Venetoclax / R- Venetoclax

INDICATION

Chronic lymphocytic leukaemia (CLL) -

Venetoclax Monotherapy (**NICE TA487 - BLUETEQ required**) until disease progression

- in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor (including front line), or
- in the absence of 17p deletion or *TP53* mutation in adult patients who have failed both chemoimmunotherapy and a B-cell receptor pathway inhibitor.

R-Venetoclax Combination Therapy (**NICE TA561 - BLUETEQ required**) 2-year fixed duration

- in the presence of 17p deletion or *TP53* mutation in adult patients who are unsuitable for or have failed a B-cell receptor pathway inhibitor, or
- in the absence of 17p deletion or *TP53* mutation in adult patients who have failed at least one line of CD20 chemoimmunotherapy.

R-Venetoclax is a valid treatment approach in BCR inhibitor naive patients at first or subsequent relapses. There are response and survival data from clinical trials and non-trial data of Venetoclax monotherapy in those who have received prior BCR inhibitors, and so at present Venetoclax monotherapy is typically recommended in that setting.

TREATMENT INTENT

Induction and maintenance

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of systemic anti-cancer treatment (SACT) and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, phosphate, LFTs, glucose, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. Urine pregnancy test - before cycle 1 of each new SACT in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
5. ECG +/- Echo - if clinically indicated.
6. Record performance status (WHO/ECOG).
7. Record height and weight.
8. Consent - 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.
9. Ensure pre-SACT counselling in line with NPSA recommendation and SACT measures.

10. Treatment should be agreed in the relevant MDT.
11. Assess the level of risk of tumor lysis syndrome (TLS) and provide prophylactic hydration and anti-hyperuricemic accordingly.
12. This SACT regimen is usually delivered during an inpatient stay for high or sometimes moderate risk of TLS but can be used in the ambulatory setting for patient(s) meeting criteria. Refer to local Ambulatory Care Operational Policy.

DRUG REGIMEN

CYCLE 1 (Escalation phase)

DAY 1 **Week 1 VENETOCLAX** 20mg once daily for 7 days

DAY 8 **Week 2 VENETOCLAX** 50mg once daily for 7 days

DAY 15 **Week 3 VENETOCLAX** 100mg once daily for 7 days

DAY 22 **Week 4 VENETOCLAX** 200mg once daily for 7 days

CYCLE 2 onwards

DAY 1 **Week 5 VENETOCLAX** 400mg once daily for 28 days

CYCLE 2 (Rituximab-Venetoclax indications)

DAY 8* **Pre-medication:**
At least 30 minutes prior to infusion: Hydrocortisone 100mg IV, Paracetamol 1g PO and Chlorphenamine 10mg IV
RITUXIMAB (375mg/m2) IV infusion in 500ml sodium chloride 0.9%

CYCLE 3 - 7

DAY 8* **Pre-medication:**
At least 30 minutes prior to infusion: Hydrocortisone 100mg IV, Paracetamol 1g PO and Chlorphenamine 10mg IV
RITUXIMAB (500mg/m2) IV infusion in 500ml sodium chloride 0.9%

* **Rituximab** should be administered after the patient has completed the dose-titration schedule and has received the **recommended daily dose of 400 mg venetoclax for 7 days**. Each cycle is 28 days.

Rituximab first dose - If lymphocyte count >25 x 10^9/L:

- Give 50 mg/m^2 (or 100 mg flat dose) of Rituximab on day 1
- Give the rest (i.e. 325 mg/m^2) on day 2
- Give 500 mg/m^2 on day 1 of subsequent cycles

Note: Venetoclax should be taken with a meal preferably breakfast. Venetoclax is available in 10mg, 50mg and 100mg strength tablets.

ADMINISTRATION

VENETOCLAX ADMINISTRATION

Ramp up schedule: The 5-week dose-titration phase is designed to gradually reduce tumor burden (debulk) and decrease the risk of tumour lysis syndrome (TLS). Their dose management, including during the dose-titration phase, will be conducted in accordance with their risk for developing TLS and may include dose delay and/or dose reduction as required for prophylaxis and management of TLS. If dose escalation is delayed due to scheduling, patients should continue on their current dose until the next dose increase can be arranged.

