Venetoclax and Obinutuzumab

INDICATION
First line treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL) or Small Lymphocytic Lymphoma (SLL):

1. In the presence of 17p deletion or TP53 mutation (NICE TA663- BLUETEQ required).
   OR
2. In the absence of 17p deletion or TP53 mutation in adult patients for whom Fludarabine, Cyclophosphamide and Rituximab (FCR), or Bendamustine plus Rituximab (BR), is unsuitable (NICE TA663- BLUETEQ required).
   OR
3. In the absence of 17p deletion or TP53 mutation in adult patients for whom FCR or BR is suitable (Cancer Drug Fund NICE TA663- BLUETEQ required).

(Note: There are 3 different BLUETEQ forms for the 3 options above).

TREATMENT INTENT
Disease modification.

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, urate, calcium, magnesium, creatinine, phosphate, LFTs, LDH, glucose, Igs, β2 microglobulin, hepatitis B core antibody (HBcAb) and hepatitis B surface antigen Ag (HBsAg), hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent, TP53 mutation analysis.
4. Urinary pregnancy test – before cycle 1 of each new chemotherapy course 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. 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.
8. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
9. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
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-hyperuricemics accordingly.
12. Withhold antihypertensive treatments 12 hours before, during and 1 hour after the infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medicines.
13. Ensure pre-SACT counseling in line with NPSA recommendation and SACT measures.

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**DRUG REGIMEN**

**CYCLE 1**

**DAY 1**
Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
**OBINUTUZUMAB*** 100mg IV infusion in 100mL sodium chloride 0.9%

**DAY 2**
Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
**OBINUTUZUMAB*** 900mg IV infusion in 250mL sodium chloride 0.9%

**DAYS 8 & 15**
Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
**OBINUTUZUMAB*** 1000mg IV infusion in 250mL sodium chloride 0.9%

**DAY 22**
Week 1 **VENETOCLAX** 20mg once daily for 7 days

**CYCLE 2**

**DAY 1**
Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
**OBINUTUZUMAB*** 1000mg IV infusion in 250mL sodium chloride 0.9%

**DAY 1**
Week 2 **VENETOCLAX** 50mg once daily for 7 days

**DAY 8**
Week 3 **VENETOCLAX** 100mg once daily for 7 days

**DAY 15**
Week 4 **VENETOCLAX** 200mg once daily for 7 days

**DAY 22**
Week 5 **VENETOCLAX** 400mg once daily for 7 days

**CYCLES 3-6**

**DAY 1**
Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
**OBINUTUZUMAB*** 1000mg IV infusion in 250mL sodium chloride 0.9%

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

**CYCLES 7-12**

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

*See sections below for administration information including pre-medication and infusion rates

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.

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Clinical Features</th>
<th>Treatment Location</th>
<th>TLS Management</th>
</tr>
</thead>
</table>
| High          | Lymph Node ≥5cm and ALC ≥25 or Lymph Node ≥10cm regardless of ALC | Inpatient or ambulatory care pathway if approved | - Rasburicase 7.5mg IV 30-60 minutes prior to dosing on day 1 of each dose escalation AND
- Allopurinol 300mg daily (preferably morning) starting from 48-72 hours before 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 ambulatory care pathway if approved | Consultant decision. |
| 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.

OBINUTUZUMAB ADMINISTRATION

The patient should be adequately hydrated prior to treatment. On cycle 1, day 1 + 2, administer 500mL normal saline 0.9% over 1 hour before administering obinutuzumab.

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L.130
Venetoclax and Obinutuzumab
Authorised by CLL lead Dr Toby Eyre
Published: January 2021
Review: May 2023
Version 1.2
Withhold antihypertensive treatments 12 hours before, during and 1 hour after the infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their antihypertensive medicines.

