Chronic lymphocytic leukaemia bendamustine and rituximab

ID: 3811 v.2 **Endorsed** Essential Medicine List

Patients with leukaemia should be considered for inclusion into clinical trials. Link to ALLG website and ANZCTR website.

Treatment schedule - Overview

Cycle 1

Drug	Dose	Route	Day
Rituximab	375 mg/m^2	IV infusion	1
Bendamustine *	90 mg/m^2	IV infusion	1 and 2

Cycle 2 to 6

Drug	Dose	Route	Day
Rituximab	500 mg/m^2	IV infusion	1
Bendamustine *	90 mg/m^2	IV infusion	1 and 2

*Bendamustine doses in this protocol are expressed as bendamustine hydrochloride

Frequency: 28 days

Cycles: 6 unless disease progression or unacceptable toxicity

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Drug status: **Rituximab**: is on the PBS general schedule

Bendamustine is TGA registered but not PBS listed for this indication.

Cost: ~ $3,470 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		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
Hydrocortisone	100 mg (IV)	30 minutes before treatment
Rituximab	375 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% as per graded administration rate
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Bendamustine	90 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes *
Day 2		

Day 2		
Dexamethasone	8 mg (PO)	ONCE a day with or after food (or in divided doses).
Bendamustine	90 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes *

Day 3 and 4		
Dexamethasone	8 mg (PO)	with or after food (or in divided doses). Note: dexamethasone doses on day 3 and 4 may not be required and may be reduced or omitted at the clinician's discretion. **

Cycle 2 to 6

Day 1		
Paracetamol	1,000 mg (PO)	60 minutes before treatment
Loratadine	10 mg (PO)	60 minutes before treatment
Hydrocortisone	100 mg (IV)	30 minutes before treatment
Rituximab	500 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% as per graded administration rate
Palonosetron	0.25 mg (IV bolus)	30 minutes before chemotherapy
Bendamustine	90 mg/m^2 (IV infusion)	in 500 mL sodium chloride 0.9% over 30 to 60 minutes *

Day 2		
Dexamethasone	8 mg (PO)	ONCE a day with or after food (or in divided doses).
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Day 3 and 4		
Dexamethasone	8 mg (PO)	with or after food (or in divided doses). Note: dexamethasone doses on day 3 and 4 may not be required and may be reduced or omitted at the clinician's discretion. **

*Bendamustine doses in this protocol are expressed as bendamustine hydrochloride

** Link to ID 7 Prevention of chemotherapy induced nausea and vomiting

Frequency: 28 days

Cycles: 6 unless disease progression or unacceptable toxicity

Indications and patient population

- Previously untreated CD20 positive B-cell chronic lymphocytic leukaemia (CLL)
  - Alternative therapy should be considered for patients with 17p deletion.

Clinical information

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 bendamustine and rituximab Read more about Hypersensitivity reaction

Premedication	The product information states that premedication is required for this treatment. Please refer to the treatment schedule for suggested premedication regimen. This may be substituted to reflect institutional policy.
Emetogenicity MODERATE	Suggested default antiemetics have been added to the treatment schedule, and may be substituted to reflect institutional policy. A steroid has been included both as an antiemetic and premedication for hypersensitivity in this protocol. 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
Cardiac toxicity	In patients with cardiac disorders the concentration of potassium in the blood must be closely monitored and ECG measurement must be performed during treatment with bendamustine. Potassium supplementation must be given when K+ < 3.5 mEq/L. Read more about cardiac toxicity associated with anti-cancer drugs
Rituximab rapid infusion	This regimen is not in line with the product monograph, however published literature indicates that it can be completed safely. Read more about the rapid infusion of rituximab
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.
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
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
Antifungal prophylaxis	Read more about antifungal prophylaxis drugs and doses.
Irradiated blood components	The use of irradiated of blood components is recommended for patients receiving this treatment. Read more about the indications for the use of irradiated blood components
Blood tests	FBC, EUC, eGFR, LFTs and LDH at baseline, and prior to each cycle 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 (pre-treatment blood test)	
less than 1.0	Delay treatment until recovery
Platelets x 10^9/L (pre-treatment blood test)	
less than 75	Delay treatment until recovery to greater than 100

Renal impairment	
Creatinine clearance (mL/min)	
greater than 10	No dose reduction

There is limited data available in patients with severe renal impairment

Hepatic impairment *	
Serum bilirubin (micromol/L) **	
less than 20	No dose reduction
20 to 51	Consider reducing bendamustine dose by 30%
greater than 51	No data is available in patients with severe hepatic impairment

