**Systemic Anti-Cancer Therapy Protocol**

# Obinutuzumab and CVP
# Previously Untreated Follicular Lymphoma

**PROTOCOL REF: MPHAOCVPHA**
**(Version No: 1.0)**

## Approved for use in:

Obinutuzumab in combination with CVP is recommended as an option for **untreated advanced follicular lymphoma (FL)** in adults (that is, first as induction treatment with chemotherapy, then alone as maintenance therapy), only if the person has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more.

- The patient has a confirmed histological diagnosis of grade 1-3a CD20 –positive FL
- The patient has bulky stage II disease (>7cm) or stage III disease or stage IV disease.
- No planned treatment breaks of more than 6 weeks beyond the expected cycle length are allowed
- ECOG PS 0-2

**Blueteq registration required: see blueteq for full eligibility criteria**

## Dosage:

### Cycle 1 ONLY:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| **Obinutuzumab** | 1000mg | IV infusion | Day 1 |
| **Cyclophosphamide** | 750mg/m$^2$ | IV infusion | Day 1 |
| **Vincristine*** | 1.4mg/m$^2$ (max 2mg dose) | IV infusion | Day 1 |
| **Prednisolone** | 100mg | Orally | Days 1-5 |
| **Obinutuzumab** | 1000mg | IV infusion | Day 8 |
| **Obinutuzumab** | 1000mg | IV infusion | Day 15 |

## Cycle 2-8

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| **Obinutuzumab** | 1000mg | IV infusion | Day 1 |
| **Cyclophosphamide** | 750mg/m$^2$ | IV infusion | Day 1 |
| **Vincristine*** | 1.4mg/m$^2$ (max 2mg dose) | IV infusion | Day 1 |
| **Prednisolone** | 100mg | Orally | Days 1-5 |

* For those patients >70, consider vincristine dose of 1mg.

**Each cycle is a 21 day cycle up to a maximum of 8 cycles**

Patients may then be eligible or Obinutuzumab maintenance therapy – please refer to separate protocol.

## Administration:

- Obinutuzumab is for intravenous use and should be given as an intravenous infusion through a dedicated line after dilution.
- If a planned dose of obinutuzumab is missed, it should be administered as soon as possible; do not omit it or wait until the next planned dose.
- Obinutuzumab should not be administered as an intravenous push or bolus.
- Obinutuzumab has no or negligible influence on the ability to drive and use machines. IRRs are very common during the first infusion, and patients experiencing infusion related symptoms should be advised not to drive or use machines until symptoms abate.

## Emetogenic risk:

Highly emetogenic

## Supportive Treatments:

**Pre-medication:** (see treatment schedule table below)

- Paracetamol orally 1g to be taken 30 minutes prior to the infusion
- Chlorphenamine intravenously 10mg to be taken 30 minutes prior to the infusion
- Intravenous dexamethasone should be administered at least 60 minutes prior to the first dose of obinutuzumab (cycle 1, day 1).
- Patients with Grade 3 IRRs with the previous infusion OR those with a lymphocyte counts > 25 x $10^9$/L prior to the next treatment should have intravenous dexamethasone 20mg 60 minutes prior to the infusion. Please note that the IV

dexamethasone may be omitted if Day 1 or oral prednisolone (100mg) taken at least 60 minutes before start of obinutuzumab infusion.

**Take home medication:**

- Ondansetron 8mg two times a day for 5 days
- Metoclopramide 10mg three times a day when required
- Docusate 100mg two times a day when required
- Allopurinol 300mg daily (reduce dose if the patient has renal dysfunction) for the first two cycles.

