Wrightington, Wigan and Leigh NHS
NHS Foundation Trust

Regimen: **Obinutuzumab and Venetoclax (BLUETEQ)**

Document History					
Version Number 1.2~~1~~		Issue Date 05/02/2021		Review date 05/02/24	
Changes from previous version:					
Authors					
Haematologist	Dr Meswani	Pharmacist	Karen Moss	Nurse Specialist	Jo Margerison

Name	DOB	Hospital No.	Consultant	Allergies

Indications	Venetoclax plus Obinutuzumab is recommended as an option for untreated Chronic lymphocytic leukaemia (CLL) in adults, only if; - There is a 17p deletion or TP53 mutation OR - There is no 17p deletion or TP53 mutation, and Fludarabine plus Cyclophosphamide and Rituximab (FCR), or Bendamustine plus Rituximab (BR), is unsuitable, and Ventetoclax plus Obinutuzumab is recommended for use within the Cancer Drugs Fund as an option for untreated CLL in adults, only if; - There is no 17p deletion and TP53 mutation and FCR or BR is unsuitable, and - The conditions in the managed access agreement for venetoclax plus Obinutuzumab are followed. (Note-There are different BLUETEQ forms for the 3 options above)

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Pre-treatment evaluation checklist

Mandatory Fields: (Incomplete fields can result in delayed treatment)

Height (cm)	
Weight (kg)	
Surface area (m^2); if adjusted state SA used to dose	
Calculated creatinine clearance (ml/min)	
WHO Performance Status:	
Testing for Hepatitis B, Hepatitis C and HIV	Date_____
Sperm banking or oocyte/embryo preservation must be offered to males <55yrs and pre-menopausal women concerned about fertility	□
Women of childbearing potential must use effective contraception during and for 18 months after treatment with Obinutuzumab	□
Consented by:	Date_____
ECG +/- Echo – if clinically indicated	□
Provide contact details for Clinical Nurse Specialist for further information	□
Concurrent medications prescribed	□
Assess the level of risk of Tumour Lysis Syndrome and provide prophylactic hydration and anti-hyperuricemics accordingly	□
Complete Current Medication List and discontinue any inappropriate medication (e.g. immunosuppressive drugs)	□
Advise patient to omit any anti-hypertensive medications due with 12 hours of the first infusion of Obinutuzumab	□
Pre-med prescribed	□
Dose modifications considered and/or a Growth-Colony Stimulating Factor. Details:	□
Cancer care suite informed for date	Date_____
Arrangements made to discuss at MDT	Date_____
Patient given blood form for at least 1 week prior to chemo	□
Blueteq form requested	□
Patient willing to follow treatment plan during Venetoclax dose escalation	

Consultant / Speciality Doctor Signature _____ Date _____

Investigations prior to each course

FBC, U&E, Bone, LFT eGFR

Must include uric acid, phosphate, potassium, calcium, magnesium and creatinine as indicators of TLS

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Current Medication List

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Drug Regimen - Cycle 1				
Day	**Drug**	**Dose**	**Route**	**Comments**
Day 1	Obinutuzumab	100mg	IV	See below for infusion speed
Day 2	Obinutuzumab	900mg	IV	See below for infusion speed
Day 8	Obinutuzumab	1000mg	IV	See below for infusion speed
Day 15	Obinutuzumab	1000mg	IV	See below for infusion speed
Day 22	Venetoclax	20 mg	PO	Once a day f~~F~~or 7 days
Drug Regimen - Cycle 2				
Day 1	Obinutuzumab	1000mg	IV	See below for infusion speed
Day 1	Week 2 Venetoclax	50 mg	PO	Once a day f~~F~~or 7 days
Day 8	Week 3 Venetoclax	100 mg	PO	Once a day f~~F~~or 7 days
Day 15	Week 4 Venetoclax	200 mg	PO	Once a day f~~F~~or 7 days
Day 22	Week 5 Venetoclax	400 mg	PO	Once a day f~~F~~or 7 days
Drug Regimen - Cycle 3-6				
Day 1	Obinutuzumab	1000 mg	IV	See below for infusion speed
Day 1	Venetoclax	400 mg	PO	Once a day f~~F~~or 28 days
Drug Regimen - Cycles 7 – 12				
Day 1	Venetoclax	400mg	PO	Once a day f~~F~~or 28 days