** Based on the exclusion of other causes of hepatic impairment (e.g. Gilbert's syndrome, haemolysis)*
*** Units converted from mg/dL to micromol/L to reflect common reporting parameters used in Australia*

Non-haematological toxicity

Grade 3	Delay treatment until recovery consider reducing bendamustine dose by 50% If the toxicity resolves and the previous dose is tolerated the reduced dose may be increased again
Grade 4	Withhold chemotherapy

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*

Bendamustine

No specific clinically significant drug-drug interactions. No formal clinical drug interaction studies with bendamustine have been conducted however there is potential for CYP1A2 inhibitors (e.g. aciclovir, ciprofloxacin and fluvoxamine).

Rituximab

	Interaction	Clinical management
Antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion

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

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.

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

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

- baseline weight

Hydration if prescribed.

Treatment - Time out

Rituximab

Prior to administration:

- check baseline observations
- check for previous adverse events during previous infusions
- verify premedication has been taken. If not, administer 30 to 60 minutes prior to rituximab administration:
  - paracetamol 1000 mg orally AND
  - loratadine 10 mg orally (or similar antihistamine)
  - a steroid may also be included as a premed according to local guidelines

Initial infusion:

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

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have completely resolved, recommence the infusion at half the rate prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Transient hypotension may occur. Consider withholding antihypertensive medication for 12 hours before and during infusion.

Subsequent infusions:

If an adverse event was experienced with initial infusion recommence infusion at the same rate as initial infusion

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

If an infusion reaction occurs, temporarily discontinue the infusion and notify medical officer

- when symptoms have resolved, recommence the infusion at **half the rate** prior to the reaction
- for severe reactions **stop** infusion and manage as per emergency

Read more about rapid infusion rituximab

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Bendamustine

Prior to administration check:

- blood pressure (hypertensive crisis has been reported with bendamustine, hypertension should be well controlled prior to treatment with bendamustine)
- baseline ECG, then regularly throughout treatment for patients with cardiac disorders
- monitor potassium levels throughout treatment, potassium supplements must be given when K+ < 3.5 mEq/L.

Administer bendamustine (irritant with vesicant properties):

- via IV infusion over 30 to 60 minutes
- flush with ~ 100 mL of sodium chloride 0.9%

Stop infusion at first sign of reaction:

- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.
- for severe reactions seek medical assistance immediately and do not restart infusion
- hypersensitivity are more common after the first cycle

Remove IV cannula and/or deaccess TIVAD or CVAD.

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

Day 2

Approximate treatment time: 60 minutes

Safe handling and waste management

Safe administration

General patient assessment prior to each day of treatment.

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

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Hydration if prescribed.

Pre treatment medication

Verify antiemetics taken or administer as prescribed.

Chemotherapy - Time out

Bendamustine

Prior to administration check:

- blood pressure (hypertensive crisis has been reported with bendamustine, hypertension should be well controlled prior to treatment with bendamustine)
- baseline ECG, then regularly throughout treatment for patients with cardiac disorders
- monitor potassium levels throughout treatment, potassium supplements must be given when K+ < 3.5 mEq/L.

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- if symptoms are mild and resolve when infusion is stopped, consider recommencing infusion after review by medical officer at a slower rate.

- for severe reactions seek medical assistance immediately and do not restart infusion
- hypersensitivity are more common after the first cycle

Remove IV cannula and/or deaccess TIVAD or CVAD.

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

Discharge information

Antiemetics

- Antiemetics as prescribed.

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	
Taste and smell alteration	Read more about taste and smell changes

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
Abdominal pain	Dull ache, cramping or sharp pains are common with some anti-cancer drugs. These are caused by either increased or decreased gastrointestinal motility and can be associated with diarrhoea or constipation.
Anorexia	Loss of appetite accompanied by decreased food intake. Read more about anorexia
Arthralgia and myalgia	Generalised joint pain or and/or stiffness and muscle aches, often worse upon waking or after long periods of inactivity. Can improve with movement. May be mild or severe, intermittent or constant and accompanied by inflammation. Read more about arthralgia and myalgia
Constipation	
Diarrhoea	Read more about treatment induced diarrhoea
Fatigue	Read more about fatigue
Fluid retention and oedema	An excess amount of fluid around the cells, tissues or serous cavities of the body, leading to swelling.
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)	
Anaemia	Abnormally low levels of red blood cells (RBCs) or haemoglobin in the blood. Read more about anaemia
CD3+ and CD4+ T-cell suppression	Long-lasting suppression of CD3+ and CD4+ T-cells is commonly found after treatment with bendamustine. This may predispose to recurrent infection which can occur in the late follow up phase.
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)

