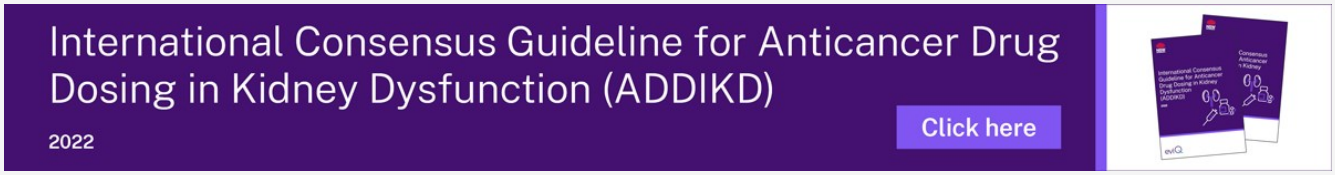
Non-Hodgkin lymphoma O-CVP (oBINUTUZumab CYCLOPHOSPHamide vinCRISTine prednisolone)

ID: 3595 v.3 **Endorsed**

Patients with lymphoma should be considered for inclusion into clinical trials. Link to ALLG website, ANZCTR website and Lymphoma Australia website.

The anticancer drug(s) in this protocol may have been included in the ADDIKD guideline. Dose recommendations in kidney dysfunction have yet to be updated to align with the ADDIKD guideline. Recommendations will be updated once the individual protocol has been evaluated by the reference committee. For further information refer to the ADDIKD guideline. To assist with calculations, use the eviQ Estimated Glomerular Filtration Rate (eGFR) calculator.



Related pages:

- Non-Hodgkin lymphoma oBINUTUZumab maintenance

Treatment schedule - Overview

Cycle 1

Drug	Dose	Route	Day
Prednisolone	100 mg ONCE a day	PO	1 to 5
oBINUTUZumab	1,000 mg	IV infusion	1
vinCRISTine	1.4 mg/m^2 (Cap dose at 2 mg)	IV infusion	1
CYCLOPHOSPHamide	750 mg/m^2	IV infusion	1
oBINUTUZumab	1,000 mg	IV infusion	8 and 15

Cycle 2 to 8

Drug	Dose	Route	Day
Prednisolone	100 mg ONCE a day	PO	1 to 5
oBINUTUZumab	1,000 mg	IV infusion	1
vinCRISTine	1.4 mg/m^2 (Cap dose at 2 mg)	IV infusion	1
CYCLOPHOSPHamide	750 mg/m^2	IV infusion	1

Frequency: 21 days

Cycles: 8

Drug status: **Obinutuzumab:** (PBS authority)

All other drugs in this protocol are on the PBS general schedule

Prednisolone is available as **1 mg**, **5 mg** and **25 mg** tablets

Cost: ~ $18,680 per cycle

Treatment schedule - Detail

The supportive therapies (e.g. antiemetics, premedications, etc.), infusion times, diluents, volumes and routes of administration, if included, are listed as defaults. They may vary between institutions and can be substituted to reflect individual institutional policy.

*Antiemetics if included in the treatment schedule are based upon recommendations from national and international guidelines. These are **defaults only** and may be substituted to reflect individual institutional policy. Select here for recommended doses of alternative antiemetics.*

Cycle 1

Day 1		
Prednisolone	100 mg (PO)	ONCE a day on days 1 to 5.* Take in the morning with food.
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
oBINUTUZumab	1,000 mg (IV infusion)	in 250 mL sodium chloride 0.9%. Start at 50 mg/hr. Rate can be increased by 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
vinCRISTine	1.4 mg/m^2 (IV infusion) (Cap dose at 2 mg)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
CYCLOPHOSPHamide	750 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes

Day 2 to 5		
Prednisolone	100 mg (PO)	ONCE a day on days 1 to 5.* Take in the morning with food.

Day 8 and 15		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment. ** May be omitted - please see below for criteria.
Dexamethasone	20 mg (IV)	60 minutes before treatment. ** May be omitted - please see below for criteria.
oBINUTUZumab	1,000 mg (IV infusion)	in 250 mL sodium chloride 0.9%. Start at 100 mg/hr. Rate can be increased by 100 mg/hr every 30 minutes, to a maximum of 400 mg/hr. ***

Cycle 2 to 8

Day 1		
Prednisolone	100 mg (PO)	ONCE a day on days 1 to 5.* Take in the morning with food.
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment. **May be omitted - please see below for criteria.
oBINUTUZumab	1,000 mg (IV infusion)	in 250 mL sodium chloride 0.9%. Start at 100 mg/hr. Rate can be increased by 100 mg/hr every 30 minutes, to a maximum of 400 mg/hr. ***
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy

Day 1		
vinCRISTine	1.4 mg/m^2 (IV infusion) (Cap dose at 2 mg)	in 50 mL sodium chloride 0.9% over 5 to 10 minutes via minibag
CYCLOPHOSPHamide	750 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes

Day 2 to 5		
Prednisolone	100 mg (PO)	ONCE a day on days 1 to 5.* Take in the morning with food.

* Dose for day 1 should be taken 60 minutes before obinutuzumab infusion.

**** For subsequent obinutuzumab infusions (cycle 1, day 8 onwards):**

- **Antihistamine** premedication may be omitted for subsequent infusions if no infusion related reactions (IRR) occurred with the previous infusion.
- **Intravenous corticosteroid** premedication may be omitted for subsequent infusions if no grade 1 or 2 IRR occurred with the previous infusion. If a grade 3 IRR occurred OR lymphocyte count > 25 x10^9/L prior to next treatment, intravenous corticosteroid premedication should be continued.

*** If the patient experienced a grade 2 or higher infusion related reaction during the previous administration, commence at 50 mg/hr. The rate of infusion should be titrated up at 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.

Frequency: 21 days

Cycles: 8

Indications and patient population

- Previously untreated CD20-positive follicular lymphoma

Clinical information

Safety alert vincristine administration	For safe administration of vincristine refer to the safety alert issued by the Australian Commission on Safety and Quality in Health Care
Venous access required	IV cannula (IVC) or central venous access device (CVAD) is required to administer this treatment. Read more about central venous access device line selection
Hypersensitivity/infusion related reaction	High risk with obinutuzumab. Hypotension may occur during obinutuzumab infusion. Evaluate individual patient benefits and risks and consider withholding antihypertensive treatments for 12 hours prior to and during, and for one hour after each infusion. Read more about Hypersensitivity reaction

Premedication	The product information states that the premedication for obinutuzumab should consist of an analgesic/antipyretic, an antihistamine and an intravenous corticosteroid for the first initial dose. **For subsequent infusions:** • **Antihistamine** premedication may be omitted for subsequent infusions if no infusion related reactions (IRR) occurred with the previous infusion. • **Intravenous corticosteroid*** premedication may be omitted for subsequent infusions if no grade 1 or 2 infusion related reactions (IRR) occurred with the previous infusion. If a grade 3 IRR occurred OR lymphocyte counts > 25 x10^9/L prior to next treatment, intravenous corticosteroid premedication should be continued. • **Analgesic/antipyretic** premedication is given before all infusions. A suggested default premedication has been added to the treatment schedule, and may be substituted to reflect institutional policy. **Note:** hydrocortisone is not recommended as it has not been effective in reducing the rate of infusion reactions. ** IV corticosteroid (may be substituted by oral corticosteroids if contained within the chemotherapy regimen)*
Emetogenicity MODERATE	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. As a steroid has been included as part of this protocol, additional antiemetic steroids are not required. For patients with a prior episode of chemotherapy induced nausea or vomiting, a NK1 receptor antagonist may be available on the PBS in combination with a $5HT_3$ antagonist and steroid. Ensure that patients also have sufficient antiemetics for breakthrough emesis: Metoclopramide 10 mg three times a day when necessary (maximum of 30 mg/24 hours, up to 5 days) OR Prochlorperazine 10 mg PO every 6 hours when necessary. Read more about preventing anti-cancer therapy induced nausea and vomiting
Progressive multifocal leukoencephalopathy	Use of monoclonal antibodies may be associated with an increased risk of progressive multifocal leukoencephalopathy (PML), a rare but potentially fatal opportunistic viral infection of the brain. Patients must be monitored for any new or worsening neurological symptoms. Read more about progressive multifocal leukoencephalopathy and the Therapeutic Goods Administration Medicines Safety update on progressive multifocal leukoencephalopathy from the Australian Government, Department of Health.
Cardiac toxicity	Arrhythmias (such as atrial fibrillation and tachyarrhythmia), angina pectoris, acute coronary syndrome, myocardial infarction and heart failure may occur with obinutuzumab, particularly in patients with underlying cardiac disease. These cardiac events may occur as part of an infusion-related reaction and can be fatal. Monitor patients for signs and symptoms of cardiac toxicity or fluid overload and refer to cardiologist if suspected. Read more about cardiac toxicity associated with anti-cancer drugs
Obinutuzumab short duration infusion (SDI)	Administration of obinutuzumab by short duration infusion is not in line with the product monograph, however published literature indicates that it can be completed safely in patients who meet the appropriate criteria. Read more about obinutuzumab short duration infusion
Peripheral neuropathy	Assess prior to each treatment. Based on clinical findings, temporary omission, dose reduction or cessation of the vinca alkaloid may be indicated; review by medical officer before commencing treatment. Read more about peripheral neuropathy Link to chemotherapy-induced peripheral neuropathy screening tool
Constipation	Prescribe prophylactic laxatives to prevent constipation related to the use of vinca alkaloids.

