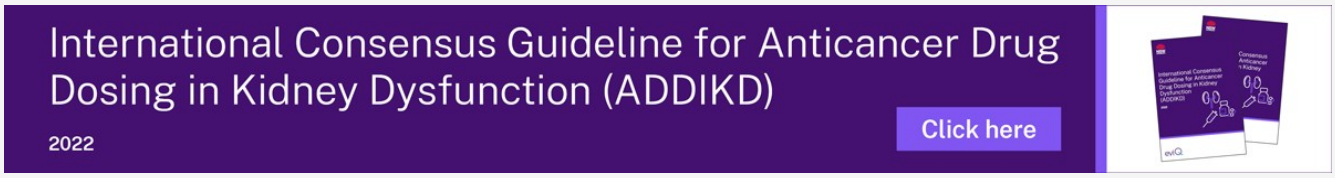
Non-Hodgkin lymphoma rituximab

ID: 125 v.8 **Endorsed** Essential Medicine List

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.



Treatment schedule - Overview

Cycle 1 to 4

Drug	Dose	Route	Day
Rituximab	375 mg/m^2	IV infusion	1

Frequency: 7 days

Cycles: 4 to 6
4 cycles - CD20 positive low-grade B-cell non-Hodgkin lymphoma or follicular B-cell non-Hodgkin lymphoma that does not meet GELF criteria
6 cycles - previously untreated splenic marginal zone lymphoma
See relevant evidence sections.

Notes:
In follicular lymphoma that has responded to initial therapy, the evidence supports the use of maintenance rituximab once every 2-3 months for 2 years.[1, 2]

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

Cost: ~ $360 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 to 4

Day 1		
Paracetamol	1,000 mg (PO)	60 minutes before treatment

Day 1		
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

Frequency: 7 days

Cycles: 4 to 6
4 cycles - CD20 positive low-grade B-cell non-Hodgkin lymphoma or follicular B-cell non-Hodgkin lymphoma that does not meet GELF criteria
6 cycles - previously untreated splenic marginal zone lymphoma
See relevant evidence sections.

Indications and patient population - Relapsed/refractory low-grade non-Hodgkin lymphoma

- Relapsed/refractory CD20 positive low-grade B-cell non-Hodgkin lymphoma

Indications and patient population - Follicular lymphoma

- Follicular B-cell non-Hodgkin lymphoma with low tumour burden not meeting Groupe d'Etude des Lymphomes Folliculaires (GELF) criteria

Indications and patient population - Splenic marginal zone lymphoma

- Previously untreated splenic marginal zone lymphoma

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 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 MINIMAL	No antiemetics should be routinely administered before treatment in patients without a history of nausea and vomiting. If patients experience nausea and/or vomiting, consider using the low antiemetic prophylaxis regimen. Read more about preventing anti-cancer therapy induced nausea and vomiting
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.
Tumour lysis risk	Assess patient for risk of developing tumour lysis syndrome. Read more about prevention and management of tumour lysis syndrome.
Antiviral prophylaxis	Read more about antiviral prophylaxis drugs and doses
Biosimilar drug	Read more about biosimilar drugs on the Biosimilar Awareness Initiative page
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).

No dose modifications required

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*

Rituximab		
	Interaction	**Clinical management**
Antihypertensives	Additive hypotensive effect	Consider withholding antihypertensive medications 12 hours prior to the rituximab infusion
Immunosuppressants (eg. abatacept and baricitinib etc.)	Increased risk of infection	Concurrent use not recommended. If an immunosuppressant must be used, monitor closely for signs of infection

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

Handling of monoclonal antibodies and waste management

Safe administration

General patient assessment prior to each day of treatment.

Prime IV line(s).

Insert IV cannula or access TIVAD or CVAD.

Pre treatment medication

Verify antiemetics taken or administer as 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

Remove IV cannula and/or deaccess TIVAD or CVAD.