TLS assessment and management: All patients should be assessed for their risk of TLS with a recent CT scan and consented in the outpatient clinic. TLS risk should be documented on ARIA note section and the clinic letter.

If the start of treatment is delayed by more than 4 weeks, a risk assessment should be repeated. **The assigned TLS risk should not be downgraded during dose escalation.**

Risk Category	Clinical Features	Treatment Location	TLS Management
High	Lymph Node ≥5cm and ALC ≥ 25 or Lymph Node ≥10cm regardless of ALC	Inpatient ***(or*** Specialised Ambulatory Unit *)	• Rasburicase 7.5mg IV 30-60 minutes prior to dosing on day 1 of each dose escalation. **AND** • Allopurinol 300mg daily (preferably morning) starting 48-72 hours prior to the first dose of venetoclax and continue until day 7 of venetoclax 400mg. • Omit allopurinol on the days of rasburicase. (reduce to allopurinol 100mg OD if CrCl < 20mL/min)
Intermediate	Lymph Node <5cm and ALC ≥ 25 or Lymph node 5-10 cm and ALC < 25	Inpatient ***(or*** Specialised Ambulatory Unit *)	Consultant decision.
		Day Case	As per high-risk patient.
Low	Lymph Node <5cm and ALC < 25	Day Case	• Allopurinol 300mg daily starting from 3 days before the first dose of venetoclax and continue until Day 7 of venetoclax 400mg. • No rasburicase is required. • TLS monitoring not required after the 50mg ramp up phase

Refer to ambulatory pathway exclusions within this protocol and local ambulatory SACT policy. Consider Creatinine clearance in general assessment of TLS risk.

Missed Dose: 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 restart titration.

RITUXIMAB ADMINISTRATION

Antihypertensives: Consider withholding anti-hypertensive medications for 12 hours prior to rituximab.

Pre-medication: All patients must receive pre-medication at least 30 mins prior to administration:

- Paracetamol 1000mg PO single dose
- Chlorphenamine 10mg IV bolus
- Hydrocortisone 100mg IV bolus

First Infusion: The initial infusion is 50mg/h for the first 30 minutes. Thereafter, if no reaction, the rate can be escalated in 50mg/h increments every 30 minutes to a maximum rate of 400mg/h.

Subsequent infusions: After the first infusion, subsequent infusions can be given at either the licensed rate or rapid rate.

- **Licensed rate** - Subsequent doses of rituximab can be infused at an initial rate of 100 mg/h and increased by 100 mg/h increments at 30-minute intervals, to a maximum of 400 mg/h.
- **Rapid rate** *(for those eligible to receive rapid infusion*)* - For rituximab solutions prepared in 500 ml sodium chloride 0.9%. Infuse 100 ml of the rituximab infusion (20% of the dose) over 30 minutes. Then infuse the remaining 400 ml (80% of the dose) over 60 minutes (total infusion time 90 minutes). Monitor patient for adverse effects.

  *Patients who have received one full dose (500mg/m2) infusion at standard rate without a grade 2 or more infusion-related reaction (IRR).

DURATION

R-Venetoclax combination: Venetoclax should be taken for 24 months from the first day of rituximab or discontinued earlier if there is disease progression or unacceptable toxicity.

Venetoclax monotherapy: Until disease progression or unacceptable toxicity.

RESTAGING

Clinical response should be assessed on a monthly basis for the first 3 months, prior to CT scanning.

DOSE MODIFICATIONS

RITUXIMAB

No routine dose modifications.

VENETOCLAX

Table 1: Dose modification for toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	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 (see table 2 below) 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 2 below).
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic toxicities	1st occurrence	Interrupt venetoclax Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in table 2 when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the treating physician.

Hematologic Toxicities		
Grade 3 or 4 neutropenia (ANC < 1 x10^9/L) with infection or fever; or Grade 4 hematologic toxicities except lymphopenia (e.g. ANC <0.5 x10^9/L or Plt < 25 x10^9/L)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to Grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in table 2 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the treating physician.