Corticosteroids	Diabetic patients should monitor their blood glucose levels closely. To minimise gastric irritation, advise patient to take immediately after food. Consider the use of a H2 antagonist or proton pump inhibitor if appropriate. Read more about acute short term effects from corticosteroids
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 one of treatment. Patients should be closely monitored for thrombocytopenia throughout treatment, especially during the first cycle, and use of concomitant medications that may worsen haemorrhagic risk (e.g. antiplatelets, anticoagulants) should be taken into consideration. Correlating the timing of thrombocytopenia after obinutuzumab can assist in differentiating from other causes. In clinical trials, thrombocytopenia was reported in 10.4% of patients treated with obinutuzumab.
Tumour lysis risk	Assess patient for risk of developing tumour lysis syndrome. Read more about prevention and management of tumour lysis syndrome.
Pneumocystis jirovecii pneumonia (PJP) prophylaxis	Read more about prophylaxis of pneumocystis jiroveci (carinii) in cancer patients
Antiviral prophylaxis	Read more about antiviral prophylaxis drugs and doses
Growth factor support	G-CSF (short or long-acting) is available on the PBS for chemotherapy induced neutropenia depending on clinical indication and/or febrile neutropenia risk. Access the PBS website
Blood tests	FBC, EUC, eGFR, LFTs, LDH and BSL at baseline, prior to each treatment, and as clinically indicated.
Hepatitis B screening and prophylaxis	Routine screening for HBsAg and anti-HBc is recommended prior to initiation of treatment. Prophylaxis should be determined according to individual institutional policy. Read more about hepatitis B screening and prophylaxis in cancer patients requiring cytotoxic and/or immunosuppressive therapy
Vaccinations	Live vaccines are contraindicated in cancer patients receiving immunosuppressive therapy and/or who have poorly controlled malignant disease. Refer to the recommended schedule of vaccination for immunocompromised patients, as outlined in the Australian Immunisation Handbook. Read more about COVID-19 vaccines and cancer.
Fertility, pregnancy and lactation	Cancer treatment can have harmful effects on fertility and this should be discussed with all patients of reproductive potential prior to commencing treatment. There is a risk of foetal harm in pregnant women. A pregnancy test should be considered prior to initiating treatment in females of reproductive potential if sexually active. It is important that all patients of reproductive potential use effective contraception whilst on therapy and after treatment finishes. Effective contraception methods and adequate contraception timeframe should be discussed with all patients of reproductive potential. Possibility of infant risk should be discussed with breastfeeding patients. Read more about the effect of cancer treatment on fertility

Dose modifications

Evidence for dose modifications is limited, and the recommendations made on eviQ are intended as a guide only. They are generally conservative with an emphasis on safety. Any dose modification should be based on clinical judgement, and the individual patient's situation including but not limited to treatment intent (curative vs palliative), the anti-cancer regimen (single

versus combination therapy versus chemotherapy versus immunotherapy), biology of the cancer (site, size, mutations, metastases), other treatment related side effects, additional co-morbidities, performance status and patient preferences.Suggested dose modifications are based on clinical trial findings, product information, published guidelines and reference committee consensus . The dose reduction applies to each individual dose and not to the total number of days or duration of treatment cycle unless stated otherwise. Non-haematological gradings are based on Common Terminology Criteria for Adverse Events (CTCAE) unless otherwise specified. Renal and hepatic dose modifications have been standardised where possible. For more information see dosing considerations & disclaimer .

The dose recommendations in kidney dysfunction (i.e.renal impairment) displayed may not reflect those in the ADDIKD guideline and have been included for historical reference only. Recommendations will be updated once the individual protocol has been evaluated by the reference committee, with this version of the protocol then being archived. Clinicians are expected to refer to the ADDIKD guideline prior to prescribing in kidney dysfunction.
International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIKD).

Note: All dose reductions are calculated as a percentage of the starting dose

Haematological toxicity	
ANC x 10^9/L, Platelets x 10^9/L (pre-treatment blood test)	
ANC less than 1.0 and/or platelets less than 75	Delay treatment until recovery. Consider adding G-CSF depending on the individual institutions current practice. If thrombocytopenia occurs within 24 hours of obinutuzumab administration, consider omitting obinutuzumab, or alternatively, resume same dose and monitor with supportive management (i.e. transfusions, intravenous immunoglobulins).[1, 2]

Renal impairment	
Creatinine clearance (mL/min)	
10 to 50	Reduce cyclophosphamide dose by 25%
less than 10	Reduce cyclophosphamide dose by 50%

Hepatic impairment		
Hepatic dysfunction		
Bilirubin (micromol/L)	AST/ALT (units)	
26 to 51 *OR*	60 to 180	Reduce vincristine by 50%
greater than 51 AND	n/a	Reduce vincristine by 50%
greater than 51 AND	greater than 180	Omit vincristine

Infusion-related reactions (IRR)	
Grade 1 or 2	Reduce infusion rate of obinutuzumab and manage symptoms.
Grade 3	First occurrence: interrupt obinutuzumab infusion and manage symptoms. Once resolved, restart infusion at no more than half the rate of the infusion rate when IRR occurred. Second occurrence: immediately interrupt obinutuzumab infusion and manage symptoms. Discontinue obinutuzumab and continue treatment or consider switching to another protocol if appropriate.
Grade 4	Immediately interrupt the obinutuzumab infusion and discontinue obinutuzumab. Continue treatment or consider switching to another protocol if appropriate.

Peripheral neuropathy	
Grade 2	Consider omitting vincristine

Interactions

Drug interactions in eviQ protocols are under review and being updated to align with current literature. Further site-wide updates and changes will occur in due course. References & Disclaimer

The drug interactions shown below are not an exhaustive list. For a more comprehensive list and for detailed information on specific drug interactions and clinical management, please refer to the specific drug product information and the following key resources:

- *MIMS - interactions tab (includes link to a CYP-450 table) (login required)*
- *Australian Medicines Handbook (AMH) – interactions tab (login required)*
- *Micromedex Drug Interactions (login required)*
- *Cancer Drug Interactions*
- *Cytochrome P450 Drug Interactions*

Cyclophosphamide		
	Interaction	**Clinical management**
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Increased toxicity of cyclophosphamide possible due to increased conversion to active (and inactive) metabolites	Avoid combination or monitor for cyclophosphamide toxicity
CYP3A4 inhibitors (e.g. aprepitant, azole antifungals, clarithromycin, erythromycin, grapefruit juice, ritonavir etc.)	Reduced efficacy of cyclophosphamide possible due to decreased conversion to active (and inactive) metabolites	Avoid combination or monitor for decreased clinical response to cyclophosphamide
Nephrotoxic drugs (e.g. aminoglycosides, amphotericin, contrast dye, frusemide, NSAIDs)	Additive nephrotoxicity	Avoid combination or monitor kidney function closely
Amiodarone	Possible additive pulmonary toxicity with high-dose cyclophosphamide (i.e. doses used prior to stem cell transplant; 60 mg/kg daily or 120 to 270 mg/kg over a few days)	Avoid combination or monitor closely for pulmonary toxicity
Allopurinol, hydrochlorothiazide, indapamide	Delayed effect. Increased risk of bone marrow depression; probably due to reduced clearance of active metabolites of cyclophosphamide	Avoid combination, consider alternative antihypertensive therapy or monitor for myelosuppression
Ciclosporin	Reduced efficacy of ciclosporin due to reduced serum concentration	Monitor ciclosporin levels; adjust dosage as appropriate; monitor response to ciclosporin
Suxamethonium	Prolonged apnoea due to marked and persistent inhibition of cholinesterase by cyclophosphamide	Alert the anaesthetist if a patient has been treated with cyclophosphamide within ten days of planned general anaesthesia

Prednisolone		
	Interaction	**Clinical management**
Antidiabetic agents (e.g. insulin, glibenclamide, glicazide, metformin, pioglitazone, etc)	The efficacy of antidiabetic agents may be decreased	Use with caution and monitor blood glucose
Azole antifungals (e.g. fluconazole, itraconazole, ketoconazole, posaconazole)	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity
Oestrogens (e.g. oral contraceptives)	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity. Dose reduction of prednisolone may be required
Ritonavir	Increased toxicity of prednisolone possible due to reduced clearance	Avoid combination or monitor for prednisolone toxicity

Obinutuzumab		
	Interaction	**Clinical management**
Antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to, throughout and 1 hour after the obinutuzumab infusion

Vincristine		
	Interaction	**Clinical management**
CYP3A4 and P-gp inhibitors (e.g. amiodarone, aprepitant, azole-antifungals, ritonavir, lapatinib, nilotinib, sorafenib, macrolides, ciclosporin, grapefruit juice etc.)	Increased toxicity of vincristine possible due to reduced clearance	Monitor for vincristine toxicity (esp. neurotoxicity, paralytic ileus)
CYP3A4 inducers (e.g. carbamazepine, phenytoin, phenobarbitone, rifampicin, St John's wort etc.)	Reduced efficacy of vincristine possible due to increased clearance	Monitor for decreased clinical response to vincristine
Mitomycin	Acute shortness of breath and severe bronchospasm has occurred following use of vincristine in patients who had received mitomycin simultaneously or within 2 weeks	Use combination with caution
Ototoxic drugs (e.g. cisplatin, aminoglycosides, frusemide, NSAIDs)	Additive ototoxicity	Avoid combination or perform regular audiometric testing