## Extravasation risk:

Obinutuzumab – neutral

Cyclophosphamide – non-vesicant

Vincristine – vesicant

**Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'**

## Dosing in renal and hepatic impairment:

<table>
<tr><td rowspan="3">Renal</td><td>Obinutuzumab</td><td>No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance > 30mL/min). The safety of obinutuzumab has not been established in patients with severe renal impairment (patients with a creatinine clearance < 30mL/min).</td></tr>
<tr><td>Cyclophosphamide</td><td>Decreased renal excretion may result in patients with severe renal impairment
<table>
<tr><th>CrCl (mL/min)</th><th>Recommended Dose</th></tr>
<tr><td>> 20</td><td>No dose reduction</td></tr>
<tr><td>10-20</td><td>25% dose reduction</td></tr>
<tr><td>< 10</td><td>50% dose reduction</td></tr>
</table></td></tr>
<tr><td>Vincristine</td><td>No dose reduction necessary</td></tr>
</table>

| | | |
|---|---|---|
| **Hepatic** | Obinutuzumab | The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established. |
| | Cyclophosphamide | No dose reduction necessary |

| | | |
|---|---|---|
| | Vincristine | <table><tr><th>Parameter</th><th>Recommended Dose</th></tr><tr><td>Bilirubin 26-51µmol/L **OR** AST/ALT 60-80</td><td>50% dose reduction</td></tr><tr><td>Bilirubin > 50µmol/L **AND** AST/ALT normal</td><td>50% dose reduction</td></tr><tr><td>Bilirubin > 51µmol/L **AND** AST/ALT > 180</td><td>Omit</td></tr></table> |

## Interactions:

- No formal drug-drug interaction studies have been performed with obinutuzumab
- Mould active azoles (e.g. posconazole) should be avoided in combination with vincristine as there is an increased risk of neurotoxicity. Fluconazole can be given but signs of neurotoxicity should be monitored.
- Phenytoin given with vincristine may reduce blood levels of the anticonvulsant and to increase seizure activity. Therapeutic Drug Monitoring (TDM) for phenytoin would be advised.
- The safety of immunisation with live or attenuated viral vaccines following obinutuzumab has not been studied and vaccination with live virus vaccines is not recommended during treatment and until B-cell recovery.
- Please consult the relevant summary of product characteristics via https://www.medicines.org.uk/emc for the full list of interactions.

## Treatment Schedule:

| Day | Drug | Dose | Route | Diluent and rate |
|---|---|---|---|---|
| **CYCLE 1** | | | | |
| **1** | **Dexamethasone** | **20mg** | IV | To be administered as a slow IV bolus - 60 minutes prior to the infusion<br>May be omitted if oral prednisolone given at least 60 minutes before Obinutuzumab dose |
| | **Paracetamol** | **1000mg** | PO | To be administered 30 minutes prior to the infusion |
| | **Chlorphenamine** | **10mg** | IV | Bolus – to be administered 30 minutes prior to the infusion |
| | **Obinutuzumab** | **1000mg** | IV | In 250mL Sodium Chloride 0.9% (see rate below) |
| | **Prednisolone** | **100mg** | PO | Orally once a day for 5 days |

| | | | | |
|---|---|---|---|---|
| | **Cyclophosphamide** | **750mg/m$^2$** | IV | In 250mL Sodium Chloride 0.9% over 30 minutes |
| | **Vincristine*** | **1.4mg/m$^2$** (max 2mg dose) | IV **ONLY** | In 50mL Sodium Chloride 0.9% over 5-10 minutes – **fatal is given any other route** |
| **8** | **Paracetamol** | **1000mg** | PO | To be administered 30 minutes prior to the infusion |
| | **Chlorphenamine** | **10mg** | IV | Bolus – to be administered 30 minutes prior to the infusion |
| | **Obinutuzumab** | **1000mg** | IV | In 250ml Sodium Chloride 0.9% (see rate below) |
| **15** | **Paracetamol** | **1000mg** | PO | To be administered 30 minutes prior to the infusion |
| | **Chlorphenamine** | **10mg** | IV | Bolus – to be administered 30 minutes prior to the infusion |
| | **Obinutuzumab** | **1000mg** | IV | In 250ml Sodium Chloride 0.9% (see rate below) |
| **CYCLE 2-8** | | | | |
| **1** | **Paracetamol** | **1000mg** | PO | To be administered 30 minutes prior to the infusion |
| | **Chlorphenamine** | **10mg** | IV | Bolus – to be administered 30 minutes prior to the infusion |
| | **Obinutuzumab** | **1000mg** | IV | In 250ml Sodium Chloride 0.9% |
| | **Prednisolone** | **100mg** | PO | Orally once a day for 5 days |