Note: When resuming treatment with venetoclax after interruption due to TLS, the instructions for prophylaxis for tumor lysis syndrome should be followed.

Table 2: Dose modification for toxicity during treatment

Dose at Interruption, mg	Restart Dose, mg[a]
400	300
300	200
200	100
100	50
50	20
20	10

[a] Continue the reduced dose for 1 week before increasing the dose

Venetoclax dose modifications for use with CYP3A and P-gp Inhibitors:

- **Strong CYP3A inhibitors:**
  Exclude during initiation and the dose-titration phase and consider alternative medications. If the patient requires use of these medications after titration phase, use with caution and reduce the venetoclax dose by at least 75% during co-administration.
  Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.
- **Moderate CYP3A inhibitors and P-gp inhibitors:**
  Avoid concomitant use of venetoclax with moderate CYP3A inhibitors and P-gp inhibitors at initiation and during the dose-titration phase. Consider alternative treatments. If a moderate CYP3A inhibitor or P-gp inhibitor must be used, reduce the initiation and titration doses of venetoclax by at least 50%.
  Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Venetoclax Renal/Hepatic Impairment

Renal Impairment	
CrCl <80mL/min	Consider increased risk of TLS. At discretion of the treating consultant, more intensive TLS prophylaxis and increased TLS monitoring may be recommended.
CrCl 30mL/min	No dose adjustment required.
CrCl <30mL/min or dialysis	No information available.

Creatinine clearance (CrCl) as measured by institutional standard calculation e.g. Wright formula

Hepatic Impairment	
Mild-Moderate (Child Pugh A/B)	No dose adjustment. Patients with moderate impairment should be closely monitored for toxicity.
Severe (Child-Pugh C)	Reduce dose by 50%. Monitor closely for signs of toxicity.

CONTRAINDICATIONS

Renal failure or other significant co-morbidities that increase the risk of TLS. Patients should be treated in centres with experience in managing TLS.

INVESTIGATIONS

Weekly during titration phase, then reduce as appropriate.

- FBC.
- Creatinine and U&Es: uric acid, potassium, phosphate, and calcium.
- LFTs.

CONCURRENT MEDICATIONS

Tumour Lysis Management	Refer to “Management of Tumour Lysis Syndrome” section and local guideline
Aciclovir	200 mg three times a day
Co-trimoxazole	Consider PCP prophylaxis for all relapsed patients with a history of recurrent infections, and for patients on immunoglobulin replacement. 480 mg daily on Mon/ Wed/ Fri for duration of treatment and for 3 months afterwards (Consider reducing the dose to 480 mg twice weekly during neutropenic periods)

EMETIC RISK

Low.

EXTRAVASATION RISK

Rituximab: neutral

DRUG INTERACTIONS

Venetoclax interacts extensively with CYP3A4 and P-gp inhibitors and inducers, see **Appendix 1** for a list of CYP3A and P-gp inhibitors and inducers. Note this list is not conclusive. Always refer to the product SPC and consult with a pharmacist.

Patients must not consume grapefruit or grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruit within the 3-day period prior to the first venetoclax administration and until the last day of treatment is completed due to possible CYP3A mediated metabolic interaction.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

(Consult with pharmacist and refer to SPC for full details)

The most common adverse reactions (≥20%) of any grade were neutropenia, diarrhoea, nausea, anemia, upper respiratory tract infection, fatigue, hyperphosphataemia, vomiting and constipation.

The most frequent **serious adverse reactions** (≥2%) were pneumonia, febrile neutropenia, and **tumour lysis syndrome**.

PROPHYLAXIS AND MANAGEMENT OF TUMOUR LYSIS SYNDROME

(Refer to the "ADMINISTRATION" section and OUHFT TLS protocol for guidance)

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS during the initial 5-week dose-titration phase. Changes in electrolytes consistent with TLS development can occur as early as 6 – 8 hours following the first dose of venetoclax and at each dose increase.