Evidence

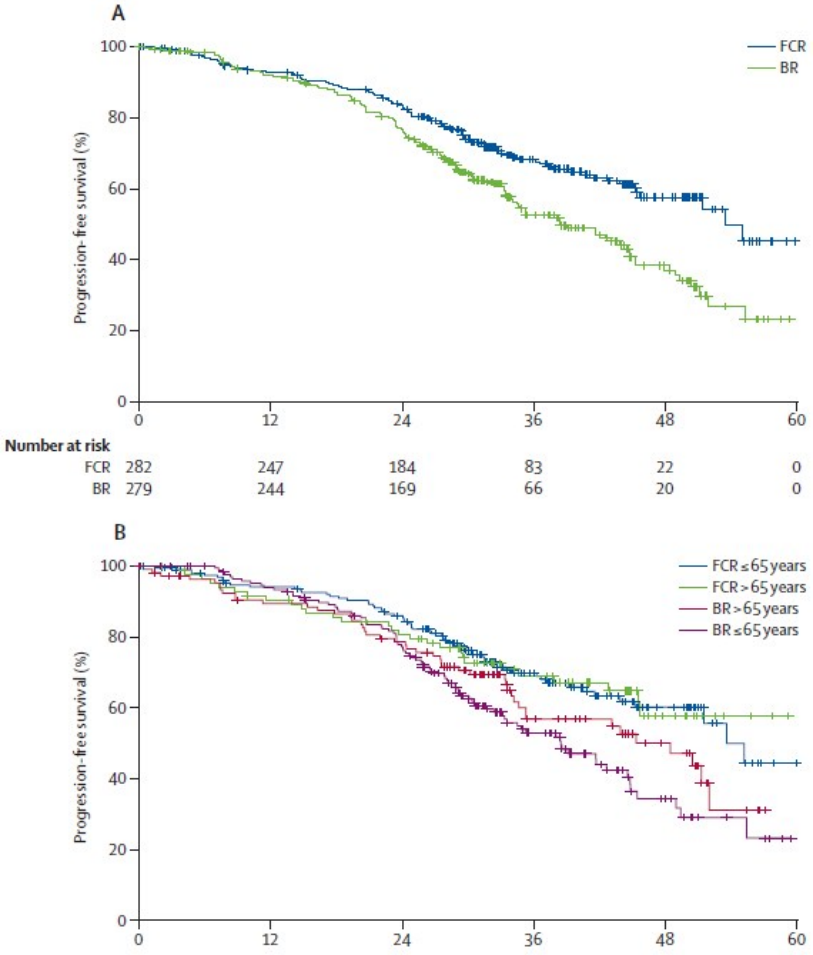
The evidence supporting this protocol is provided by a phase 3 multicentre non-inferiority international randomised trial by Eichhorst et al. involving 564 patients comparing bendamustine and rituximab with fludarabine, cyclophosphamide and rituximab (FCR) in patients with symptomatic non-del (17p) chronic lymphocytic leukaemia (CLL).[1] Patients were randomly assigned to receive 6 cycles of either FCR (fludarabine 25 mg/m^2 for 3 days, cyclophosphamide 250 mg/m^2 for 3 days and rituximab 375 mg/m^2 on day 0 for cycle 1 and then 500 mg/m^2 day 1 for further cycles) or bendamustine and rituximab (bendamustine 90 mg/m^2 for 2 days and rituximab as per FCR dosing). The primary endpoint was progression-free survival (PFS) with the objective to assess non-inferiority of bendamustine and rituximab to standard therapy.[1]

Efficacy

After a median follow up of 37.1 months, the median PFS for bendamustine and rituximab at 41.7 months which did not meet criteria for non-inferiority compared with FCR at 55.2 months (HR 1.643, 90.4% CI 1.308-2.064). However, PFS in age >65 was not

significantly different between both groups.[1]

Figure 1: Progression-free survival for (A) all patients (B) per age of FCR vs. bendamustine and rituximab[1]



Toxicity

Toxicities of bendamustine and rituximab are similar to that described in other studies in indolent lymphoma. However, when compared with FCR there was less severe infection.