General		
	Interaction	**Clinical management**
Warfarin	Anti-cancer drugs may alter the anticoagulant effect of warfarin.	Monitor INR regularly and adjust warfarin dosage as appropriate; consider alternative anticoagulant.
Direct oral anticoagulants (DOACs) e.g. apixaban, rivaroxaban, dabigatran	Interaction with both CYP3A4 and P-gp inhibitors /inducers. DOAC and anti-cancer drug levels may both be altered, possibly leading to loss of efficacy or toxicity (i.e. increased bleeding).	Apixaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. If treating VTE, avoid use with strong CYP3A4 and P-gp inducers. Rivaroxaban: avoid concurrent use with strong CYP3A4 and P-gp inhibitors. Dabigatran: avoid combination with strong P-gp inducers and inhibitors. If concurrent use is unavoidable, monitor closely for efficacy/toxicity of both drugs.
Digoxin	Anti-cancer drugs can damage the lining of the intestine; affecting the absorption of digoxin.	Monitor digoxin serum levels; adjust digoxin dosage as appropriate.
Antiepileptics	Both altered antiepileptic and anti-cancer drug levels may occur, possibly leading to loss of efficacy or toxicity.	Where concurrent use of an enzyme-inducing antiepileptic cannot be avoided, monitor antiepileptic serum levels for toxicity, as well as seizure frequency for efficacy; adjust dosage as appropriate. Also monitor closely for efficacy of the anti-cancer therapy.
Antiplatelet agents and NSAIDs	Increased risk of bleeding due to treatment related thrombocytopenia.	Avoid or minimise combination. If combination deemed essential, (e.g. low dose aspirin for ischaemic heart disease) monitor for signs of bleeding.
Serotonergic drugs, including selective serotonin reuptake inhibitors (SSRIs e.g. paroxetine) and serotonin noradrenaline reuptake inhibitors (SNRIs e.g. venlafaxine)	Increased risk of serotonin syndrome with concurrent use of 5-HT3 receptor antagonists (e.g. palonosetron, ondansetron, granisetron, tropisetron, dolasetron, etc.)	Avoid combination. If combination is clinically warranted, monitor for signs and symptoms of serotonin syndrome (e.g. confusion, agitation, tachycardia, hyperreflexia). For more information link to TGA Medicines Safety Update
Vaccines	Diminished response to vaccines and increased risk of infection with live vaccines.	Live vaccines (e.g. BCG, MMR, zoster and varicella) are contraindicated in patients on immunosuppressive therapy. Use with caution in patients on non-immunosuppressive therapy. For more information; refer to the recommended schedule of vaccination for cancer patients, as outlined in the Australian Immunisation Handbook

Administration cycle 1

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual

product information monographs via the TGA website for further information.

Day 1

Approximate treatment time: 8 hours (initial); 4 to 6 hours (subsequent)

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Prime IV line(s) with sodium chloride 0.9%.

Insert IV cannula or access TIVAD or CVAD.

- baseline weight

Hydration if prescribed

Treatment - Time out

Prednisolone

- administer orally ONCE a day on **days 1 to 5**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Obinutuzumab

Prior to administration:

- check baseline observations
- check for previous adverse events with drug infusions
- verify premedication has been taken. If not, administer 60 minutes prior to obinutuzumab administration:
  - paracetamol 1000 mg orally AND
  - loratadine 10 mg orally (or similar antihistamine)
  - IV corticosteroid (may be substituted by oral corticosteroids if contained within the chemotherapy regimen)

Initial infusion:

- **commence** obinutuzumab infusion at 50 mg/hr for 30 minutes
- repeat observations prior to each rate increase
- **increase rate** by 50 mg/hr every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%

Hypotension may occur during obinutuzumab infusion. Consider withholding antihypertensive medication for 12 hours before, during, and for one hour after each infusion (if appropriate).

If a patient experiences any grade infusion related reaction (IRR) during infusion, adjust the infusion as outlined below:

Grade 4 (life threatening)

- stop infusion and permanently discontinue therapy

Grade 3 (severe)

- temporarily interrupt infusion and treat symptoms
- upon resolution of symptoms, restart the infusion at no more than half the previous rate (the rate being used at the time that the IRR occurred)
- if patient dose not experience any further IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

- stop infusion and permanently discontinue therapy if patients experience a second occurrence of a grade 3 IRR

Grade 1-2 (mild to moderate)

- reduce infusion rate and treat symptoms
- upon resolution of symptoms, continue infusion
- if patient dose not experience any IRR symptoms, infusion rate escalation may resume at the increments and intervals as appropriate for the treatment dose.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Cyclophosphamide

Administer cyclophosphamide:

- via IV infusion over 30 to 60 minutes
- flush with ~ 50 mL of sodium chloride 0.9%
- rapid infusion can cause dizziness, rhinitis, nausea and perioral numbness. If symptoms develop, slow infusion rate.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Days 8, 15

Handling of monoclonal antibodies and waste management

Safe administration

General patient assessment prior to each day of treatment.

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Prime IV line(s) with sodium chloride 0.9%.

Insert IV cannula or access TIVAD or CVAD.

- weigh patient before each treatment

Treatment - Time out

Obinutuzumab

Prior to administration:

- check baseline observations
- check for previous adverse events with drug infusions
- verify premedication has been taken. If not, administer 60 minutes prior to obinutuzumab administration:
- paracetamol 1000 mg orally AND
- loratadine 10 mg orally (or similar **antihistamine** premedication may be omitted for subsequent infusions if no infusion related reactions (IRR) occurred with the previous infusion)
- IV corticosteroid if a grade 3 IRR occurred with the previous infusion OR lymphocyte counts > 25 x 10^9 /L prior to next treatment.

Subsequent infusions:

If **no IRR or a Grade 1 IRR occurred** with the previous infusion:

- **commence** obinutuzumab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- **increase rate** by 100 mg/hr every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%

If a **Grade 2 IRR or higher occurred** with the previous infusion:

- **commence** obinutuzumab infusion at 50 mg/hr
- repeat observations prior to each rate increase
- increase rate by 50 mg/hr every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~100 mL of sodium chloride 0.9%

Hypotension may occur during obinutuzumab infusion. Consider withholding antihypertensive medication for 12 hours before, during, and for one hour after each infusion (if appropriate).

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions (reproductive risk only) for 7 days after completion of drug(s).

Discharge information

Prednisolone tablets

- Prednisolone tablets with written instructions on how to take them.

Antiemetics

- Antiemetics as prescribed.

Laxatives

- Ensure patient has prophylactic laxatives.

Prophylaxis medications

- Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, PJP prophylaxis, antifungals, antivirals.

Patient information

- Ensure patient receives patient information sheet.

Administration cycles 2 to 8

eviQ provides safe and effective instructions on how to administer cancer treatments. However, eviQ does not provide every treatment delivery option, and is unable to provide a comprehensive list of cancer treatment agents and their required IV line giving set/filter. There may be alternative methods of treatment administration, and alternative supportive treatments that are also appropriate. Please refer to the individual product information monographs via the TGA website for further information.

Day 1

Approximate treatment time: 8 hours (initial); 4 to 6 hours (subsequent)

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

Peripheral neuropathy assessment tool

Any toxicity grade 2 or greater may require dose reduction, delay or omission of treatment and review by medical officer before commencing treatment.

Prime IV line(s) with sodium chloride 0.9%.

Insert IV cannula or access TIVAD or CVAD.

- weigh patient before each treatment

Treatment - Time out

Prednisolone

- administer orally ONCE a day on **days 1 to 5**
- to be taken in the morning with or immediately after food

Note: if a dose is forgotten or vomited, contact treating team.

Obinutuzumab

Prior to administration:

- check baseline observations
- check for previous adverse events with drug infusions
- verify premedication has been taken. If not, administer 60 minutes prior to obinutuzumab administration:
- paracetamol 1000 mg orally AND
- loratadine 10 mg orally (or similar **antihistamine** premedication may be omitted for subsequent infusions if no infusion related reactions (IRR) occurred with the previous infusion)
- IV corticosteroid if a grade 3 IRR occurred with the previous infusion OR lymphocyte counts > 25 x 10^9 /L prior to next treatment.

Subsequent infusions:

If **no IRR or a Grade 1 IRR occurred** with the previous infusion:

- **commence** obinutuzumab infusion at 100 mg/hr
- repeat observations prior to each rate increase
- **increase rate** by 100 mg/hr every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~ 100 mL of sodium chloride 0.9%

If a **Grade 2 IRR or higher occurred** with the previous infusion:

- **commence** obinutuzumab infusion at 50 mg/hr
- repeat observations prior to each rate increase
- increase rate by 50 mg/hr every 30 minutes to a maximum of 400 mg/hr if observations are stable
- flush with ~100 mL of sodium chloride 0.9%

Hypotension may occur during obinutuzumab infusion. Consider withholding antihypertensive medication for 12 hours before, during, and for one hour after each infusion (if appropriate).