Risk assessment for tumor lysis syndrome: The risk of TLS is a continuum based on multiple factors, including comorbidities. Patients with high tumor burden (e.g., any lymph node with a diameter ≥ 5 cm or high absolute lymphocyte count (ALC ≥25 $x10^9$/l) are a greater risk of TLS when initiating venetoclax. Reduced renal function (CrCl < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment. Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (e.g., CT scan) should be performed for all patients. In addition, blood chemistry (creatinine, uric acid, potassium, phosphorus, and calcium) assessments should be performed in all patients prior to starting treatment with correction of pre-existing abnormalities corrected.

Prophylaxis for tumor lysis syndrome

The prophylaxis measures listed below should be followed. More intensive measures (including hospitalization) should be employed as overall risk increases:

Hydration - Patients should be adequately hydrated prior to starting treatment with venetoclax and during the dose-titration phase. The recommended volume is 1.5 to 2.0 L (approximately 6 – 8 glasses) of water each day. Patients should be instructed to drink water starting 2 days before and on the day of the first dose, and every time the dose is increased. IV fluids should be administered as indicated based on overall risk of TLS or for those who cannot maintain an adequate level of oral hydration. For subjects for whom volume overload is considered a significant risk, hospitalization should be considered.

Anti-hyperuricemic agents - Anti-hyperuricemic agents should be administered 2 – 3 days prior to starting treatment with venetoclax in patients with high uric acid levels or at risk of TLS and may be continued through the titration phase.

Laboratory Assessments -

Pre-dose: For all patients, blood chemistries should be assessed within 72 hours prior to the initial dose to evaluate kidney function and correct pre-existing abnormalities. Blood chemistries should be reassessed within 72 hours prior to each subsequent dose increase during the titration phase.

Post-dose: For patients at risk of TLS, blood chemistries should be monitored at 6 – 8 hours and at 24 hours after the first dose of venetoclax. Electrolyte abnormalities should be corrected promptly. The next dose of venetoclax should not be administered until the 24-hour blood chemistry results have been evaluated. The same monitoring schedule should be followed at each subsequent dose increase.

> **<u>Low risk TLS patients</u> only require monitoring for TLS bloods at 20 mg and 50 mg dose ramp up staging. They do not require additional TLS monitoring at the 100mg, 200mg, 400mg ramp up according to the SPC providing the initial ramp up at 20mg and 50mg was uncomplicated.**

Hospitalization - Based on clinician's assessment, patients at greater risk of TLS require hospitalization or intensive ambulatory monitoring, with each dose escalation of venetoclax for close monitoring through the first 24 hours. If dose escalation is delayed due to scheduling, patients should continue on their current dose until the next dose increase can be arranged.

TREATMENT RELATED MORTALITY

1%.

AMBULATORY TREATMENT

This regimen is eligible for treatment within a specialised ambulatory unit (e.g. Oxford Cancer Ambulatory Care Unit) for moderate or high-risk TLS as an alternative to inpatient admission. Specific patient restrictions apply, as stated below, in addition to usual eligibility criteria outlined in local ambulatory cancer treatment policy:

Exclusions to treatment:

- Age >80 years or significant frailty.
- Creatinine clearance (CrCl) <30ml/min or dependence on dialysis.
- Clinically significant cardiac impairment.
- G6PD deficiency.
- Co-morbid conditions needing careful fluid management e.g. diabetes insipidus.
- Drug-interactions (unavoidable) having potential to need careful adjustment and monitoring of medications for other co-morbid conditions. Consult pharmacist.
- Expected poor compliance with treatment directions/monitoring requirements.

Patients not eligible for this pathway should be planned for inpatient admission during titration. Ambulatory treatment involves a number of visits and may not be suitable for all patients.

Important notes:

- Consent should be given for ambulatory treatment at clinic assessment. An electronic referral form for AC treatment should be completed.
- Patients should be **prescribed and supplied allopurinol in advance**, ideally in clinic, to allow treatment start 2-3 days prior to venetoclax cycle 1, day 1. They should be advised to omit this on the day of venetoclax (where rasburicase will be given).
- Patients will receive a pre-assessment telephone call from ambulatory nurse to confirm arrangements and explain hydration/fluid balance.
- **Patients should receive intravenous hydration (approximately 1 - 1.5L over 8 hours at a rate of 150ml/min) on the day of dose escalation** during their stay in the unit and be advised to continue with oral hydration when discharged home.
- Venetoclax take-home supply should remain on the unit and not be given to the patient until day 2 bloods have been reviewed for TLS.