Cycle Frequency	Repeat every 28 days for 12 cycles fixed durations Venetoclax is given for a total of 12 cycles, each cycle consisting of 28 days: 6 cycles in combination with Obinutuzumab

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Medication Concurrent	- **Allopurinol*** 300 mg once daily, can be stopped once venetoclax dose titration complete if no signs of TLS - * Allopurinol should be started at least 3 days before starting venetoclax - **Metoclopramide** 10 mg up to three times a day when required - **Co-Trimoxazole** 960 mg daily Monday, Wednesday and Friday - **Aciclovir** 400 mg po twice daily - **GCSF**- in clinically indicated due to treatment related neutropenia (e.g. filgrastim 300mcg sc starting day 5 of regimen for 5 days) - If the patient is allergic or intolerant to any of the above-named medicines, this should be discussed with the consultant for an alternative
Hydration	Patient should receive prophylactic hydration to reduce the risk of tumour lysis syndrome during cycle 1. Patients should drink plenty of water 2 days before initiating treatment. Patients should be instructed to drink 1.5 to 2.0 L of water orally and/or intravenous administered. Encourage 2L oral fluids daily during initial treatment phase.
Treatment duration	~~Until disease progression~~ 12 cycles (cycles 1-6 Obinutuzumab and Venetoclax, cycles 7-12 Venetoclax only)

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Treatment Plan for venetoclax	**To monitor for evidence of TLS** **To ensure bloods are monitored pre venetoclax, plus 6 and 24 hours following dose increment.** **Cycle 1 day 22:** - On cancer care: receive oral dose of venetoclax-. Patient remains on the unit. Previous days bloods sufficient for dosing. - Bloods done 6 hours post venetoclax dose (see investigations required above) - Liaise with consultant immediately upon receipt of blood results - Depending on blood results, consultant to decide on admission or discharge from cancer care **Cycle 1 Day 23:** - If discharged previous day, patient attends cancer care for bloods in the morning. Patient waits until results received. - Liaise with consultant immediately upon receipt of blood results - Depending on blood results, consultant to decide on admission or discharge from cancer care - If discharge, Patient given next 6 days supply of venetoclax to take home **Cycle 2 day 1, 8, 15 and 22:** - Patient arrives 8am on cancer care, has pre-venetoclax bloods done (see investigations required above) - Liaise with consultant immediately upon receipt of blood results and dose of venetoclax given on consultants say so - Patient receives oral dose of venetoclax. Patient remains on unit - Bloods done 6 hours post venetoclax dose (see investigations required above) - Liaise with consultant immediately upon receipt of blood results - Depending on blood results, consultant to decide on admission or discharge from cancer care **Cycle 2 Day 2, 9, 16 and 23:** - If discharged previous day, patient attends cancer care for bloods in the morning. Patient waits until results received. - Liaise with consultant immediately upon receipt of blood results - Depending on blood results, consultant to decide on admission or discharge from cancer care - If discharge, Patient given next 6 days supply of venetoclax to take home **Cycle 3 onwards:** - Visits to cancer care for pre and post venetoclax bloods no longer necessary
Stopping criteria	Clinical or radiological evidence of disease progression Unacceptable toxicity Patient choice Significant deterioration in Performance status or any other CTC grade 4 toxicity