Discharge information

Prophylaxis medication

- Prophylaxis medication (if prescribed) i.e. tumour lysis prophylaxis and 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
Flu-like symptoms	
Headache	

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
Fatigue	Read more about fatigue
Nausea and vomiting	Read more about prevention of treatment induced nausea and vomiting
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
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 - Relapsed/refractory low-grade non-Hodgkin lymphoma

There have been a few studies examining weekly rituximab in relapsed/refractory lymphoma. A phase 3 multi-centre study of 166 patients by McLaughlin et al. examined the efficacy of rituximab given once weekly for 4 consecutive weeks for relapsed or refractory CD20+ low-grade or follicular B-cell lymphoma.[3] A phase 2 study by Piro et al. also established the safety and efficacy of 8 weekly doses of rituximab in the same patient population.[4] A randomized trial by Ghielmini et al. compared the standard 4-week regimen with a prolonged regimen (standard regimen followed by 4 additional doses given every 2 months) in 202 patients with newly diagnosed or refractory/relapsed follicular lymphoma.[5]

Efficacy

In the study by McLaughlin et al., 6% of patients achieved complete remission (CR) and 42% partial response (PR). Of the remaining patients, 56 of 75 demonstrated at least a decrease in measurable disease. At a median follow-up of 11.8 months, the projected time to progression was 13 months with 53 of the 76 patients who responded still in remission.[3]

Ghielmini et al. (n= 185) demonstrated an overall response rate (ORR) of 52% with 8% CR following the standard 4-weekly schedule of rituximab. Chemotherapy-naive patients demonstrated a statistically significantly (p=0.0097) greater response rate (RR) of 67% with 9% CR when compared to those who had been previously treated (RR 46%, CR 8%). Event-free survival (EFS) in those randomised to receive the standard rituximab schedule was 11.8 months.[5]

Toxicity

McLaughlin et al. reported the majority of adverse events occurred during the first infusion and were grade 1 or 2; fever and chills being the most common.[3] Similarly, Ghielmini et al. reported the majority of non-haematological toxicity to be mild infusion-related reactions during the first infusion of rituximab.[5]

According to the drug product information the most common adverse reactions of rituximab (incidence ≥ 25%) observed in patients with relapsed or refractory low-grade or follicular NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia. For patients treated with weekly rituximab monotherapy, 38% reported respiratory events (all grades) and infections occurred in 31% of patients with 4% experiencing grade 3 and 4 events.[6] Grade 3 and 4 cytopenias reported included neutropenia (4%), anaemia (1%), and thrombocytopenia (2%).[7]