| **Day** | **Drug** | **Dose** | **Route** | **Diluent and rate** |
|---|---|---|---|---|
| **CYCLE 2-8 continued** | | | | |
| | **Cyclophosphamide** | **750mg/m$^2$** | IV | In 250mL Sodium Chloride 0.9% over 30 minutes |
| | **Vincristine*** | **1.4mg/m$^2$** (max 2mg dose) | IV **ONLY** | In 50mL Sodium Chloride 0.9% over 5-10 minutes – **fatal is given any other route** |

**Cycle frequency is every 21 days up to a maximum of 8 cycles**

Patients may then be eligible or Obinutuzumab maintenance therapy – please refer to separate protocol.

**Patients with a Grade 3 IRRs with the previous infusion should have intravenous corticosteroid at least 1 hour prior to the next obinutuzumab infusion.**

Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations or obinutuzumab as outlined below.

- 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 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.

**Obinutuzumab rate:**

First dose: Administer at 50mg/hour – the rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr. Incremental escalation of the infusion rate should be considered only in the absence of Infusion Related Reactions (IRRs).

Subsequent doses: If no IRR or if an IRR Grade 1 occurred during the previous infusion when the final infusion rate was 100 mg/hr or faster, infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr. If the patient experienced an IRR of Grade 2 or higher during the previous infusion administer at 50 mg/hr. The rate of infusion can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400mg/hr

Monitor observations as routine including 30 minutes after each dose increment to identify infusion reactions. Incremental escalation of the infusion rate should be considered only in the absence of Infusion Related Reactions (IRRs).

## Main Toxicities:

| Induction treatment with Obinutuzumab |
| --- |
| Upper respiratory tract infection, sinusitis, urinary tract infection, pneumonia, herpes zoster, oral herpes, rhinitis, pharyngitis, lung infection, influenza nasopharyngitis, squamous cell carcinoma of the skin, neutropenia, thrombocytopenia, anaemia, leukopenia, tumour lysis syndrome, hyperuricaemia, hypokalaemia, insomnia, depression, anxiety, headache, ocular hyperaemia, atrial fibrillation and cardiac failure, hypertension, cough, nasal congestion, rhinorrhoea, diarrhoea, constipation, alopecia, pruritus, dysuria, urinary incontinence, pyrexia, asthenia, chest pain, reduction in WCCs and neutropenia, weight increase and infusion related reactions. |

**Tumour lysis syndrome (TLS) prophylaxis:** Patients with a high tumour burden and/or renal impairment (CrCl < 70mL/min) are considered at risk of TLS and should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricostatics (e.g. allopurinol), or suitable alternative treatment such as urate oxidase (e.g. rasburicase), starting 12-24 hours prior to start of obinutuzumab infusion as per standard practice. Patients should continue to receive repeated prophylaxis prior to each subsequent infusion, if deemed appropriate.

**Hypotension:** it is important to note that hypotension is a symptom of the potential infusion related reaction (IRR), which may occur during obinutuzumab intravenous infusions. **Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each infusion and for the first hour after administration.**