Table 1: Comparison of severe adverse events for all patients[1]

	Bendamustine and rituximab	FCR
Death	N = 29	N = 30
Severe infection CTCAE ≥ 3	N = 74	N = 111
Grade ≥ 3 neutropenia	59%	85%

Figure 2: Adverse events for all patients[1]

	Fludarabine, cyclophosphamide, and rituximab				Bendamustine and rituximab			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Adverse events per patient including all patients*								
Patients with adverse events	11 (4%)	56 (20%)	192 (69%)	13 (5%)	22 (8%)	104 (37%)	116 (42%)	14 (5%)
Haematological toxic effects	3 (1%)	60 (21%)	193 (69%)	0	4 (1%)	79 (28%)	109 (39%)	0
Neutropenia	2 (1%)	63 (23%)	172 (62%)	0	1 (<1%)	66 (24%)	98 (35%)	0
Leukocytopenia	2 (1%)	116 (42%)	109 (39%)	0	1 (<1%)	104 (37%)	31 (11%)	0
Thrombocytopenia	9 (3%)	37 (13%)	23 (8%)	0	10 (4%)	29 (10%)	11 (4%)	0
Anaemia	3 (1%)	28 (10%)	10 (4%)	0	2 (1%)	24 (9%)	5 (2%)	0
Infections total	103 (37%)	97 (35%)	8 (3%)	6 (2%)	114 (41%)	61 (22%)	6 (2%)	7 (2%)
Bacterial infection	6 (2%)	5 (2%)	0	0	5 (2%)	5 (2%)	1 (<1%)	0
Fungal infection	6 (2%)	2 (1%)	1 (<1%)	0	5 (2%)	0	0	0
Viral infection	50 (18%)	22 (8%)	1 (<1%)	1 (<1%)	41 (15%)	9 (3%)	0	1 (<1%)
Unspecified pathogen	116 (42%)	67 (24%)	2 (1%)	2 (1%)	123 (44%)	38 (14%)	4 (1%)	1 (<1%)
Pneumonia	12 (4%)	29 (10%)	4 (1%)	1 (<1%)	13 (5%)	22 (8%)	0	2 (1%)
Sepsis	0	6 (2%)	1 (<1%)	2 (1%)	0	1 (<1%)	1 (< 1%)	3 (1%)
Secondary neoplasia	1 (<1%)	7 (2%)†	9 (3%)‡	4 (1%)§	2 (1%)	6 (2%)¶	3 (1%)‖	3 (1%)**
Allergic conditions	8 (3%)	12 (4%)	3 (1%)	0	12 (4%)	21 (8%)	6 (2%)	0
Cardiac and pulmonary disorders	11 (4%)	19 (7%)	5 (2%)	2 (1%)	12 (4%)	16 (6%)	4 (1%)	4 (1%)
Gastrointestinal disorders	20 (7%)	19 (7%)	2 (1%)	1 (<1%)	15 (5%)	16 (6%)	2 (1%)	0
Neurological and psychiatric disorders	12 (4%)	10 (4%)	2 (1%)	0	13 (5%)	8 (3%)	3 (1%)	0
Skin reactions	28 (8%)	8 (3%)	0	0	25 (9%)	9 (3%)	1 (<1%)	0
Pyrexia	16 (6%)	1 (<1%)	0	0	15 (5%)	6 (2%)	0	0
Renal disorders	3 (1%)	7 (3%)	2 (1%)	0	3 (1%)	2 (1%)	0	0
Fatigue	6 (2%)	2 (1%)	0	0	3 (1%)	2 (1%)	0	0
Arthritis and arthralgia	7 (2%)	0	1 (<1%)	0	7 (2%)	1 (1%)	1 (<1%)	0
Trauma and orthopaedic problems	5 (2%)	7 (2%)	0	0	6 (2%)	8 (3%)	0	0
Laboratory abnormalities	5 (2%)	7 (2%)	0	0	6 (2%)	8 (3%)	0	0
Urticaria	1 (<1%)	0	0	0	2 (1%)	3 (2%)	0	0
Other	25 (9%)	12 (4%)††	0	0	18 (6%)‡‡	16 (6%)§§	2 (1%)	0

References

1 Eichhorst B., A. Fink, and J. Bahlo et al. 2016. "First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial." Lancet Oncol. 2016 Jul;17(7):928-942