Evidence - Follicular lymphoma

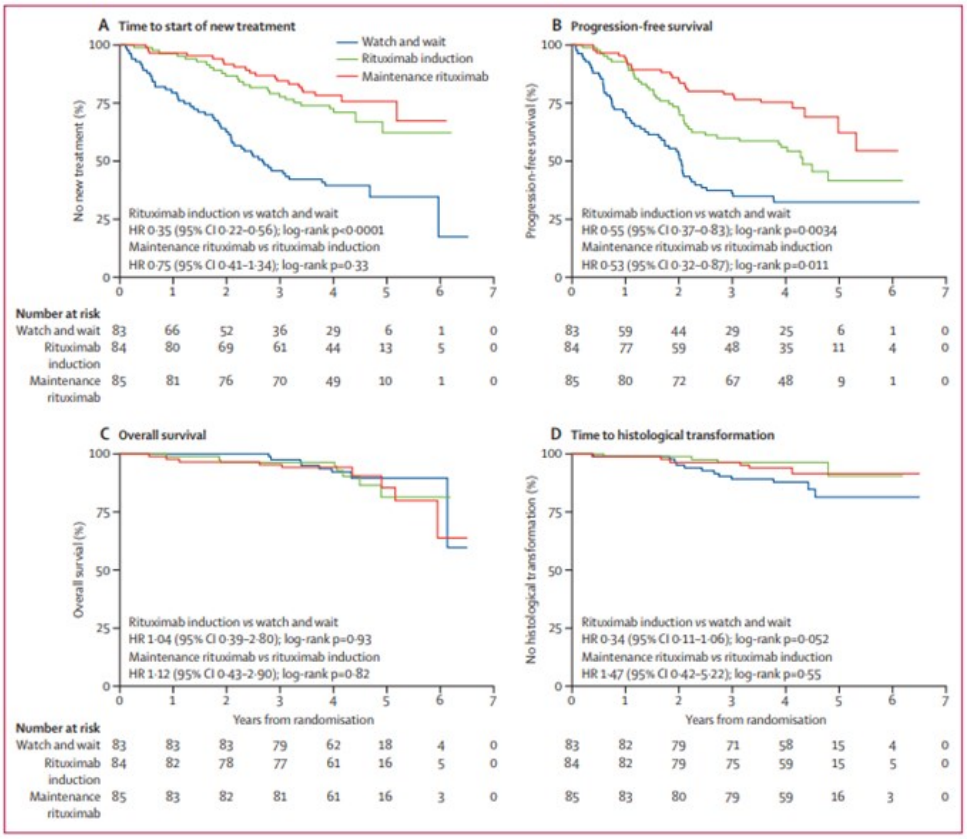
Rituximab (R) single agent as first-line therapy has been studied in a few studies. Colombat et al. reported an overall response rate (ORR) of 73% in 50 patients with low-burden stage II to IV follicular lymphoma who received single-agent rituximab as 4 weekly infusions upfront.[8] Ardeshna et al. published a multicenter phase 3 study of 463 patients with advanced stage, asymptomatic, non-bulky follicular lymphoma who were randomised 1:1:1 to rituximab induction, rituximab induction plus maintenance or a wait-and-watch approach; the primary endpoints were time to start of new treatment and quality of life. [2]

The EORTC phase 3 trial reported by van Oers et al. discusses the role of rituximab maintenance treatment in long-term outcomes in relapsed/resistant follicular non-Hodgkin lymphoma (median follow-up of 6 years). After first receiving induction with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) (n= 231) or R-CHOP (n = 234), patients were then randomly assigned to receive either rituximab maintenance (rituximab 375 mg/m^2 IV every 3 months until relapse or a maximum of 2 years) (n =167) or observation (n = 167).[1]

Efficacy

In the study by Ardeshna et al. at a median follow-up of 46 months, there was a significant difference in time to starting a new treatment, with 88% in the maintenance rituximab group not needing treatment at 3 years versus 46% in the watchful waiting group ($p < 0.001$).[2]

Figure. Kaplan-Meier curves showing time to start of new treatment (A), PFS (B), overall survival (C) and time to histological transformation (D)[2]



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In the phase 3 trial conducted by van Oers et al., rituximab maintenance demonstrated improved progression-free survival (PFS) after both CHOP and R-CHOP. After CHOP, the maintenance rituximab arm had a PFS of 42.2 months versus 11.6 months in the observation arm (P < 0.001); and after R-CHOP, the maintenance rituximab arm had a PFS of 51.8 months versus 23 months in the observation arm (P< 0.004).[1]

Toxicity

The phase 3 study by Ardeshna et al. reported no improvement in quality of life for patients in the rituximab induction group compared with the watchful waiting group. There were 18 serious adverse events reported in the rituximab groups (four in the rituximab induction group and 14 in the maintenance rituximab group), 12 of which were grade 3 or 4 (five infections, three allergic reactions, and four cases of neutropenia), all of which fully resolved.[2]

Maintenance rituximab treatment was well tolerated, with the only significant toxicity being an increase in grade 3 to 4 neutropenia (10.8% versus 5.4% in the observation arm), contributing to the overall increased infection rate of 9% in the maintenance rituximab arm (versus 2.4% in the observation arm).[1]

Evidence - Splenic marginal zone lymphoma

A search of the literature did not find strong evidence to support the use of rituximab monotherapy in the treatment of splenic marginal zone lymphoma. Data regarding the use of rituximab as first-line therapy in splenic marginal zone lymphoma (SMZL) are from retrospective studies. The expert reference panel supported the publication of the protocol on the basis of the information summarised below.