**Pre-medications:**

<table>
<thead>
<tr>
<th>Pre-meds required</th>
<th>Cycle 1 Days 1 &amp; Day 2</th>
<th>Subsequent infusions</th>
<th>Cycle 1 Days 8 &amp; 15 and Cycles 2-6</th>
<th>Patients with a grade 3 (severe) IRR with the previous infusion OR with a lymphocyte count &gt;25 x 10^9/L prior to next treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>Patients without any IRR Symptoms</td>
<td>Patients with grades 1-2 (mild to moderate) IRR with the previous infusions</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone iv 20mg, completed at least 60 minutes prior to infusion</td>
<td>✓</td>
<td></td>
<td>⬤</td>
<td></td>
</tr>
<tr>
<td>Chlorphenamine iv 10mg, At least 30 minutes prior to infusion</td>
<td>✓</td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paracetamol 1g PO, At least 30 minutes prior to infusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

*Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.*

**Infusion Rates:**

These are the recommended starting infusion rates assuming the patient has not experienced infusion related reactions in the prior infusion; otherwise, the infusion rate should be no more than half the previous rate.

**Cycle 1 Day 1:** Infuse at 25mg/hr over 4 hours. DO NOT increase the infusion rate.

**Cycle 2 Day 2:** The recommended initial rate for infusion is 50mg/hr; after the first 60 minutes, if can be escalated in 50mg/hr increments every 30 minutes to a maximum rate of 400mg/hr.

**Subsequent infusions:** subsequent doses of obinutuzumab can be infused at an initial rate of 100mg/hr, and increased by 100mg/hr increments at 30 minutes intervals, to a maximum of 400mg/hr.

Note: For guidance on infusion rates in the case of infusion related reactions. See adverse effects section below.

**Delayed or missed Dose:** If a planned dose of obinutuzumab is missed, it should be administered as soon as possible.

If toxicity occurs before cycle 1 day 8 or day 15, requiring delay of treatment, these doses should be administered after resolution of toxicity. All subsequent doses from cycle 2 will be shifted to accommodate for the delay of Cycle 1.

**CYCLE FREQUENCY**

Every 28 days for 12 cycles.
Obinutuzumab cycles 1 – 6 only, venetoclax continues as single agent treatment thereafter.

**RESTAGING**

Clinical response should be assessed on a monthly basis for the first 3 months.
DOSE MODIFICATIONS

Table 1: Venetoclax dose modifications for toxicities

<table>
<thead>
<tr>
<th>Event</th>
<th>Occurrence</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor Lysis Syndrome</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood chemistry changes or symptoms suggestive of TLS</td>
<td>Any</td>
<td>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 have to 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).</td>
</tr>
<tr>
<td><strong>Non-Hematologic Toxicities</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| 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. Venetoclax dose modification for toxicity

<table>
<thead>
<tr>
<th>Dose at Interruption, mg</th>
<th>Restart Dose, mg(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>300</td>
<td>200</td>
</tr>
<tr>
<td>200</td>
<td>100</td>
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<td>100</td>
<td>50</td>
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<tr>
<td>50</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

\(^a\)Continue the reduced dose for 1 week before increasing the dose

Dose modifications for use with CYP3A and P-gp Inhibitors (for a list, see appendix 1)

- **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**

<table>
<thead>
<tr>
<th>Renal Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &lt;80mL/min</td>
</tr>
<tr>
<td>CrCl 30mL/min</td>
</tr>
<tr>
<td>CrCl &lt;30mL/min or dialysis</td>
</tr>
</tbody>
</table>

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. |

**Obinutuzumab Renal/Hepatic Impairment**

<table>
<thead>
<tr>
<th>Renal Impairment*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl 30-89mL/min</td>
</tr>
<tr>
<td>CrCl &lt;30mL/min</td>
</tr>
</tbody>
</table>

*Patients with renal impairment CrCl <50mL/min are more at risk of IRRs, neutropenia and thrombocytopenia.
Hepatic Impairment

The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.

CONTRAINDICATIONS

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

Concomitant use of strong CYP3A inhibitors at initiation and during the dose-titration phase.

INVESTIGATIONS

Weekly during titration phase, then reduce as appropriate.

- FBC.
- Creatinine and U&Es: uric acid, potassium, phosphate, and calcium.
- Liver function Tests.
- Glucose.