## Investigations and treatment plan

| | Pre | Cycle 1 D1 | Cycle 1 D8 | Cycle 1 D15 | Cycle 2 | Cycle 3 | Ongoing |
|---|---|---|---|---|---|---|---|
| Informed Consent | x | | | | | | |
| Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2 | x | | | | | | |
| Clinical Assessment (include PS and Toxicity assessment) | x | x | | | x | x | Every cycle |
| SACT Assessment | x | x | x | x | x | x | Prior to every dose |
| Weight | x | x | | | x | x | Every cycle |
| Height | x | | | | | | |
| FBC | x | x | | | x | x | Every cycle |
| U&E, LFT and Bone profile | x | x | | | x | x | Every cycle |
| Creatinine Clearance (Cockcroft and Gault) | x | | | | | | |
| Blood pressure | x | x | x | x | x | x | Continuous monitoring required if on Obinutuzumab |
| Temp, respiratory rate, pulse | | x | x | x | x | x | Continuous monitoring required if on Obinutuzumab |
| Pregnancy test | x | | | | | | Where appropriate |
| Bone marrow assessment | | | | | | | Where clinically indicated |
| Radiological imaging | x | | | | | | Repeat end of treatment |

## Dose Modifications and Toxicity Management:

### Haematological toxicity

| ***Note: no dose modifications required for first cycle*** | |
|---|---|
| **Neutrophils (x10$^9$/L)** | **Modification** |
| <1 on day of treatment | Delay cycle by 1 week. Discuss use of G-CSF or dose reductions for further cycles with consultant |
| Any febrile neutropenia following any cycle of CHOP | All subsequent cycles should be given with GCSF support. Consider dose reduction. |
| Febrile neutropenic episode despite G-CSF support | Consider reduction of cyclophosphamide by 50% for all subsequent cycles |
| **Platelets (x10$^9$/L)** | **Modification** |
| <100 on day of treatment | Delay cycle by 1 week. |
| Second delay due to thrombocytopenia | Consider reducing dose of cyclophosphamide by 50% for all subsequent cycles |

Neutropenia: Patients who experience neutropenia should be closely monitored with regular laboratory tests until resolution. It treatment is necessary it should be administered in accordance with local guidelines and the administration G-CSF should be considered. Any signs of concomitant infection should be treated appropriately. Dose delays should be considered in case of severe or life threatening neutropenia. It is strongly recommended that patients with severe neutropenia lasting more than 1 week receive antimicrobial prophylaxis throughout the treatment period until resolution to Grade 1 or 2. Antiviral and antifungal prophylaxis should be considered. Late onset neutropenia (occurring ≥ 28 days after the end of treatment) or prolonged neutropenia (lasting more than 28 days after treatment has been completed/stopped) may occur. Patients with renal impairment (CrCl < 50mL/min) are more at risk of neutropenia.

Thrombocytopenia: Severe and life-threatening thrombocytopenia including acute thrombocytopenia (occurring within 24 hours after the infusion) has been observed during treatment with obinutuzumab. Fatal haemorrhagic events have also been reported in Cycle 1 in patients treated with obinutuzumab. Patients should be closely

monitored for thrombocytopenia, especially during the first cycle; regular laboratory tests should be performed until the event resolves, and dose delays should be considered in case of severe or life-threatening thrombocytopenia.

**Non-Haematological toxicity**

Neurotoxicity:

| Grade | Modification |
|---|---|
| Grade 2 motor weakness or grade 3 sensory toxicity | Dose reduce Vincristine to 50% |
| Higher grades of neurological toxicity | Omit Vincristine |

## References:


1. Summary of Product Characteristics, Gazyvaro 1000mg concentrate for solution for infusion, Roche, available from https://www.medicines.org.uk/emc [accessed on the 16th August 2019]
2. Summary of Product Characteristics, Vincristine Sulphate 1mg/ml, Hospira UK Ltd, available from https://www.medicines.org.uk/emc [accessed on the 16th August 2019]
3. Summary of Product Characteristics, Cyclophosphamide 500mg powder for solution for injection or infusion, Sandoz Limited, available from https://www.medicines.org.uk/emc [accessed on the 16th August 2019]
4. NICE TA 513 Obinutuzumab for untreated advanced follicular lymphoma – Published 21 March 2018
5. Marcus R., Davies A., Obinutuzumab for the First Line Treatment of Follicular Lymphoma. The New England Journal of Medicine, 2017; 377: 1331-1344