Source	Study & year published	Supports use	Is the dose and regimen consistent with the protocol?	Comments
Retrospective study	Kalpadakis et al. 2013[9]	Yes	Yes	6 weekly rituximab infusions (375 mg/m^2)
Retrospective study	Kalpadakis et al. 2018[10]	Yes	Yes	6 weekly rituximab infusions (375 mg/m^2)
Retrospective study	Tsimberidou et al. 2006[11]	Yes	No	4 or 8 weekly rituximab infusions (375 mg/m^2)

Retrospective study	Else et al. 2012[12]	Yes	No	4 weekly rituximab infusions (375 mg/m^2)

Guidelines	Date published/revised	Supports use	Is the dose and regimen consistent with the protocol?	Comments
NCCN	B-cell lymphomas V.2 February 2023	Yes	No	4 weekly rituximab infusions (375 mg/m^2)
BCCA	LYRITUX February 2022	N/A	N/A	-
CCO	May 2022	N/A	N/A	-

Kalpadakis et al. reported the outcomes of 106 patients with symptomatic SMZL from 3 centres treated with 6 weekly doses of rituximab 375 mg/m^2 (induction), followed by maintenance every 2 months for up to 2 years or follow-up in responders.[10] This study was an update from an earlier retrospective analysis which also compared outcomes of patients with symptomatic SMZL treated with single-agent rituximab (n=58) or splenectomy (n=27).[9]

Tsimberidou et al.[11] and Else et al.[12] assessed the outcomes of patients with symptomatic SMZL treated with rituximab alone or in combination with chemotherapy. Rituximab monotherapy appears as equally effective as rituximab chemotherapy combination therapy.

Efficacy

In the study by Kalpadakis et al. (n=106) in splenic marginal zone lymphoma, the overall response rate (ORR) at the end of induction with rituximab was 92%, with 44% complete response (CR), 21% unconfirmed CR and 27% partial response (PR) rates, with a median time to haematological response of 2 weeks and clinical response of 4 weeks. After a median follow-up of 57 months, the median 5 and 10-year OS were 93% and 85%. The corresponding progression-free survival (PFS) was 71% and 64%. Maintenance was associated with improved PFS but not overall survival (OS). There is no difference in PFS between those who received maintenance for 1 versus 2 years.[10]

In the earlier analysis by Kalpadakis et al., outcomes of patients with symptomatic splenic marginal zone lymphoma treated with single-agent rituximab (n=58) or splenectomy (n=27) were compared. The ORR to rituximab was 95% (45% CR, 26% unconfirmed CR, 24% PR). At a median follow-up of 3 years, the 5-year OS and PFS rates were 92% and 77%, respectively. Splenectomy resulted in ORR of 85% and 5-year OS and PFS rates of 77% and 58%, respectively.[9]

In a single institution retrospective analysis by Tsimberidou et al., patients with symptomatic splenic marginal zone lymphoma were treated with rituximab alone (n=26), chemotherapy alone (n=11) or rituximab plus chemotherapy (n=6). When compared to those who received chemotherapy alone, patients who had single-agent rituximab had superior rates of OS (88% vs 55%), 3-year OS (86% vs 45%) and 3-year failure-free survival (86% vs 45%). Outcomes in patients who received both rituximab and chemotherapy were similar to those who received rituximab alone.[11]

Else et al. retrospectively assessed 43 patients from two centres who received rituximab for splenic marginal zone lymphoma, either alone or with chemotherapy. Rituximab monotherapy appears equally as effective as rituximab chemotherapy combination (90% CR vs 79% CR).[12]

Toxicity

Else et al. reported significantly more toxicity in patients who received rituximab in combination with chemotherapy, compared to rituximab alone. Grade 3 and 4 toxicity was neutropenia (45%), thrombocytopenia (8%), and infection (11%).[12]