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Vincristine

Administer vincristine (vesicant)

- via a minibag over 5 to 10 minutes
- ensure vein is patent and monitor for signs of extravasation throughout administration
- flush with ~150 mL of sodium chloride 0.9%.

Cyclophosphamide

Administer cyclophosphamide:

- via IV infusion over 30 to 60 minutes
- flush with ~ 50 mL of sodium chloride 0.9%
- rapid infusion can cause dizziness, rhinitis, nausea and perioral numbness. If symptoms develop, slow infusion rate.

Remove IV cannula and/or deaccess TIVAD or CVAD.

Continue safe handling precautions until 7 days after completion of drug(s)

Discharge information

Prednisolone tablets

- Prednisolone tablets with written instructions on how to take them.

Antiemetics

- Antiemetics as prescribed.

Laxatives

- Ensure patient has prophylactic laxatives.

Prophylaxis medications

- Prophylaxis medications (if prescribed) i.e. tumour lysis prophylaxis, PJP prophylaxis, antifungals, antivirals.

Patient information

- Ensure patient receives patient information sheet.

Side effects

The side effects listed below are not a complete list of all possible side effects for this treatment. Side effects are categorised into the approximate onset of presentation and should only be used as a guide.

Immediate (onset hours to days)	
Hypersensitivity reaction	Anaphylaxis and infusion related reactions can occur with this treatment. Read more about hypersensitivity reaction
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
Extravasation, tissue or vein injury	The unintentional instillation or leakage of a drug or substance out of a blood vessel into surrounding tissue. This has the potential to cause damage to affected tissue. Read more about extravasation management
Flu-like symptoms	
Headache	
Hypotension	Low blood pressure can occur with this treatment.

Early (onset days to weeks)	
Neutropenia	Abnormally low levels of neutrophils in the blood. This increases the risk of infection. Any fever or suspicion of infection should be investigated immediately and managed aggressively. Read more about immediate management of neutropenic fever
Thrombocytopenia	A reduction in the normal levels of functional platelets, increasing the risk of abnormal bleeding. Read more about thrombocytopenia
Atrial fibrillation	
Constipation	
Fatigue	Read more about fatigue
Haemorrhagic cystitis	An inflammatory process, characterised by diffuse bladder mucosal inflammation resulting in haemorrhage. Patients are at risk following blood and marrow transplant (BMT) or treatment with cyclophosphamide, ifosfamide and/or radiation therapy. Read more about haemorrhagic cystitis
Insomnia	
Peripheral neuropathy	Typically symmetrical sensory neuropathy, affecting the fingers and toes, sometimes progressing to the hands and feet. It is associated with several classes of anti-cancer drugs. These include taxanes, platinum-based compounds, vinca alkaloids and some drugs used to treat multiple myeloma. Read more about peripheral neuropathy
Side effects of corticosteroids	Insomnia, oedema, increased risk of infection e.g. oral thrush, gastric irritation, worsening of peptic ulcer disease, increased blood sugar levels, loss of diabetic control, mood and behavioural changes - including anxiety, euphoria, depression, mood swings, increased appetite and weight gain, osteoporosis and fractures (long term use), bruising and skin fragility are associated with corticosteroid use.
Skin rash	Anti-cancer drugs can cause a number of changes in the skin with maculo-papular rash the most common type of drug-induced skin reaction. Read more about skin rash

Late (onset weeks to months)	
Alopecia	Hair loss may occur from all parts of the body. Patients can also experience mild to moderate discomfort of the hair follicles, and rarely pain as the hair is falling out. Read more about alopecia and scalp cooling
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
Progressive multifocal leukoencephalopathy (PML)	A rare opportunistic viral infection of the brain, usually leading to death or severe disability, can occur with monoclonal antibodies (e.g. rituximab, obinutuzumab, ofatumumab, brentuximab vedotin) and other targeted therapies (e.g. ibrutinib, ruxolitinib, idelalisib). Onset may occur up to months after the final dose. Read more about progressive multifocal leukoencephalopathy (PML)

Delayed (onset months to years)	
Pulmonary toxicity	Pulmonary toxicity may include damage to the lungs, airways, pleura and pulmonary circulation. Read more about pulmonary toxicity associated with anti-cancer drugs

Evidence

The evidence of Obinutuzumab-CVP is mostly derived from the multicentre phase 3, open labelled GALLIUM study, which compared the combination of obinutuzumab-chemotherapy (G-chemo) versus rituximab-chemotherapy (R-chemo) in previously untreated advanced stage follicular lymphoma. It has limitations when it comes to comparing the different chemotherapy backbones as

patients were not randomly assigned to each chemotherapy backbone.[3]

1202 patients were randomised 1:1 to receive either G-chemo or R-chemo. The choice of chemotherapy regimen was left to investigators discretion between cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); cyclophosphamide, vincristine, and prednisone (CVP); or bendamustine. Responding patients (complete or partial response at the end of induction) continued on to receive maintenance treatment with the same antibody treatment every 2 months for 2 years, until disease progression or withdrawal from the trial.[3]

Primary end point was progression free survival (PFS) and secondary end points included overall response (OR) rate at the end of induction therapy, event-free survival, disease-free survival, duration of response, overall survival (OS), time to new anti-lymphoma treatment (TTNAT), and safety.[3]

Baseline data of each chemotherapy backbone showed some notable differences between groups. More patients receiving CHOP were in the FLIPI high-risk group (47% compared to 40% in bendamustine and 35% in CVP). Patients in the bendamustine arm had more comorbidities (24% with Charlson comorbid index score ≥1 vs 17% [CHOP] and 19% [CVP]). There was a higher population of patients ≥ 80years in the bendamustine and CVP group (3% in both groups) compared to CHOP (1%).[3]

A secondary analysis of the GALLIUM study was conducted to evaluate the prognostic value of PET-CT responses after first-line immunochemotherapy in the GALLIUM study. As per protocol, during the trial, PET scans (mandatory in the first 170 patients enrolled at sites with available PET facilities, and optional thereafter), acquired at baseline and end of induction, were assessed prospectively by investigators and an independent review committee (IRC). Pet scans were done in 669 (65%) of 1029 patients enrolled after July 26, 2011, at 103 of the 177 recruiting centres. Results from the investigators and IRC found that PET is a better imaging modality with better predictive ability than contrast-enhanced CT for response assessment.[4]

Efficacy

After a median follow up of 41.1 months, there was a significant increase in PFS in patients treated with G-chemo compared to R-chemo (HR, 0.68; 95% CI, 0.54 to 0.87; P =.0016). No OS benefit was seen between these 2 groups. TTNAT was slightly better in the G-chemo group with 14% needing the next line of treatment compared to 20% in the R-chemo group (HR 0.68, 95% CI 0.52-0.90, p=0.007). Complete or partial response rate was not significantly different between the two groups regardless of whether CT imaging or CT plus PET was used.[3, 5]

The benefit of obinutuzumab over rituximab was seen with all three chemotherapy backbones with Hazard ratios for investigator-assessed PFS of 0.63 (95% CI, 0.46 to 0.88) for bendamustine, 0.72 (0.48 to 1.10) for CHOP, and 0.79 (0.42 to 1.47) for CVP.[3]