CONCURRENT MEDICATIONS

| Tumour Lysis Management | Refer to “Management of Tumour Lysis Syndrome” (Appendix 2) section and local guideline
| Allopurinol prophylaxis may begin at initiation of obinutuzumab and can continue throughout venetoclax escalation, for ease of patient compliance there is no need to interrupt allopurinol treatment prior to venetoclax initiation |

| Aciclovir | 200 mg three times a day |

EMETIC RISK

Low

EXTRAVASATION RISK

Obinutuzumab: 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.

Patients should avoid consuming 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 grade 3/4 adverse events in the phase 3 trial include: neutropenia (52%), thrombocytopenia (13%), and infections (17.5%).

Other common adverse events reported include (≥10%): anemia (16%), IRRs (44%), diarrhea (27%), nausea (18%), pyrexia (22%), fatigue (15%), cough (16%).

The most common serious adverse events include (≥2%): pneumonia, febrile neutropenia, IRR (5%), pyrexia (see Appendix 2).

Infusion-Related Toxicities (IRRs) (see Appendix 3): Obinutuzumab should be administered as per infusion protocol. Infusion-related reactions (IRRs) such as rashes, allergic and anaphylactic reactions or cytokine release syndrome (dyspnoea, bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria and angio-oedema) should be treated promptly. It is recommended, that the infusion should be temporarily interrupted or slowed until the adverse event has subsided and then re-started at 50% of the previous dose.

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.
- 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 will receive a pre-assessment telephone call from an ambulatory nurse to confirm arrangements.
- **Patients should receive intravenous hydration (approximately 1 - 1.5L over 8 hours at a rate of 150ml/min) on the day of venetoclax 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 post-escalation bloods have been reviewed for TLS.

**REFERENCES**

3. NICE. TA663 Venetoclax with Obinutuzumab for untreated chronic lymphocytic leukaemia. Published 09 December 2020. Available at [https://www.nice.org.uk/guidance/ta663](https://www.nice.org.uk/guidance/ta663)

**REVIEW**

<table>
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<th>Name</th>
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<th>Version</th>
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<td>New Document</td>
<td>Dec 2020</td>
<td>1.0</td>
<td>Dec 2021</td>
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<td>May 2021</td>
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<td>TLS risk and other updates</td>
<td>June 2021</td>
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<td>according to latest venetoclax &amp; Obinutuzumab SmPC. Formatting.</td>
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</tr>
</tbody>
</table>
APPENDIX 1

Note this list is not conclusive. Always refer to the product SPC and consult with a pharmacist.

**Strong CYP3A Inhibitors**
Exclusion 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.
APPENDIX 2

PROPHYLAXIS AND MANAGEMENT OF TUMOUR LYYSIS 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.

**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.

**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.
APPENDIX 3

Infusion-Related Toxicities (IRRs):

Ensure there is a doctor and experienced nurse available during administration of all doses on cycle 1 and subsequent doses if the patient previously reacted.

Monitor the patient closely during the infusion.

Have symptomatic rescue medication readily available for administration in case of occurrence of IRRs. Have emergency resuscitation facilities available during infusion. Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations as outlined in the table below:

<table>
<thead>
<tr>
<th>IRR grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 4 (life threatening)</td>
<td>Infusion must be stopped and therapy must be permanently discontinued.</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Infusion must be temporarily stopped and symptoms treated.</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.</td>
</tr>
<tr>
<td></td>
<td>The day 1 (cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.</td>
</tr>
<tr>
<td></td>
<td>if the patient experiences a second occurrence of a grade 3 IRR, the infusion must be stopped and therapy permanently discontinued.</td>
</tr>
<tr>
<td>Grade 1-2 (mild to moderate)</td>
<td>The infusion rate must be reduced and symptoms treated.</td>
</tr>
<tr>
<td></td>
<td>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).</td>
</tr>
<tr>
<td></td>
<td>If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.</td>
</tr>
<tr>
<td></td>
<td>The day 1 (cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.</td>
</tr>
</tbody>
</table>