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Additional Notes	Antihypertensives should be withheld 12 hours before the first 100mg dose of Obinutuzumab. However, some patients can develop hypertension during infusions. If this occurs, then antihypertensives should not be withheld prior to further doses of Obinutuzumab, and the patient should take them as normal. Venetoclax should be taken with meals preferably with the breakfast Venetoclax is metabolised via CYP3A so concomitant use with inducers or inhibitors should be avoided. Avoid use of strong inhibitors of CYP3A (ketoconazole, Posaconazole, itraconazole, voriconazole, clarithromycin) during dose escalation phase. If used during steady dose phase the venetoclax dose should be reduced by 75% If moderate inhibitors of CYP3A (Fluconazole, diltiazem, ciprofloxacin, erythromycin) used a 50% dose reduction of venetoclax should be applied in both titration and maintenance phase P-gp inhibitors (amiodarone, clarithromycin, ciclosporin, colchicine, diltiazem, erythromycin, felodipine, ketoconazole, lansoprazole, omeprazole – please note this is not an exhaustive list) will raise serum level of venetoclax - 50 % dose reduction advised to venetoclax dose if used concurrently with such a medication Venetoclax may inhibit metabolism of dabigatran and digoxin Avoid grapefruit juice and Seville oranges CYP3A inducers should be avoided throughout treatment due to potential to increase metabolism of venetoclax and decrease efficacy. Obinutuzumab should be given as a split dose for the first administration (100 mg then 900 mg). If the initial 100 mg is administered without issue the second 900 mg dose can be given on day 1 also instead of the next day. However, the 900mg dose is invariably given on day 2 of cycle 1. If patient is likely to require rasburicase, ensure allopurinol is taken on the morning of the preceding days so a 24 hour time period can occur between the last allopurinol dose and the rasburicase infusion. Allopurinol should not be taken on any day that rasburicase is given to the patient. If rasburicase is started on the day venetoclax commences, they will need to be told to withhold allopurinol on C1 D22 and only restart it on D23.

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CYCLE 1											
Date											
Weight / BSA											
Hb											
WCC											
Neutrophils											
Platelets											
		Cycle 1 Day 1		**Cycle 1 Day 2**		**Cycle 1 Day 8**		**Cycle 1 Day 15**		**Cycle 1 Day 22**	
Dose modifications due to toxicities											
		Dose	**Given**	**Dose**	**Given**	**Dose**	**Given**	**Dose**	**Given**	**Dose**	**Given**
Paracetamol (at least 30 min before Obinutuzumab)	PO	**1g**		**1g**		**1g**		**1g**			
Chlorphenamine (at least 30 min before Obinutuzumab)	IV	**10mg**		**10mg**		**10mg**		**10mg**			
Dexamethasone (at least 1 hour before Obinutuzumab)	IV	**20 mg**		**20 mg**		**20 mg**		**20 mg**			
Obinutuzumab	IV	**100 mg**		**900 mg**		**1000 mg**		**1000 mg**			
Venetoclax	PO	-	-	-	-	-	-	-	-	**20mg**	
Prescribed by											
Regimen and calculation checked (pharmacist)											
Pharmacist Dispensing date and check											