According to the drug product information the most common adverse reactions of rituximab (incidence ≥ 25%) observed in patients with relapsed or refractory low-grade or follicular NHL are infusion reactions, fever, chills, infection, asthenia, and lymphopenia. For patients treated with weekly rituximab monotherapy, 38% reported respiratory events (all grades) and infections occurred in 31% of patients with 4% experiencing grade 3 and 4 events.[6] Grade 3 and 4 cytopenias reported included neutropenia (4%), anaemia (1%), and thrombocytopenia (2%).[7]

References

1 van Oers, M.H.J., R. Klasa, R.E. Marcus, et al. 2006. "Rituximab maintenance improves clinical outcome of relapsed/resistant follicular non-Hodgkin lymphoma in patients both with and without rituximab during induction: results of a prospective randomized phase 3 intergroup trial." Blood 108(10):3295-3301.

2 Ardeshna, K. M., W. Qian, P. Smith, et al. 2014. "Rituximab versus a watch-and-wait approach in patients with advanced-stage, asymptomatic, non-bulky follicular lymphoma: an open-label randomised phase 3 trial." Lancet Oncol 15(4):424-435.

3 McLaughlin, P., A. J. Grillo-Lopez, B. K. Link, et al. 1998. "Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program." J.Clin Oncol. 16(8):2825-2833.

4 Piro, L. D., C. A. White, A.J. Grillo-Lopez, et al. 1999 “Extended rituximab (anti-CD20 monoclonal antibody) therapy for relapsed or refractory low-grade or follicular non-Hodgkin’s lymphoma.” Ann Oncol 10(6):655-661

5 Ghielmini, M., S. F. Schmitz, S. B. Cogliatti, et al. 2004. "Prolonged treatment with rituximab in patients with follicular lymphoma significantly increases event-free survival and response duration compared with the standard weekly x 4 schedule." Blood. 103(12):4416-4423.

6 Genentech USA Inc. Rituxan (Rituximab) product information. 2020

7 Roche Australia Pty Ltd. Mabthera product information. 2019

8 Colombat, P., G. Salles, N. Brousse, et al. 2001. "Rituximab (anti-CD20 monoclonal antibody) as single first-line therapy for patients with follicular lymphoma with a low tumor burden: clinical and molecular evaluation." Blood 97(1):101-106.

9 Kalpadakis, C., G. A. Pangalis, M. K. Angelopoulou, et al. 2013. "Treatment of splenic marginal zone lymphoma with rituximab monotherapy: progress report and comparison with splenectomy." Oncologist 18(2):190-197.

10 Kalpadakis, C., G. A. Pangalis, S. Sachanas, et al. 2018. "Rituximab monotherapy in splenic marginal zone lymphoma: prolonged responses and potential benefit from maintenance." Blood 132(6):666-670.

11 Tsimberidou, A. M., D. Catovsky, E. Schlette, et al. 2006. "Outcomes in patients with splenic marginal zone lymphoma and marginal zone lymphoma treated with rituximab with or without chemotherapy or chemotherapy alone." Cancer 107(1):125-135.

12 Else, M., A. Marin-Niebla, F. de la Cruz, et al. 2012. "Rituximab, used alone or in combination, is superior to other treatment modalities in splenic marginal zone lymphoma." Br J Haematol 159(3):322-328.

Bibliography

Davis, T. A., A. J. Grillo-Lopez, C. A. White, et al. 2000. "Rituximab anti-CD20 monoclonal antibody therapy in non-Hodgkin's lymphoma: safety and efficacy of re-treatment." J.Clin Oncol. 18(17):3135-3143..