History

Version 2

Date	Summary of changes
28/04/2023	Reviewed electronically by Haematology reference committee. Increase to version 2, for review in 2 years. Updates include: • Subcutaneous rituximab information removed from the following sections - treatment schedule, clinical information, administration, side effects, patient information. • Updated side effects and dose modifications to align with the product information

Version 1

Date	Summary of changes
01/09/2020	This protocol was briefly in the ID 3794 Bendmustine and rituximab multi indication protocol prior to being developed into a new protocol with the correct rituximab dose increasing from cycle 2. Approved and published on eviQ. Review in 1 year.
21/10/2020	Note added that the 1,600mg subcutaneous product is not available in Australia.
01/10/2021	Drug status updated: rituximab SC is TGA registered but no longer PBS listed.

First approved: 1 September 2020
Last reviewed: 28 April 2023
Review due: 30 June 2025

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/3811
19 Sep 2023

Patient information - Chronic lymphocytic leukaemia (CLL) - Bendamustine and rituximab

Patient's name:

Your treatment

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

Bendamustine and rituximab

This treatment cycle is repeated every 28 days. You will usually have 6 cycles. Your doctor will advise you of the number of treatments you will have.

Day	Treatment	How it is given	How long it takes
1	**Rituximab** (*ri-TUX-i-mab*)	By a drip into a vein	**1st cycle:** About 4 to 6 hours **Cycles thereafter:** About 3 to 4 hours
1 and 2	**Bendamustine** (*ben-da-MUS-teen*)	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
• 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.	Daytime:..... 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.

Medications for blood pressure

Rituximab 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 rituximab 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.
- **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.
- **Rituximab premedication:** before your treatment with rituximab you will need to take some tablets called a premedication to help prevent you from having a reaction to the rituximab.

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.**
Taste and smell changes	• You may find that food loses its taste or tastes different. • These changes are likely to go away with time. • Do your mouth care regularly. • Chew on sugar-free gum or eat sugar-free mints. • Add flavour to your food with sauces and herbs. • Ask your doctor or nurse for eviQ patient information - Taste and smell changes during cancer treatment.
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.**
Stomach pain	• You may get: ◦ dull aches ◦ cramping or pain ◦ bloating or flatulence (gas). • **Tell your doctor or nurse immediately, or go to the nearest hospital Emergency Department if you have stomach pain that you are unable to control.**
Appetite loss (anorexia)	• You may not feel like eating. • Try to avoid drinking fluids at meal times. • Try to eat small meals or snacks regularly throughout the day. • Try to eat food that is high in protein and calories. • If you are worried about how much food you can eat, or if you are losing weight, ask to speak to a dietitian.
Joint and muscle pain and stiffness	• You may get muscle, joint or general body pain and stiffness. • Applying a heat pack to affected areas may help. • Talk to your doctor or nurse about other ways to manage these symptoms. You may need medication to help with any pain.

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.**

Diarrhoea	• You may get bowel motions (stools, poo) that are more frequent or more liquid. • You may also get bloating, cramping or pain. • Take your antidiarrhoeal medication as directed by your doctor. • Drink plenty of fluids (unless you are fluid restricted). • Eat and drink small amounts more often. • Avoid spicy foods, dairy products, high fibre foods, and coffee. • Ask your doctor or nurse for eviQ patient information - Diarrhoea during cancer treatment. • **Tell your doctor or nurse immediately, or go to your nearest hospital Emergency Department if your diarrhoea is not controlled, you have 4 or more loose bowel motions per day, and if you feel dizzy or light-headed.**
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.**
Extra fluid in the body (fluid retention)	• You may gain weight over a short amount of time. • Your hands and feet may become swollen, appear red or feel hot and uncomfortable. • Wear loose clothing and shoes that are not too tight. • Try not to stand up or walk around too much at one time. • If your ankles or legs get swollen, try raising them. • Make sure that any cuts or areas of broken skin are treated as soon as possible. • **Tell your doctor or nurse as soon as possible if you get any of the symptoms listed above or gain 1 to 2 kg in a week.** • **Tell your doctor or nurse immediately or go to the nearest hospital Emergency Department if you become short of breath.**
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)	
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.**
Infection risk (lymphopenia)	• This treatment lowers the amount of white blood cells in your body even after you have finished your treatment. A type of white blood cell that helps to fight infection are called lymphocytes. Having low level of lymphocytes is called lymphopenia. If you have lymphopenia, 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.**
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).**

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.
- 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 more 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.

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/3811
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