		If the toxicity recurs, the dose reduction guidelines in table 2 should be followed when resuming treatment following recovery. A larger dose reduction may occur at the discretion of the responsible consultant. Discontinuation of venetoclax should be considered in patients who require dose reductions to less than 100 mg for more than 2 weeks
Grade 3 or 4 haematological toxicity that delays treatment by more than 4 weeks	Discontinue	

Hepatic Impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity.

The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established.

No dose adjustments are required in patients with mild or moderate hepatic impairment. These patients should be monitored more closely for signs of toxicity at initiation and during the dose-titration phase as a trend for increased adverse events was observed in patients with moderate hepatic impairment in a population pharmacokinetic analysis.

It is not recommended to administer venetoclax to patients with severe hepatic impairment as safety in this patient group has not been established.

Renal Impairment

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

Dose adjustment is not considered necessary for obinutuzumab in those with mild to moderate renal impairment.

For venetoclax no dose adjustment is required for patients with mild or moderate renal impairment. However, patients with reduced renal function (CrCl less than 80 ml/min) may require more intensive prophylaxis and monitoring to reduce the risk of tumour lysis syndrome at initiation and during the dose-titration phase.

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.

Venetoclax should be administered to patients with severe renal impairment only if the benefit outweighs the risk and patients should be monitored closely for signs of toxicity due to increased risk of TLS.

Table 1 - **Tu↵ our Lysis Syndro↵ e TLS Manage↵ ent enetocla**

A nor↵ ality	**Dose Modification and Manage↵ ent**
Hyperkalae↵ ia	
Potassium more than ULN	

Regi en

? 6 day cycle for cycles for treat ent and cycles for aintenance ? cycles in total

Cycle

Drug	Dose	Days	Ad inistration
Obinutuzumab	100mg	1	Intravenous infusion in 100ml sodium chloride 0.9% at a rate of 25mg/hour (over 240 minutes)*
Obinutuzumab	900mg	2	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 50mg/hour*
Obinutuzumab	1000mg	8, 15	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
Venetoclax	20mg	22, 23, 24, 25, 26, 27, 28	Oral

Cycle ?

Drug	Dose	Days	Ad inistration
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*
Venetoclax	50mg	1, 2, 3, 4, 5, 6, 7	Oral
Venetoclax	100mg	8, 9, 10, 11, 12, 13, 14	Oral

- 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 when at the daily dose of 400mg, tumour lysis syndrome risk should be reassessed to determine if

- It is imperative that the time of administration of the venetoclax is recorded on ARIA and the correct blood tests are taken at the correct time as part of any increase in the dose.

- If a 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 a patient misses a dose by more than 8 hour

REGIMEN SUMMARY

Obinutuzumab-Venetoclax (Low Risk)

Cycle

Day

1. Warning – TLS Assessment and Prevention
   Administration Instructions
   There is a risk of tumour lysis syndrome in CLL patients having this regimen. Ensure the patient has been assessed for TLS risk and prescribe the appropriate prophylaxis. This regimen is for low risk individuals. Allopurinol may be required prior to the obinutuzimab; it is not included in this protocol. It is included prior to the venetoclax dose escalations. Ensure arrangements are in place to monitor the patient appropriately.

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

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

4. Methylprednisolone sodium succinate 80mg 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
   Administer 60 minutes prior to obinutuzumab

6. Obinutuzumab 100mg intravenous infusion in 100ml sodium chloride 0.9% over 240 minutes
   Administration Instructions
   Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

7. Chlorphenamine 10mg when required for infusion related reactions
   Administration Instructions

Day 2

48. Venetoclax 20mg once a day for 7 days oral
Administration Instructions
Take with or just after food. Take with a full glass of water.

Oral SACT

Cycle ?

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. Methylprednisolone sodium succinate 80mg 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

Take Home Medicines

Day

59. Venetoclax 50mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

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

61. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days

Day

62. Venetoclax 100mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Day

63. Venetoclax 200mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Day

64. Venetoclax 400mg once a day for 7 days oral
    Administration Instructions
    Take with or just after food. Take with a full glass of water.

    Oral SACT

Cycles

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

66. 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 than $25x10^9$/L

67. Mef 0L01(t)-5.771968( )6.1018c8.843.43819(i1.31968(y)10.576( )437)1.3203-0.300048(i)4.479-

Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

70. Chlorphenamine 10mg when required for infusion related reactions

Administration Instructions

For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$

DOCUMENT CONTROL