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CYCLE 2								
Date								
Weight / BSA								
Hb								
WCC								
Neutrophils								
Platelets								
		Cycle 2 Day 1		**Cycle 2 Day 8**		**Cycle 2 Day 15**		**Cycle 2 Day 22**	
Dose modifications due to toxicities								
		Dose	**Given**	**Dose**	**Given**	**Dose**	**Given**	**Dose**	**Given**
Paracetamol (at least 30 min before Obinutuzumab)	PO	**1g**		**-**		**-**		**-**	
Chlorphenamine (at least 30 min before Obinutuzumab)	IV	**10mg**		**-**		**-**		**-**	
Dexamethasone (at least 1 hour before Obinutuzumab)	IV	**20 mg**		**-**		**-**		**-**	
Obinutuzumab	IV	**1000mg**		**-**		**-**		**-**	
Venetoclax	PO	**50mg**	**-**	**100mg**	**-**	**200mg**	**-**	**400mg**	-
Prescribed by									
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CYCLE 3 - 6								
Date								
Weight / BSA								
Hb								
WCC								
Neutrophils								
Platelets								
		Cycle 3 Day 1		**Cycle 4 Day 1~~8~~**		**Cycle 5 Day 1 ~~15~~**		**Cycle 6 Day 1 ~~22~~**	
Dose modifications due to toxicities								
		Dose	**Given**	**Dose**	**Given**	**Dose**	**Given**	**Dose**	**Given**
Paracetamol (at least 30 min before Obinutuzumab)	PO	**1g**		**1g**		**1g**		**1g**	
Chlorphenamine (at least 30 min before Obinutuzumab)	IV	**10mg**		**10mg**		**10mg**		**10mg**	
Dexamethasone (at least 1 hour before Obinutuzumab)	IV	**20 mg**		**20mg**		**20mg**		**20mg**	
Obinutuzumab	IV	**1000mg**		**1000mg**		**1000mg**		**1000mg**	
Venetolcax	PO	400mg		400mg		400mg		400mg	
Prescribed by									
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Concurrent Medication Prescription									
Date									
	Cycle 1 Day 1			**Cycle 2 Day 1**			**Cycle 3 Day 1**		
Adjuvants	**Dose**	**Dispensed**	**Given by**	**Dose**	**Dispensed**	**Given by**	**Dose**	**Dispensed**	**Given by**
Metoclopramide 10mg TDS PRN PO for 28 days									
Co-Trimoxazole 960mg OD Mon/Wed/Friday for 28 days (OD if CrCl 15-30mls/min)									
Allopurinol 300mg OD (100mg OD if CrCl<20ml/min) PO for 28 days For first two cycles							**X**	**X**	**X**
Aciclovir 400mg BD for 28 days (200mg BD if CrCl<30ml/min)									
Prescribed by:									
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Toxicity	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%) The other common adverse events reported include anaemia (16%), Infusion related side effects (44%), diarrhoea (27%), nausea (18%), pyrexia (22%), fatigue (15%), cough (16%) The most common serious adverse events include (>2%) - febrile neutropenia, pneumonia, pyrexia

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Dose Modifications	
Hepatic	**Obinutuzumab:** The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made. Venetoclax – patients with mild to moderate impairment do not need any adjustments to treatment although those with moderate impairment (bilirubin 1.5-3 x Upper Limit of Normal (ULN)) may have a higher risk of toxicities associated with venetoclax therapy. Severe hepatic impairment requires 50% dose reduction
Renal	**Creatinine clearance < 80 ml/minute** Venetoclax - Caution cycle 1 due to increased TLS risk, monitor closely Obinutuzumab- No action **Creatinine clearance < 30 ml/minute** No information available in this population to recommend dose reductions - unlikely to be required but use with caution
Haematological	**Absolute neutrophil count < 1, 1st occurrence** Initiate GCSF to maintain neutrophils >1, restart venetoclax at sane dose **Absolute neutrophil count < 1, 2nd and subsequent occurrence** Consider using GCSF as clinically indicated, follow dose reduction guidelines when resuming the treatment with venetoclax after resolution. Additional dose reduction may occur at the discretion of the treating physicians. **Platelet count <50, 1st occurrence** Defer treatment, restart at same dose once platelets >50 **Platelet count <50, subsequent occurrences** Defer treatment, restart at one dose level reduction once platelet > 50

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Other non-haematological toxicities

All other non-grade 3 or 4 non-haematological toxicities;

Venetoclax – stop until resolved or returned to baseline. Consider restarting at one dose level reduction.