REFERENCES

1. Abbvie. Venclyxto Summary of Product Characteristics. Updated 15/04/2021. Accessed on 07/06/2021 via http://www.medicines.org.uk/emc
2. NICE. TA487 Venetoclax for treating chronic lymphocytic leukaemia. Published 08/11/2017. Available at http://www.nice.org.uk/guidance/ta487
3. NICE. TA561 Venetoclax with rituximab for previously treated chronic lymphocytic leukaemia. Published 27/02/2019. Available at http://www.nice.org.uk/guidance/ta561

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung Haematology Pharmacist	New Document. Annual Protocol Review.	May 2019	1.0	
Cheuk-kie Jackie Cheung Haematology Pharmacist	Clarification on rituximab schedule	Dec 2019	1.1	May 2021
Lymphoma protocol review 2020	Addition of timing of rasburicase	June 2020	1.3	May 2022
Donna Constantine Haematology Pharmacist	Addition of ambulatory details and specific ambulatory eligibility criteria	January 2021	1.4	May 2022
Lymphoma protocol review 2021	TLS risk and other updates according to latest Venetoclax SmPC Format alignment with other venetoclax based protocols	June 2021	1.5	May 2023
Donna Constantine Haematology Pharmacist	Typo correction	July 2021	1.6	May 2023

APPENDIX 1

Strong CYP3A Inhibitors

Exclude concomitant use of venetoclax with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, mibefradil, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, posaconazole, saquinavir, telaprevir, telithromycin, voriconazole) at initiation and during ramp-up titration phase.

For patients who have completed the ramp-up titration phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when used concomitantly with strong CYP3A inhibitors. Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor 2 to 3 days after discontinuation of the inhibitor.

Moderate CYP3A Inhibitors and P-gp or BCRP Inhibitors

Avoid concomitant use of moderate CYP3A inhibitors (e.g., erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil) or P-gp inhibitors (e.g., amiodarone, azithromycin, captopril, carvedilol, cyclosporine, felodipine, quercetin, quinidine, ranolazine, ticagrelor) with venetoclax. Consider alternative treatments.

If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. Monitor patients more closely for signs of toxicities.

CYP3A Inducers

Avoid concomitant use of venetoclax with strong CYP3A inducers (e.g., carbamazepine, phenytoin, rifampin, St. John's Wort) or moderate CYP3A inducers (e.g. bosentan, efavirenz, etravirine, modafinil, nafcillin).

Consider alternative treatments with less CYP3A induction.

NURSING CARE PLAN: VENETOCLAX / R-VENETOCLAX

Indication: Chronic lymphocytic leukaemia (CLL)
Frequency: Venetoclax monotherapy is continued until disease progression and R-Venetoclax is for 2 years.
Alopecia: Potential hair thinning in some people.
Emetic risk: Low
If required: Rituximab is administered after the patient has completed the dose-titration schedule and has received the recommended daily dose of 400 mg venetoclax for 7 days. Each cycle is 28 days. Rituximab is given from Cycle 2, Day 8 (first dose of Rituximab may be split if lymphocyte count is >25)

Rituximab is set up on Day 8 of Cycle 2 to Cycle 7 on ARIA
During Cycle 2, patient should attend the day treatment unit (DTU) or ward on
Day 1: Venetoclax titration and tumour lysis bloods
Day 2: Tumour lysis bloods
Day 8: Rituximab and collect enough Venetoclax for 28 days.
Cycle 3 to Cycle 7, patient will only need to attend on Day 8 of each cycle.

VENETOCLAX: B-cell lymphoma-2 inhibitor (BCL-2)
Administered orally (this will be dispensed by pharmacy as a TTO if given on DTU)
Emetic risk: low
Side Effects: neutropenia, fever, headache, diarrhoea, constipation, nausea/vomiting, anaemia, upper respiratory tract infection, pneumonia, UTI, thrombocytopenia, fatigue and tumour lysis syndrome (TLS).