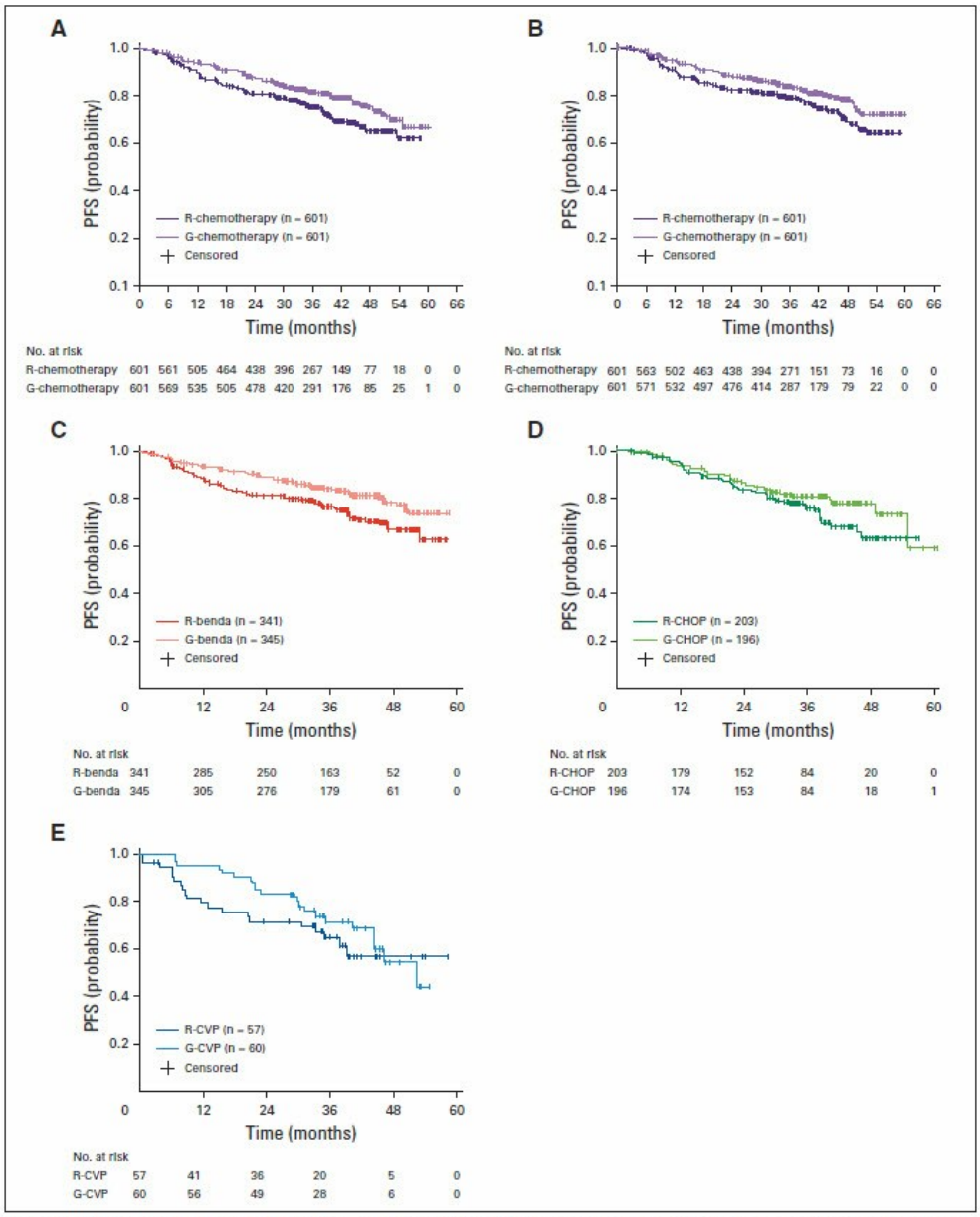


Fig 2. Kaplan-Meier plots of progression-free survival (PFS) in all patients with follicular lymphoma assessed by (A) investigator, and (B) independent review committee. (C-E) Investigator-assessed PFS by chemotherapy group: (C) bendamustine; (D) cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP); (E) cyclophosphamide, vincristine, and prednisone (CVP). G-benda, obinutuzumab plus bendamustine; G-chemotherapy, obinutuzumab plus chemotherapy; R-benda, rituximab plus bendamustine; R-chemotherapy, rituximab plus chemotherapy.

Table 2. Summary of Efficacy Results (follicular lymphoma intention-to-treat population)

End Point	Obinutuzumab Plus Chemotherapy (n = 601)	Rituximab Plus Chemotherapy (n = 601)
Observation time, months, median (range)	41.1 (0-61.1)*	41.0 (0.1-61.8)
Investigator-assessed PFS		
Events	120 (20)	161 (27)
Estimated 3-year PFS, % (95% CL)	82 (78, 85)	75 (71, 78)
HR (95% CL)	0.68 (0.54, 0.87)	
Stratified log-rank *P* value†	.0016	
IRC-assessed PFS		
Events	108 (18)	141 (23)
Estimated 3-year PFS, % (95% CL)	83 (80, 86)	79 (75, 82)
HR (95% CL)	0.72 (0.56, 0.93)	
Stratified log-rank *P* value†	.012	
Treatment response (CT plus PET scan) at end of induction, investigator assessed according to 2007 revised response criteria[10]		
CR or PR	254 of 297 (86)	242 of 298 (81)
Percentage difference (95% CL), stratified	4.3 (−1.8, 10.5)	
Stratified *P* value, Cochran-Mantel-Haenszel test†	.17	
CR	184 of 297 (62)	169 of 298 (57)
Percentage difference (95% CL), stratified	5.2 (−2.8, 13.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test†	.32	
Treatment response (CT plus PET scan) at end of induction, assessed by IRC according to Lugano 2014 criteria[11]		
CMR or PMR	248 of 297 (84)	234 of 298 (79)
Percentage difference (95% CL)	5.0 (−1.5, 11.5)	
Stratified *P* value, Cochran-Mantel-Haenszel test†	.30	
CMR	232 of 297 (78)	217 of 298 (73)
Percentage difference (95% CL)	5.3 (−1.8, 12.4)	
Stratified *P* value, Cochran-Mantel-Haenszel test†	.18	
Time to start of new antilymphoma treatment		
Events	86 (14)	120 (20)
Estimated 3-year TTNT, % (95% CL)	87 (84, 90)	81 (78, 84)
HR (95% CL)	0.68 (0.52, 0.90)	
Stratified log-rank *P* value†	.007	
Overall survival		
Events	43 (7)	52 (9)
Estimated proportion alive at 3 years, % (95% CL)	94 (92, 96)	92 (90, 94)
HR (95% CL)	0.82 (0.54, 1.22)	
Stratified log-rank *P* value†	.32	

NOTE. Data are No. (%) unless otherwise shown.
Abbreviations: CL, confidence limits; CMR, complete metabolic response; CR, complete response; CT, computed tomography; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IRC, independent review committee; PET, positron emission tomography; PFS, progression-free survival; PMR, partial metabolic response; PR, partial response; TTNT, time to next treatment.
*Observation time of 0 months corresponds to patients who were lost to follow up immediately after enrolment, with no additional follow up obtained in the updated analysis.
†Stratified for FLIPI and chemotherapy regimen.

Table 3. Summary of Efficacy Results by Chemotherapy Regimen (follicular lymphoma intention-to-treat population)

End Point	Bendamustine		CHOP		CVP	
	Obinutuzumab (n = 345)	Rituximab (n = 341)	Obinutuzumab (n = 196)	Rituximab (n = 203)	Obinutuzumab (n = 60)	Rituximab (n = 57)
Investigator-assessed PFS						
Events	60 (17)	88 (26)	39 (20)	53 (26)	21 (35)	20 (35)
Estimated 3-year PFS, % (95% CL)	84 (79, 88)	76 (71, 81)	81 (74, 86)	76 (68, 81)	71 (57, 81)	64 (49, 76)
HR (95% CL)	0.63 (0.46, 0.88)		0.72 (0.48, 1.10)		0.79 (0.42, 1.47)	
Stratified log-rank *P* value*	.0062		.13		.46	
IRC-assessed PFS						
Events	58 (17)	79 (23)	37 (19)	47 (23)	13 (22)	15 (26)
Estimated 3-year PFS, % (95% CL)	85 (81, 89)	81 (76, 85)	82 (75, 87)	77 (70, 82)	77 (63, 86)	77 (63, 86)
HR (95% CL)	0.67 (0.48, 0.94)		0.83 (0.54, 1.28)		0.70 (0.33, 1.49)	
Stratified log-rank *P* value*	.02		.40		.35	
Time to new antilymphoma treatment						
Events	47 (14)	72 (21)	28 (14)	33 (16)	11 (18)	15 (26)
Estimated proportion not started new treatment at 3 years, % (95% CL)	87 (83, 91)	80 (75, 84)	87 (82, 91)	85 (80, 90)	87 (75, 93)	74 (61, 84)
HR (95% CL)	0.62 (0.43, 0.89)		0.89 (0.54, 1.47)		0.60 (0.27, 1.30)	
Stratified log-rank *P* value*	.009		.65		.19	
Treatment response (CT plus PET scan) at end of induction, investigator assessed according to 2007 revised response criteria[10]						
CR or PR	148 of 173 (86)	131 of 165 (79)	91 of 103 (88)	91 of 103 (88)	15 of 21 (71)	20 of 30 (67)
Percentage difference (95% CL)	6.2 (−2.3, 14.6)		0.0 (−9.3, 9.3)		4.8 (−23.8, 33.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.11		.98		.72	
CR	109 of 173 (63)	100 of 165 (61)	68 of 103 (66)	63 of 103 (61)	7 of 21 (33)	6 of 30 (20)
Percentage difference (95% CL)	2.4 (−8.3, 13.1)		4.9 (−8.8, 18.5)		13.3 (−14.3, 41.0)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.63		.52		.36	
Treatment response (CT plus PET scan) at end of induction, assessed by IRC according to Lugano 2014 criteria[11]						
CMR or PMR	149 of 173 (86)	137 of 165 (83)	85 of 103 (83)	80 of 103 (78)	16 of 21 (76)	19 of 30 (63)
Percentage difference (95% CL)	3.1 (−4.9, 11.1)		4.9 (−6.6, 16.3)		12.9 (−15.1, 40.9)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.38		.35		.40	
CMR	144 of 173 (83)	127 of 165 (77)	76 of 103 (74)	71 of 103 (69)	14 of 21 (67)	18 of 30 (60)
Percentage difference (95% CL)	6.3 (−2.6, 15.1)		4.9 (8.0, 17.7)		6.7 (−23.0, 36.3)	
Stratified *P* value, Cochran-Mantel-Haenszel test*	.13		.44		.80	

NOTE. Data are No. (%) unless otherwise shown.
Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CL, confidence limits; CMR, complete metabolic response; CR, complete response; CT, computed tomography; CVP, cyclophosphamide, vincristine, and prednisone; FLIPI, Follicular Lymphoma International Prognostic Index; HR, hazard ratio; IRC, independent review committee; PET, positron emission tomography; PFS, progression-free survival; PMR, partial metabolic response; PR, partial response.
*Stratified for FLIPI and chemotherapy regimen.