Tumour Lysis Syndrome (TLS);

Laboratory tumour lysis syndrome

Uric Acid	>475 µmol/l or 25% increase from baseline
Potassium	>5.9 or 25% increase from baseline
Phosphate	>2.0 or 25% increase from baseline
Calcium	< 1.76 or 25% decrease from baseline

If biochemistry changes suggestive of TLS occur during the venetoclax escalation phase, withhold the following dose:

- If markers resolve within 24-48 hours, resume at the same dose
- Clinical TLS or biochemical markers that do not resolve within 48 hours, resume at reduced dose

NB: patients at high risk of TLS include;

- Lymphocyte count > $25x10^9$/L or high tumour burden
- CrCl < 80ml/min
- Those deemed at high risk should receive rasburicase in place of allopurinol initially – see Venetoclax administration

Dose modification for Toxicity during Venetoclax Treatment

Dose at interruption (mg)	Restart Dose (mg)
400	**300**
300	**200**
200	**100**
100	**50**
50	**20**
20	**10**

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Reference	1.Abbvie.Veneclyxto Summary of Product Characteristics. Updated 21/04/20. https://www.medicines.org.uk/emc/product/2267/smpc 2. Roche. Gazyvaro.Summary of Product Characteristics, Updated 26/03/2020 https://www.medicines.org.uk/emc/medicine/29057 3. NICE.TA663 Venetoclax with Obinutuzumab for untreated chronic lymphocytic leukaemic.Published 09 December 2020. Available at https://www.nice.org.uk/guidance/ta663 4. Venetoclax + Obinutuzumab in treatment naïve CLL Protocol – The Christie NHS Foundation Trust – accessed via iQEMO 5. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. https://onlinelibrary.wiley.com/doi/epdf/10.1111/bjh.13403

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Method of administration

- Obinutuzumab is for intravenous use
- It should be given as an intravenous infusion through a dedicated line after dilution
- Obinutuzumab infusions should not be administered as an intravenous push or bolus

Standard infusion rate in the absence of infusion reactions/hypersensitivity

Cycle	Day of treatment	Rate of infusion
Cycle 1	Day 1 (100 mg)	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2 (or Day 1 continued) (900 mg)	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr. If the patient experienced an infusion during the previous infusion, start with administration at 25mg/hr. The rate of infusion can be escalated in increments of 50mg/hr every 30 minutes up to a maximum of 400mg/hr
	Day 8	If no infusion reaction occurred during the previous infusion, subsequent infusions can be started at 100mg/hr and increased by 100mg/hr every 30 minutes to a maximum of 400mg/hr
	Day 15	
Cycles 2-6	Day 1	

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Management of Infusion Related Reactions

IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations of Obinutuzumab.

- Grade 4 (life threatening): Infusion must be stopped and therapy must be permanently discontinued.

- Grade 3 (severe): Infusion must be temporarily stopped 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) and, 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.
  - The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr. after 1 hour, but not increased further.
  - The infusion must be stopped and therapy permanently discontinued if the patient experiences a second occurrence of a Grade 3 IRR.

- Grade 1-2 (mild to moderate): The infusion rate must be reduced and symptoms treated.
  - Infusion can be continued upon resolution of symptoms and, 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.
  - The Day 1 (Cycle 1) infusion rate may be increased back up to 25 mg/hr. after 1 hour, but not increased further.

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Treatment of Cytokine Release Syndrome or Serious Adverse Reaction

STOP INFUSION IMMEDIATELY

PROMPTLY SEEK MEDICAL ASSISTANCE AND TREAT SYMPTOMS

Commence FAST FLOWING SALINE INFUSION

↓

Give PARACETAMOL 1g PO (If more than 4 hours post pre-med.)

↓

Administer if required:
PIRITON 10mgs IV
DEXAMETHASONE 20mg IV

↓

Consider:
OXYGEN THERAPY and
SALBUTAMOL 5mg NEBULISERS

ANAPHYLACTIC AND HYPERSENSITIVE REACTIONS

Usually occurs within a few minutes of commencing the infusion.
Follow guidance from *ANAPHYLAXIS POLICY*

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Venetoclax Administration

Ramp up schedule –This 5 week dose titration phase is designed to gradually reduce tumour burden (debulk) and decrease the risk of Tumour Lysis Syndrome. 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.

Tumour Lysis assessment and management – All patients should be assessed for their risk of TLS with a recent CT scan and consented in the outpatient clinic.