RITUXIMAB: Monoclonal antibody for CD 20.
Administered as IV infusion.
Classification of extravasation: neutral.
Emetic risk: low.
Side effects: risk of anaphylaxis, severe dyspnoea, bronchospasm and hypoxia

- Infusion reactions (Most common during first infusion - PREMED 30 MINS PRIOR TO INFUSION): fever, chills, rigors, urticaria, nausea, hypotension, dizziness, cough, chest tightness, back pain.
- Rituximab can cause hypotension. Consider withholding anti-hypertensives 12 hours prior to Rituximab (especially first dose).
- Risk of tumour-lysis syndrome, especially with bulky disease.
- Post infusion side effects: flu-like symptoms, fever, diarrhoea
- **For first Rituximab:**
  - Ensure patient is treated on a bed.
  - In DTU setting *(where the patient is visually in front of the nursing station with very close observation):* Record baseline vital observations and then if patient reacts. In the specialist ambulatory or ward setting: record vital observations every 30 minutes for the first two hours and then hourly. To have close observation.
  - Have anaphylaxis box nearby.
  - Increment drug infusion rate as per protocol. *Note there are different rates for first and subsequent treatments and for different doses.*
  - Educate patients re possible reactions and the importance of reporting any symptoms immediately.

- **If patient reacts to Rituximab:**
  - Stop infusion.
  - Record observations.
  - Seek an immediate medical review.
  - Consider administration of Hydrocortisone, Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.

- Restart infusion at same or previous rate after 30 minutes if symptoms resolved.

Regime Specific Considerations

- Dose should be taken with a meal. Patients should avoid grapefruit, Seville orange and starfruit throughout treatment.
- See protocol for Venetoclax dose loading details

- **In the DTU setting**
- Patients will need to be booked to come for 9am for urgent baseline bloods (FBC/ U+E's/ LFT's, full tumour lysis bloods including urate) +/- pre-hydration and review. Venetoclax must be given no later than 11am on day 1 of each dose of drug escalation to allow tumour lysis bloods to be repeated 6 hours later (these need to be sent urgently to ensure they are reviewed by the end of the day).
- On DTU, patients will be given Venetoclax as part of their TTO. They are directed to take this by the nursing team when baseline bloods and medical review are completed. Patient will need to remain on the unit until the post tumour lysis bloods have been reviewed by the Haem SpR.
- Patient attends DTU on day 2 for TLS bloods and review 23 or 24 hours post venetoclax dose. The next dose of venetoclax should not be administered until these bloods have been reviewed
- Ensure patient is drinking at least 2L fluids daily

Low risk TLS patients only require monitoring for TLS bloods at 20 mg and 50 mg dose ramp up staging. They do not require additional TLS monitoring at the 100mg, 200mg, 400mg ramp up according to the SPC providing the initial ramp up at 20mg and 50mg was uncomplicated.

- **In the specialist ambulatory setting (e.g. ACU)**
- Patients will need arrangements for full bloods (FBC/ U+E's / LFT's) with TLS bloods (U&Es including creatinine, urate, calcium and phosphate) no more than 48 hours prior to planned dose.
- Patients should have a supply of allopurinol and start 48-72 hours prior to venetoclax alongside oral hydration. They will need to be booked to arrive for 8:30am for prompt dosing of rasburicase and venetoclax dosing no later than 10am.
- TLS bloods should be repeated 6-8 hours later and sent urgently before 5pm to CH lab. These bloods must be interpreted by the Haem SpR before patient leaves the unit. Patient attends ACU on day 2 for TLS bloods and review 23 or 24 hours post venetoclax dose. The next dose of venetoclax should not be administered until these bloods have been reviewed.
- Patients will be given Venetoclax as part of their TTO; this should be given to the patient on day 2 (not before). They are directed to take this by the nursing team when bloods and medical review are completed.
- Ensure patient is drinking at least 2L fluids daily