Toxicity

There were more patients with Grade 3-5 AEs in the G-chemo arm compared to R-chemo (75% vs 69% respectively). Within limitations, in those receiving G-chemo, there were 69% grade 3-5 AEs in the CVP arm compared to 89% in the G-CHOP arm and 69% in the G-Bendamustine arm. The higher rate in the G-CHOP arm were mainly driven by cytopenias. Infection rates were higher in

the bendamustine group. [3]

Table 4. Summary of Adverse Events in the FL Safety Population by Treatment Arm and Chemotherapy Regimen

Patients Reporting ≥ 1 AE	G Plus Bendamustine (n = 338)	R Plus Bendamustine (n = 338)	G Plus CHOP (n = 193)	R Plus CHOP (n = 203)	G Plus CVP (n = 61)	R Plus CVP (n = 56)	G Plus Chemotherapy (n = 595)	R Plus Chemotherapy (n = 597)
AEs (any grade)	338 (100)	331 (98)	191 (99)	201 (99)	61 (100)	56 (100)	593 (100)	585 (98)
Grade 3-5 AEs	233 (69)	228 (67)	171 (89)	151 (74)	42 (69)	30 (54)	449 (75)	409 (69)
Neutropenia	100 (30)	102 (30)	137 (71)	111 (55)	28 (46)	13 (23)	265 (45)	226 (38)
Leucopenia	11 (3)	15 (4)	39 (20)	34 (17)	1 (2)	1 (2)	51 (9)	50 (8)
Febrile neutropenia	18 (5)	13 (4)	22 (11)	14 (7)	2 (3)	2 (4)	42 (7)	29 (5)
Infusion-related reactions	18 (5)	10 (3)	17 (9)	9 (4)	2 (3)	3 (5)	40 (7)	22 (4)
Pneumonia	23 (7)	17 (5)	5 (3)	8 (4)	0	4 (7)	28 (5)	29 (5)
Thrombocytopenia	20 (6)	11 (3)	15 (8)	5 (2)	1 (2)	0	36 (6)	16 (3)
Anemia	8 (2)	5 (1)	15 (8)	8 (4)	1 (2)	0	24 (4)	13 (2)
Dyspnea	6 (2)	3 (1)	8 (4)	3 (1)	2 (3)	3 (5)	17 (3)	9 (2)
Serious AEs	176 (52)	160 (47)	76 (39)	67 (33)	26 (43)	19 (34)	281 (47)	246 (41)
Deaths*	28 (8)	37 (11)	11 (6)	9 (4)	3 (5)	6 (11)	42 (7)	52 (9)
Fatal AEs	20 (6)	16 (5)	3 (2)	4 (2)	1 (2)	1 (2)	24 (4)	21 (4)
Fatal AEs occurring before start of NACT	16 (5)	14 (4)	3 (2)	4 (2)	1 (2)	1 (2)	20 (3)	19 (3)
AEs causing treatment discontinuation	52 (15)	48 (14)	32 (17)	31 (15)	11 (18)	9 (16)	98 (16)	88 (15)
Selected AE categories of special interest (grade 3-5)								
Neutropenia†	107 (32)	107 (32)	142 (74)	115 (57)	29 (48)	14 (25)	278 (47)	236 (40)
Infections‡	89 (26)	66 (20)	23 (12)	25 (12)	8 (13)	7 (13)	121 (20)	98 (16)
Opportunistic infections, including herpes zoster§	10 (3)	6 (2)	5 (3)	2 (1)	0	0	15 (3)	8 (1)
Second neoplasms‖	21 (6)	12 (4)	7 (4)	7 (3)	1 (2)	2 (4)	29 (5)	21 (4)
Nonmelanoma skin cancer	7 (2)	3 (1)	0	0	1 (2)	0	8 (1)	3 (1)
Hematologic tumors¶	3 (1)	0	3 (2)	0	0	0	6 (1)	0
Other solid tumors	11 (3)	9 (3)	4 (2)	7 (3)	0	2 (4)	15 (3)	18 (3)
Cardiac events#	13 (4)	12 (4)	6 (3)	5 (2)	4 (7)	0	23 (4)	17 (3)

NOTE. Data presented as No. (%). Grade ≥ 3 adverse event preferred terms are those with frequency of ≥ 5% for any antibody plus chemotherapy combination shown.
Abbreviations: AE, adverse event; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CVP, cyclophosphamide, vincristine, and prednisone; FL, follicular lymphoma; G, obinutuzumab; NACT, new anticancer therapy; R, rituximab.
*One additional patient died (randomly assigned to G plus bendamustine) but was excluded from the FL safety population because they did not receive any study drug; this patient was included in the FL intention-to-treat population.
†Neutropenia and associated complications reported as AEs (not based on laboratory values).
‡Any adverse event in system organ class Infections and Infestations.
§Fungal infections, cytomegalovirus, herpes zoster, and *Pneumocystis jiroveci* pneumonia.
‖Malignant or unspecified tumors occurring > 6 months after first study drug intake (standardized Medical Dictionary for Regulated Activities query).
¶Hodgkin disease (n = 3), acute myeloid leukemia (n = 2), and acute lymphocytic leukemia (n = 1).
#Any adverse event in system organ class Cardiac Disorders.

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5. Marcus, R., A. Davies, K. Ando, et al. 2017. "Obinutuzumab for the First-Line Treatment of Follicular Lymphoma." N Engl J Med 377(14):1331-1344.

History

Version 3

Date	Summary of changes

Date	Summary of changes
22/06/2023	Protocol updated, increase to v..3. Updated sections include: • clinical information - updated hypersensitivity/ infusion related reaction, thrombocytopenia related to obinutuzumab, cardiac toxicity added • dose modifications - management of infusion-related reactions, management for thrombocytopenia • obinutuzumab administration • side effects

Version 2

Date	Summary of changes
16/05/2022	"Obinutuzumab short duration infusion" block added to clinical information. Version number changed to v.2
11/11/2022	Protocol reviewed electronically by the Haematology Reference Committee, nil changes. Review in 2 years

Version 1

Date	Summary of changes
11/03/2019	New protocol developed out of session, discussed by Haematology Reference Committee electronically via email.
29/03/2019	Protocol approved and published on eviQ v.1. Review in 1 year.
10/10/2019	Clinical information updated with PBS expanded indications for G-CSF.
15/04/2020	Evidence updated. Protocol for review in 2 years.
24/01/2022	Pulmonary toxicity added to side effects.

First approved: 29 March 2019
Last reviewed: 11 November 2022
Review due: 31 December 2024

The currency of this information is guaranteed only up until the date of printing, for any updates please check:
https://www.eviq.org.au/p/3595
26 Nov 2023

Patient information - Non-Hodgkin lymphoma - O-CVP (obinuzutumab, cyclophosphamide, vincristine, prednisolone)

Patient's name:

Your treatment

The treatment schedule below explains how the drugs for this treatment are given.

O-CVP (obinutuzumab, cyclophosphamide, vincristine, prednisolone)			
This treatment cycle is repeated every 21 days. You will usually have 6 to 8 cycles. Your doctor will advise you of the number of treatments you will have.			
Cycle 1			
Day	**Treatment**	**How it is given**	**How long it takes**
1 to 5	**Prednisolone** (*pred-NIS-oh-lone*)	Take orally ONCE a day in the morning with food on days 1 to 5 only. If you forget to take your tablets or vomit your tablets, contact your treating team	
1, 8 and 15	**Obinutuzumab** (*OH-bi-nue-TOOZ-ue-mab*)	By a drip into a vein	(Day 1) About 4 to 8 hours; (Days 8 and 15) About 3 hours
1	**Vincristine** (*vin-KRIS-teen*)	By a drip into a vein	About 5 to 10 minutes
	Cyclophosphamide (*SYE-kloe-FOS-fa-mide*)	By a drip into a vein	About 1 hour
Cycles 2 to 6			
Day	**Treatment**	**How it is given**	**How long it takes**
1 to 5	**Prednisolone**	Take orally ONCE a day in the morning with food on days 1 to 5 only. If you forget to take your tablets or vomit your tablets, contact your treating team	
1	**Obinutuzumab**	By a drip into a vein	About 3 hours
	Vincristine	By a drip into a vein	About 5 to 10 minutes
	Cyclophosphamide	By a drip into a vein	About 1 hour

When to get help

Anticancer drugs (drugs used to treat cancer) can sometimes cause serious problems. It is important to get medical help immediately if you become unwell.

IMMEDIATELY go to your nearest hospital Emergency Department, or contact your doctor or nurse if you have any of the following at any time:	**Emergency contact details** Ask your doctor or nurse from your treating team who to contact if you have a problem
	Daytime:.....

- a temperature of 38°C or higher
- chills, sweats, shivers or shakes
- shortness of breath
- uncontrolled vomiting or diarrhoea
- pain, tingling or discomfort in your chest or arms
- you become unwell.

Night/weekend:

Other instructions:

During your treatment immediately tell the doctor or nurse looking after you if you get any of the following problems:

- leaking from the area where the drugs are being given
- pain, stinging, swelling or redness in the area where the drugs are being given or at any injection sites
- a skin rash, itching, feeling short of breath, wheezing, fever, shivers, or feeling dizzy or unwell in any way (allergic reaction).