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

Risk category	Clinical features	Treatment location	TLS Management
High	Lymph node > 5 cm OR CrCL <50 ml/min	To be decided	Rasburicase on day 1 of each dose escalation AND Allopurinol 300 mg daily (preferably morning) starting from 3 days before the first dose of Venetoclax and continue until day 7 of venetoclax 400 mg. Omit Allopurinol on the day of Rasburicase, (reduce to allopurinol 100 mg OD if CrCL <20 ml/min
Intermediate	Lymph node <5 CM and CrCL 50-80 ml/min		Consultant decision
Low	Lymph node <5 cm AND CrCL>80 ml/min		Allopurinol 300 mg daily starting from 3 days before the first dose of Venetoclax and continue until Day 7 of venetoclax 400 mg No Rasburicase is required.

Regimen: **Obinutuzumab and Venetoclax (BLUETEQ)**

Document History					
Version Number 1.2~~1~~		Issue Date 05/02/2021		Review date 05/02/24	
Changes from previous version:					
Authors					
Haematologist	Dr Meswani	Pharmacist	Karen Moss	Nurse Specialist	Jo Margerison

Name	DOB	Hospital No.	Consultant	Allergies

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.

Wrightington, Wigan and Leigh NHS
NHS Foundation Trust

Regimen: **Obinutuzumab and Venetoclax (BLUETEQ)**

Document History					
Version Number 1.2~~1~~		Issue Date 05/02/2021		Review date 05/02/24	
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Authors					
Haematologist	Dr Meswani	Pharmacist	Karen Moss	Nurse Specialist	Jo Margerison

Name	DOB	Hospital No.	Consultant	Allergies

Case Note Copy

Consent Form 3
Patient agreement to investigation or treatment
(procedure where consciousness not impaired)

Name of Procedure
(Include brief explanation if medical term not clear)

Obinutuzumab and Venetoclax

Statement of health professional (to be filled in by health professional with appropriate knowledge of proposed procedure, as specified in consent policy)

I have explained the procedure to the patient. In particular, I have explained:

The intended benefits:
Treat CLL

Serious of frequently occurring risks: Life threatening infections, bleeding and blood clots. Potentially permanent damage to heart/lungs/liver/kidneys/gut/nerves/skin/bladder. Nausea, vomiting, loss of appetite, sore mouth, taste changes, weight change, altered bowel habit, abdominal pain or discomfort. Allergic reactions and skin rashes. Hair loss. Mood changes. Altered blood sugars and diabetes. Infertility. Secondary cancers.

I have also discussed what the procedure is likely to involve, the benefits and risks of any available alternative treatments (including no treatment) and any particular concerns of those involved.

☐ **The following leaflet has been provided:** Obinutuzumab and Venetoclax patient information leaflets

Signed:_____ Date:_____

Name (PRINT):_____ Job Title:_____

Statement of interpreter (where appropriate)

I have interpreted the information above to the patient to the best of my ability and in a way in which I believe s/he can understand

Signed:_____ Date:_____ Name (PRINT)_____

Statement of patient

I agree to the procedure described above.
I understand that you cannot give me a guarantee that a particular person will perform the procedure. The person will, however, have appropriate experience.
I understand that the procedure will not involve local anaesthesia.

Signed:_____ Date:_____ Name (PRINT)_____

Confirmation of consent (to be completed by a health professional when the patient is admitted for the procedure, if the patient has signed the form in advance)

I have confirmed that the patient has no further questions and wishes the procedure to go ahead.

Signed:_____ Date:_____

Name (PRINT):_____ Job Title:_____

Wrightington, Wigan and Leigh NHS
NHS Foundation Trust

Regimen: **Obinutuzumab and Venetoclax**

Document History		
Version Number	Issue Date	Review date
1	01/07/2015	01/07/2017
Changes from previous version:		
Authors		
Haematologist	Pharmacist	Nurse Specialist

Name	DOB	Hospital No.	Consultant	Allergies

Patient Copy

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