 28ml/hour for 30 minutes
    then 21ml at 42ml/hour for 30 minutes
    then 28ml at 56ml/hour for 30 minutes
    then 35ml at 70ml/hour for 30 minutes
    then 42ml at 84ml/hour for 30 minutes
    then the remainder (approx.105ml) at 100ml/hour

    Total infusion time minimum 4 hours

17. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

18. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

19. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

20. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    When required for the relief of pyrexia. Please check if the patient has taken paracetamol. Maximum dose is 4g in 24hour. There should be 4 hours between doses.

21. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 8

22. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

23. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9/L$

24. Dexamethasone 20mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction.

25. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Maximum dose is 4g in 24 hours. There should be 4 hours between doses. Administer 60 minutes prior to Obinutuzumab.

26. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    WARNING – the rates described below are only appropriate in the absence of infusion related reactions. Please refer to the protocol for information regarding infusion rates and infusion related reactions. Rates may be adjusted as tolerated.

    Start the infusion at 100mg/hour for 30 minutes. The rate can be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400mg/hour. Infusion may be administered as follows;

    Give 12.5ml at 25ml/hour for 30 minutes
    then 25ml at 50ml/hour for 30 minutes
    then 37.5ml at 75ml/hour for 30 minutes
    then the remainder (approx. 175ml) at 100ml/hour

    Total time minimum 3 hours 15 minutes

27. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

28. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

29. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

30. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account.

31. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor.

Day 15

32. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

33. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9$/L.

34. Dexamethasone 20mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction.

35. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to Obinutuzumab.

36. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
Administration Instructions
WARNING – the rates described below are only appropriate in the absence of infusion related reactions. Please refer to the protocol for information regarding infusion rates and infusion related reactions. Rates may be adjusted as tolerated.

Start the infusion at 100mg/hour for 30 minutes. The rate can be escalated in increments of 100 mg/hour every 30 minutes to a maximum rate of 400mg/hour. Infusion may be administered as follows;

Give 12.5ml at 25ml/hour for 30 minutes
then 25ml at 50ml/hour for 30 minutes
then 37.5ml at 75ml/hour for 30 minutes
then the remainder (approx. 175ml) at 100ml/hour

Total time minimum 3 hours 15 minutes

37. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

38. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors

39. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions

40. Paracetamol 1000mg oral when required for pyrexia
Administration Instructions
For the relief of pyrexia. Please check if the patient has taken paracetamol. Maximum dose is 4g in 24hours. There should be 4 hours between doses.

41. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
Administration Instructions
For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines (day 1 only)

42. Allopurinol 300mg once a day oral starting 72 hours before the first dose of venetoclax
Administration Instructions
Start 72 hours prior to the administration of the first dose of venetoclax and stop after 7 days of the 400mg dose escalation. Please supply 38 days or nearest equivalent original pack size.

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

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

45. Co-trimoxazole 480mg once a day on Monday, Wednesday and Friday for 28 days

46. Warning Consider Mouthwashes
Administration Instructions
Consider prescribing mouthwash (from favourites) such as
- nystatin 1ml four times a day
- chlorhexidine 10ml four times a day

Take Home Medicines (Day 22 only)

47. Warning – TLS 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 prescribe the appropriate prophylaxis.

Patients 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 of water daily, starting 2 days before, on the day of the first dose, 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.

Ensure arrangements are in place to monitor the patient appropriately.

48. 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.

Cycle 2

49. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

50. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9/L$

51. Dexamethasone 20mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reactions

52. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

53. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    If patient had no significant adverse events or reactions (Grade 3 or above) in previous 3 infusions then obinutuzumab can be given over 90 minutes as a rapid infusion (666mg/hr).

    Please refer to the protocol for information regarding infusion rates and infusion related reactions. Rate may be adjusted as tolerated.

54. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9/L$

55. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

56. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

57. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

58. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines

Day 1

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

60. 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.

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

62. Co-trimoxazole 480mg once a day on Monday, Wednesday and Friday for 28 days

Day 8

63. 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.

64. 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 15

65. 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.

66. 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.

Day 22

67. 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 increase. 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.

68. Venetoclax 400mg 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.

Cycles 3, 4, 5, 6

69. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

70. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9/L$

71. Dexamethasone 20mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

72. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

73. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be adjusted according to tolerance as per the protocol.

74. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9/L$

75. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

76. Dexamethasone 20mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

77. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

78. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines

Day 1

79. Venetoclax 400mg once a day for 28 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

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

81. Co-trimoxazole 480mg once a day on Monday, Wednesday and Friday for 28 days

Cycles 7, 8, 9, 10, 11, 12

82. Venetoclax 400mg once a day for 28 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

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

84. Co-trimoxazole 480mg once a day on Monday, Wednesday and Friday for 28 days

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	May 2025	New document	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
NHS Isle of Wight
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 that occur as a result of following these guidelines. These protocols are only one source of information. They should be read in conjunction with the latest Summary of Product Characteristics and published information