Other information about your treatment

Changes to your dose or treatment delays

Sometimes a treatment may be started at a lower dose or the dose needs to be changed during treatment. There may also be times when your treatment is delayed. This can happen if your doctor thinks you are likely to have severe side effects, if you get severe side effects, if your blood counts are affected and causing delays in treatment, or if you are finding it hard to cope with the treatment. This is called a dose reduction, dose change or treatment delay. Your doctor will explain if you need any changes or delays to your treatment and the reason why.

Blood tests and monitoring

Anti-cancer drugs can reduce the number of blood cells in your body. You will need to have regular blood tests to check that your blood cell count has returned to normal. If your blood count is low, your treatment may be delayed until it has returned to normal. Your doctor or nurse will tell you when to have these blood tests.

Central venous access devices (CVADs)

This treatment may involve having chemotherapy through a central venous access device (CVAD). Your doctor or nurse will explain this to you. For more information, see the eviQ patient information sheets on CVADs.

Treatment with cyclophosphamide

You should drink at least 8 to 10 glasses of fluid (unless you are fluid restricted) for 2 days after treatment with cyclophosphamide. You should also empty your bladder often.

Medications for blood pressure

Obinutuzumab may lower your blood pressure. Tell your doctor if you are taking any blood pressure medications. Your doctor may advise you to temporarily stop your blood pressure medications before your obinutuzumab infusions.

Other medications given during this treatment

- **Anti-sickness (anti-nausea) medication:** you may be given some anti-sickness medication. Make sure you take this medication as your doctor or nurse tells you, even if you don't feel sick. This can help to prevent the sickness starting.
- **Laxatives:** you may be given some medication to prevent or treat constipation. Your doctor or nurse will tell you how and when to take the laxatives.
- **Prophylaxis medication:** you may need to take some medications to prevent infection and to help prevent or reduce some of the side effects of the chemotherapy. Your doctor or nurse will tell you how and when to take these medications.
- **Obinutuzumab premedication:** before your treatment with obinutuzumab you will need to take some tablets called a premedication to help prevent you from having a reaction to the obinutuzumab.

Side effects

Cancer treatments can cause damage to normal cells in your body, which can cause side effects. Everyone gets different side effects, and some people will have more problems than others.

The table below shows some of the side effects you may get with this treatment. You are unlikely to get all of those listed and you may also get some side effects that have not been listed.

Tell your doctor or nurse about any side effects that worry you. Follow the instructions below and those given to you by your doctor or nurse.

Immediate (onset hours to days)	

Allergic reaction	• Allergic reactions are uncommon but can be life threatening.
	• **If you feel unwell during the infusion or shortly after it, or:**
	  ◦ **get a fever, shivers or shakes**
	  ◦ **feel dizzy, faint, confused or anxious**
	  ◦ **start wheezing or have difficulty breathing**
	  ◦ **have a rash, itch or redness of the face**
	
	<u>While you are in hospital:</u> Tell your doctor or nurse immediately.
	<u>After you leave:</u> Contact your doctor or nurse immediately, or go to the nearest hospital Emergency Department.

Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • Take your anti-sickness medication as directed even if you don't feel sick. • Drink plenty of fluids (unless you are fluid restricted). • Eat small meals more frequently. • Try food that does not require much preparation. • Try bland foods like dry biscuits or toast. • Gentle exercise may help with nausea. • Ask your doctor or nurse for eviQ patient information - Nausea and vomiting during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have uncontrolled vomiting or feel dizzy or light-headed.**
Pain or swelling at injection site (extravasation)	• This treatment can cause serious injury if it leaks from the area where it is going into the vein. • This can cause pain, stinging, swelling or redness at or near the site where the drug enters the vein. • If not treated correctly, you may get blistering and ulceration. • **Tell your doctor or nurse immediately if you get any of the symptoms listed above during or after treatment.**

Flu-like symptoms	• You may get:
	  ◦ a fever
	  ◦ chills or sweats
	  ◦ muscle and joint pain
	  ◦ a cough
	  ◦ headaches.
	• Tell your doctor or nurse if you get any of the symptoms listed above.
	• **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have a temperature of 38°C or higher.**

Headache	• You can take paracetamol if you have a headache. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get a very bad headache that is not helped by pain medication.**
Low blood pressure (hypotension)	• You may get low blood pressure from this treatment. • You may feel dizzy or light-headed. • Tell your doctor if you are taking blood pressure medication. • Your doctor will monitor your blood pressure regularly while you are on this treatment. • Drink plenty of fluids (unless you are fluid restricted). • When you want to get up from a sitting or lying down position, get up slowly to let your body adjust to the new position. • Do not drive or operate machinery if you feel dizzy or light-headed. • Tell your doctor or nurse if you get any of the signs or symptoms listed above.
Early (onset days to weeks)	

Infection risk (neutropenia)	• This treatment lowers the amount of white blood cells in your body. The type of white blood cells that help to fight infection are called neutrophils. Having low level of neutrophils is called neutropenia. If you have neutropenia, you are at greater risk of getting an infection. It also means that your body can't fight infections as well as usual. This is a serious side effect, and can be life threatening. • Wash your hands often. • Keep a thermometer at home and take your temperature regularly, and if you feel unwell. • Do your mouth care regularly. • Inspect your central line site (if you have one) daily for any redness, pus or swelling. • Limit contact with people who are sick. • Learn how to recognise the signs of infection. • Ask your doctor or nurse for eviQ patient information - Infection during cancer treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following signs or symptoms:** ◦ **a temperature of 38°C or higher** ◦ **chills, shivers, sweats or shakes** ◦ **a sore throat or cough** ◦ **uncontrolled diarrhoea** ◦ **shortness of breath** ◦ **a fast heartbeat** ◦ **become unwell even without a temperature.**
Low platelets (thrombocytopenia)	• This treatment lowers the amount of platelets in your blood. Platelets help your blood to clot. When they are low, you are at an increased risk of bleeding and bruising. • Try not to bruise or cut yourself. • Avoid contact sport or vigorous exercise. • Clear your nose by blowing gently. • Avoid constipation. • Brush your teeth with a soft toothbrush. • Don't take aspirin, ibuprofen or other similar anti-inflammatory medications unless your doctor tells you to. • Tell your doctor or nurse if you have any bruising or bleeding. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if you have any uncontrolled bleeding.**
Heart palpitations	• You may get: ◦ chest pain ◦ a pounding or fluttering heart (palpitations) ◦ shortness of breath ◦ dizzy or light-headed ◦ confused ◦ more tired than usual. • Tell your doctor if you have any heart problems or are on any heart medications. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the symptoms listed above.**
Constipation	• You may have bowel motions (stools, poo) that are less frequent, harder, smaller, painful or difficult to pass. • You may also get: ◦ bloating, cramping or pain ◦ a loss of appetite ◦ nausea or vomiting. • Drink plenty of fluids (unless you are fluid restricted). • Eat plenty of fibre-containing foods such as fruit, vegetables and bran. • Take laxatives as directed by your doctor. • Try some gentle exercise daily. • **Tell your doctor or nurse if you have not opened your bowels for more than 3 days.**

Tiredness and lack of energy (fatigue)	• You may feel very tired, have no energy, sleep a lot, and not be able to do normal activities or things you enjoy. • Do not drive or operate machinery if you are feeling tired. • Nap for short periods (only 1 hour at a time) • Prioritise your tasks to ensure the best use of your energy. • Eat a well balanced diet and drink plenty of fluids (unless you are fluid restricted). • Try some gentle exercise daily. • Allow your friends and family to help. • **Tell your doctor or nurse if you get any of the symptoms listed above.**
Bladder irritation (haemorrhagic cystitis)	• You may get: ◦ blood in your urine, sometimes with blood clots ◦ pain or burning when you urinate ◦ the urge to urinate more than normal ◦ stomach or pelvic pain or discomfort. • When you go home, make sure you drink plenty of fluids (unless you are fluid restricted). • Empty your bladder often. • **Tell your doctor or nurse as soon as possible if you notice any blood in your urine.**
Difficulty sleeping (insomnia)	• You may have trouble falling or staying asleep. • Try some gentle exercise daily. • Avoid coffee, tea and other caffeinated drinks around bedtime. • Try something to relax before bed, like a bath or meditation. • If you can't sleep get up and do something quietly, such as reading, until you feel tired. • Tell your doctor or nurse if you have difficulty sleeping.
Nerve damage (peripheral neuropathy)	• You may notice a change in the sensations in your hands and feet, including: ◦ tingling or pins and needles ◦ numbness or loss of feeling ◦ pain. • You may find it difficult to do everyday activities, such as doing up buttons or picking up small objects. • Test water temperature with your elbow when bathing to avoid burns. • Use rubber gloves, pot holders and oven mitts in the kitchen. • Wear rubber shoes or boots when working in the garden or garage. • Keep rooms well lit and uncluttered. • Ask your doctor or nurse for eviQ patient information – Nerve problems during cancer treatment. • Tell your doctor or nurse if you get any of the symptoms listed above.
Side effects from steroid medication	• Steroid medication may cause: ◦ mood swings and behaviour changes ◦ an increased appetite ◦ weight gain ◦ swelling in your hands and feet ◦ stomach upsets ◦ trouble sleeping ◦ fragile skin and bruising ◦ an increase in your blood sugar level ◦ weak and brittle bones (osteoporosis) • Take your steroid medication with food to reduce stomach upset • If you have diabetes, your blood sugar levels may be tested more often. • Tell your doctor or nurse if you get any of the symptoms listed above.

