## Obinutuzumab and Chlorambucil for CLL

**Cycle one only**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Dexamethasone</td>
<td>20mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td>One hour before</td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>1gram</td>
<td>Oral</td>
<td></td>
<td>Once Only</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine</td>
<td>10mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obinutuzumab</td>
<td>100mg</td>
<td>IV infusion</td>
<td>100ml 0.9% Sodium Chloride</td>
<td>4 Hours (25mg/hour)</td>
</tr>
</tbody>
</table>

*Can give second portion 900mg Obinutuzumab on Day 1 or Day 2, due to length of infusion time.*

If no infusion reactions proceed with 900mg Obinutuzumab dose starting at 50 mg/hr, then increase infusion rate in 50 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr.

<table>
<thead>
<tr>
<th>Day 1 or 2</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obinutuzumab</td>
<td>900mg</td>
<td>IV infusion</td>
<td>250ml 0.9% Sodium Chloride</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td>0.5mg/kg</td>
<td>Oral Single dose</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

On Day 8 onwards start at 100 mg/hr, then increase infusion rate by 100 mg/hr increments every 30 minutes to a maximum rate of 400 mg/hr.

<table>
<thead>
<tr>
<th>Day 8</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obinutuzumab</td>
<td>1000mg</td>
<td>IV infusion</td>
<td>250ml 0.9% Sodium Chloride</td>
<td>See above</td>
</tr>
<tr>
<td>Day 15</td>
<td>Obinutuzumab</td>
<td>1000mg</td>
<td>IV infusion</td>
<td>250ml 0.9% Sodium Chloride</td>
<td>See above</td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td>0.5mg/kg</td>
<td>Oral Single dose</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Cycle Two Onwards**

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Dexamethasone*</td>
<td>20mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td>One hour before</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine*</td>
<td>10mg</td>
<td>IV bolus</td>
<td>via 0.9% Sodium Chloride Drip</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Paracetamol</td>
<td>1gram</td>
<td>Oral</td>
<td></td>
<td>Once Only</td>
</tr>
<tr>
<td></td>
<td>Obinutuzumab</td>
<td>1000mg</td>
<td>IV infusion</td>
<td>100ml 0.9% Sodium Chloride</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chlorambucil</td>
<td>0.5mg/kg</td>
<td>Oral Single dose</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Day 15</td>
<td>Chlorambucil</td>
<td>0.5mg/kg</td>
<td>Oral Single dose</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

*Dexamethasone and Chlorphenamine are given from cycle two onwards if patient had any infusion related reaction. May not be needed if no IRR to cycle one doses*
**Obinutuzumab and Chlorambucil for CLL**

**Cumbria, Northumberland, Tyne & Wear Area Team**

**DOSE FORM**
Chlorambucil 2 mg tablets. obinutuzumab (Gazyvaro) vial of 40 mL concentrate contains 1000mg of obinutuzumab, corresponding to a concentration before dilution of 25 mg/mL.

**CYCLE LENGTH AND NUMBER OF DAYS**
6 treatment cycles, each of 28 day duration.

**APPROVED INDICATIONS:**
As per NICE TA343: Obinutuzumab, in combination with chlorambucil, is recommended as an option for adults with untreated chronic lymphocytic leukaemia who have comorbidities that make full-dose fludarabine-based therapy unsuitable for them, only if:
- bendamustine-based therapy is not suitable and
- the company provides obinutuzumab with the discount agreed in the patient access scheme.

**PREMEDICATION**
*Prophylaxis and premedication for tumour lysis syndrome (TLS)*
Patients with a high tumour burden and/or a high circulating lymphocyte count (> 25 x 109/L) and/or renal impairment (CrCl <70 mL/min) are considered at risk of TLS and should receive prophylaxis with hydration and administration of allopurinol or rasburicase, starting 12-24 hours prior to start of obinutuzumab.

**RECOMMENDED TAKE HOME MEDICATION**
Allopurinol 300mg once daily on first cycle only
Metoclopramide 10mg Three Times Daily on days 1 to 3

**INVESTIGATIONS / MONITORING REQUIRED**
Prior to first cycle: FBC, U&Es, LFTs, LDH, bone profile, DCT, bone marrow
Prior to each cycle: FBC, U&Es, LFT, bone profile

**ASSESSMENT OF RESPONSE**
Haematological response
Palpable disease
B symptoms

**REVIEW BY CLINICIAN**
Prior to each cycle (unless being seen by a nurse / pharmacist – see below)

**ADMINISTRATION NOTES**
- Hypotension, as a symptom of infusion related reactions (IRRs), may occur during obinutuzumab treatment. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration.
- Monitor the patient closely during the first infusion, especially for the first 2 hours
- Patients who have pre-existing cardiac or pulmonary conditions should be monitored carefully throughout the infusion and the post-infusion period.
- Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuation of obinutuzumab.
Obinutuzumab and Chlorambucil for CLL

- IRRs occur predominantly during infusion of the first 1,000 mg, hence splitting of first dose. In the majority of patients, IRRs were mild to moderate and could be managed by the slowing or temporary halting of the first infusion. This may mean that the 900mg portion of the first dose may have to be given on day 2. Note some units may choose to split the first dose in to 100mg day one, 900mg day two.
- vaccination with live virus vaccines is not recommended during treatment

EXTRAVASATION  See Local Policy

TOXICITIES
Neutropenia
Thrombocytopenia
Worsening of pre-existing cardiac conditions
Infections
Hepatitis B reactivation
Progressive multifocal leukoencephalopathy (PML)

DOSE MODIFICATION / TREATMENT DELAYS
No dose modification of obinutuzumab is recommended
Dose delays should be considered in case of severe or life-threatening neutropenia.
If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not wait until the next planned dose.

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REFERENCES:
2. GAZYVARO Summary of Product Characteristics available at www.medicines.org.uk
3. NICE TA343 https://www.nice.org.uk/guidance/TA343/chapter/1-Guidance