History

Version 8

Date	Summary of changes
28/04/2023	Protocol reviewed at the Haematology Reference Committee meeting.
15/01/2024	The following changes were made: • indications and patient population - split in to multi-indication with addition of upfront follicular lymphoma and splenic marginal zone lymphoma • changes to the number of cycles from 4 cycles to, 4 to 6 cycles • evidence updates - split in to multi-indication format with relevant updates to each • amendment to cycle wording in patient information • subcutaneous rituximab information removed from the following sections – treatment schedule, clinical information, administration and patient information Version increase to V8. Review in 4 years

Version 7

Date	Summary of changes

Date	Summary of changes
9/03/2020	Biosimilar rituximab added to clinical information. Version number changed to V.7
20/04/2020	Rituximab drug status changed from TGA listed to reflect PBS changes.
25/08/2020	Protocol reviewed by Haematology reference committee, nil significant updates. Minor changes to evidence and references. For review in 4 years.
22/12/2020	Related pages updated - ID 1385 Non-Hodgkin lymphoma rituximab maintenance replaced with ID 3909 Non-Hodgkin lymphoma rituximab maintenance subcutaneous
21/09/2022	Drug status updated: rituximab SC is TGA registered but no longer PBS listed.

Version 6

Date	Summary of changes
07/06/2006	Addition of link to rapid infusion rituximab
04/07/2007	Reformatting and addition of extra information
18/09/2008	Updating of key evidence, efficacy and toxicity, references, patient information sheet
08/09/2009	Reviewed and transferred to eviQ.
16/03/2011	New format to allow for export of protocol information. Protocol version number changed to *V.2.* Antiemetics and premedications added to the treatment schedule. Additional Clinical Information, Key Prescribing table and Key Administration table combined into new section titled Clinical Considerations. Drug specific information placed behind the drug name link. Rituximab and antihypertensives interaction reworded to 'consider withholding.....'.
28/06/2011	Hydrocortisone 100 mg IV added to the treatment schedule.
19/08/2011	Full protocol review at Haematology Reference Committee meeting: - additon of statement regarding maintenance treatment of follicualr lymphoma to Notes section - addition of information on PML associated with rituximab (preclinical information and side effect) - addition of the following side effects: PML, neutropenia, thrombocytopenia, anaemia and rash - addition of data on maintenance rituximab to Evidence section and inclusion of van Oers 2010 reference
13/12/2011	PHC view added.
11/10/2013	Reviewed at categorisation meeting, not for review, review in 2 years.
11/07/2014	PHC view removed.
24/09/2014	Added link to ALLG, ANZCTR and Lymphoma Australia website with statement 'Patients with lymphoma should be considered for inclusion into clinical trials'.
17/11/2014	Safe handling precautions (waste) removed.
11/09/2015	Reviewed at RCM, no changes, updated drug costs.
31/05/2017	Transferred to new eviQ website. Version number change to V.4.
07/03/2018	**Added:** • Link to subcutaneous rituximab document underneath the treatment schedule. • Clinical information block on subcutaneous rituximab • Link to the subcutaneous rituximab document into administration section • Injection-site reaction side effect • Note about subcutaneous rituximab to the patient information • Version number changed to V.5.
25/05/2018	Protocol reviewed at Haematology Reference Committee meeting: • Treatment schedule: drug status updated. Rituximab is no longer PBS subsidised for this indication. • Version number changed to V.6.
13/09/2019	Reviewed by Haematology Reference Committee, no changes made. Review in 5 years.

First approved: 1 April 2005
Last reviewed: 15 January 2024
Review due: 30 June 2027

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/125
15 Jan 2024

Patient information - Non-Hodgkin lymphoma (NHL) - Rituximab

Patient's name:

What treatment you will have

The treatment schedule below explains how the drug for this treatment is given.

Rituximab			
This treatment cycle is repeated every 7 days. Your doctor will tell you how many treatment cycles 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

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

Treatment delays

There may 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. Your doctor will explain if you need any 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

- **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.
- **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.

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.**
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.**

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.**
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.**
Nausea and vomiting	• You may feel sick (nausea) or be sick (vomit). • 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. • Anti-sickness medication is usually not needed but may help in some people. • 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.**

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.**
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/
- Beyond Blue – 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 – https://www.foodstandards.gov.au/publications/listeriabrochuretext
- 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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