Skin rash	• You may get a red, bumpy rash and dry, itchy skin. • Moisturise your skin with a gentle non-perfumed moisturising cream like sorbolene or aqueous cream. • Do not scratch your skin. • Protect your skin from the sun by wearing sun-protective clothing, a wide-brimmed hat, sunglasses and sunscreen of SPF 50 or higher. • **Talk to your doctor or nurse about other ways to manage your skin rash.**

Late (onset weeks to months)	
Hair loss (alopecia)	• Your hair may start to fall out from your head and body. • Hair loss usually starts 2 to 3 weeks after your first treatment. • You may become completely bald and your scalp might feel tender. • Use a gentle shampoo and a soft brush. • Take care with hair products like hairspray, hair dye, bleaches and perms. • Protect your scalp from the cold with a hat, scarf or wig. • Protect your scalp from the sun with a hat or sunscreen of SPF 50 or higher. • Moisturise your scalp to prevent itching. • Ask your doctor or nurse about the Look Good Feel Better program
Low red blood cells (anaemia)	• You may feel dizzy, light-headed, tired and appear more pale than usual. • Tell your doctor or nurse if you have any of these signs or symptoms. You might need a blood transfusion. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have any chest pain, trouble breathing, or feel like your heart is racing.**
Changes in the way your brain works [progressive multifocal leukoencephalopathy (PML)]	• This treatment can affect your central nervous system. This can be very serious. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you get any of the following symptoms:** ◦ **trouble with your speech or vision** ◦ **confusion or memory loss** ◦ **changes in your personality** ◦ **weakness in your arms and legs** ◦ **poor balance or coordination** ◦ **fits (seizures).**

Delayed (onset months to years)	
Lung problems	• Lung problems are rare, but can be serious. They may occur throughout treatment or after the completion of treatment. • You may get: ◦ shortness of breath ◦ fever ◦ dry cough ◦ wheezing ◦ fast heartbeat ◦ chest pain. • Your doctor will monitor how well your lungs are working during your treatment. • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have chest pain or become short of breath.**

General advice for people having cancer treatment

Chemotherapy safety

- Learn how to keep you and your family safe while you are having anticancer drugs.
- See our patient information sheet - Chemotherapy safety at home.

Blood clot risk

- Cancer and anticancer drugs can increase the risk of a blood clot (thrombosis).
- Tell your doctor if you have a family history of blood clots.
- A blood clot can cause pain, redness, swelling in your arms or legs, shortness of breath or chest pain.
- If you have any of these symptoms go to your nearest hospital Emergency Department.

Medications and vaccinations

- Before you start treatment, tell your doctor about any medications you are taking, including vitamins or herbal supplements.
- Don't stop or start any medications during treatment without talking to your doctor and pharmacist first.
- Paracetamol is safe to take if you have a headache or other mild aches and pains. It is recommended that you avoid taking aspirin, ibuprofen and other anti-inflammatory type medications for pain while you are having treatment. However, if these medications have been prescribed by your doctor, do not stop taking them without speaking with your doctor.
- Vaccinations such as flu and tetanus vaccines are safe to receive while having treatment. Do not have any live vaccines during your treatment or for 6 months after it finishes. If you are unsure, check with your doctor before you have any vaccinations.
- People you live with should be fully vaccinated, including having live vaccines according to the current vaccination schedule. Extra care needs to be taken with hand washing and careful disposal of soiled nappies for infants who have recently received the rotavirus vaccine.

Other medical and dental treatment

- If you go to hospital or any other medical appointment (including dental appointments), always tell the person treating you that you are receiving anticancer drugs.
- Before you have any dental treatment, talk to your doctor.

Diet and food safety

- While you are receiving this treatment, it is important that you try to maintain a healthy diet.
- Grapefruit and grapefruit juice can interact with your medication and should be avoided while you are on this treatment.
- Speak to your doctor or nurse about whether drinking alcohol is safe with your treatment.
- If you have any concerns about recent weight loss or weight gain or questions about your diet, ask to speak to a dietitian.
- There are some foods that may cause infection in high risk individuals and should be avoided. For further information on foods to avoid and food hygiene please ask for a copy of the Listeria and food brochure.

Fertility

- Some cancer treatments can reduce your fertility. This can make it difficult or impossible to get pregnant or father a child.
- Talk to your doctor or nurse before you start any treatment. Depending on your situation there may be fertility sparing options available to you and/or your partner, discuss these with your doctor or nurse.

Pregnancy and breastfeeding

- Some cancer treatments can be dangerous to unborn babies. Talk to your doctor or nurse if you think there is any chance that you could be pregnant.
- Do not try to get pregnant or father a child during this treatment. Contraception should be used during treatment and after stopping treatment. Ask your doctor or nurse about what type of contraception you should use.
- If you are planning pregnancy/fatherhood after completing this treatment, talk to your doctor. Some doctors advise waiting between 6 months and 2 years after treatment.
- Do not breastfeed if you are on this treatment, as anti-cancer medications can also pass into breast milk.

Sex life and sexuality

- The desire to have sex may decrease as a result of this treatment or its side effects.
- Your emotions and the way you feel about yourself may also be affected by this treatment.
- It may help to discuss your concerns with your partner and doctor or nurse.

Risk of developing a second cancer

- Some anticancer treatments can increase your chance of developing a second cancer, this is rare. Your doctor will discuss with you the specific risks of your treatment.

Quitting smoking

- It is never too late to quit smoking. Quitting smoking is one of the best things you can do to help your treatment work better.
- There are many effective tools to improve your chances of quitting.
- Talk to your treating team for more information and referral to a smoking cessation support service.

Staying active

- Research shows that exercise, no matter how small, has many benefits for people during and after cancer treatment.
- Talk to your doctor before starting an exercise program. Your doctor can advise whether you need a modified exercise program.

For more information about cancer treatment, side effects and side effect management see our Patient and carers section.

Where to get more information

Telephone support

- Call Cancer Council on 13 11 20 for cancer information and support
- Call the Leukaemia Foundation on 1800 620 420 (Mon to Fri 9am – 5pm)
- Call the Lymphoma Nurse Support Line on 1800 953 081 (Mon to Fri 9am - 5pm)
- Call the Myeloma Australia Support Line on 1800 693 566 (Mon to Fri 9am - 5pm)

Haematology, transplant and cellular therapy information

- Arrow bone marrow transplant foundation – arrow.org.au
- Australasian Menopause Society – menopause.org.au
- Chris O'Brien Lifehouse - Total Body Irradiation - mylifehouse.org.au/departments/radiation-oncology/total-body-irradiation/
- Healthy Male Andrology Australia – healthymale.org.au/
- International Myeloma Foundation – myeloma.org
- Leukaemia Foundation – leukaemia.org.au
- Lymphoma Australia – lymphoma.org.au
- Myeloma Australia – myeloma.org.au
- NSW Agency for Clinical Innovation, Blood & Marrow Transplant Network – https://aci.health.nsw.gov.au/networks/bmtct
- NSW Agency for Clinical Innovation - aci.health.nsw.gov.au/projects/immune-effector-cell-service
- NCCN Guidelines for Patients Immunotherapy Side Effects: CAR T-Cell Therapy - nccn.org/patientresources/patient-resources/guidelines-for-patients
- Talk Blood Cancer – cmlsupport.org.uk/organisation-type/social-media-groups

General cancer information and support

- Australian Rare Cancer (ARC) Portal – arcportal.org.au/
- Beyondblue – beyondblue.org.au
- Cancer Australia – canceraustralia.gov.au
- Cancer Council Australia – cancer.org.au
- Cancer Voices Australia – cancervoicesaustralia.org
- CanTeen – canteen.org.au
- Carers Australia – carersaustralia.com.au
- Carer Help - carerhelp.com.au
- eviQ Cancer Treatments Online – eviQ.org.au
- Food Standards Australia New Zealand: Listeria & Food Safety – foodstandards.gov.au/publications/pages/listeriabrochuretext.aspx
- LGBTQI+ People and Cancer - cancercouncil.com.au/cancer-information/lgbtqi
- Look Good Feel Better – lgfb.org.au
- Patient Information - patients.cancer.nsw.gov.au
- Radiation Oncology Targeting Cancer - targetingcancer.com.au
- Redkite – redkite.org.au
- Return Unwanted Medicines – returnmed.com.au
- Staying active during cancer treatment – patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/staying-active

Quit smoking information and support

Quitting smoking is helpful even after you have been diagnosed with cancer. The following resources provide useful information and support to help you quit smoking. Talk to your treating team about any other questions you may have.

- Call Quitline on 13 QUIT (13 78 48)
- iCanQuit – iCanQuit.com.au
- Patient Information - patients.cancer.nsw.gov.au/coping-with-cancer/physical-wellbeing/quitting-smoking

- Quitnow – quitnow.gov.au

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https://www.eviq.org.au/pi/3595
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