South African National Department of Health
Brief Report of Rapid Review
Component: Tertiary

TITLE: Rituximab for indolent lymphomas

Date: June 2022 template update (original review November 2020)

Medicine: Rituximab
Medicine (ATC): L01XC02
Indication: C82, C83.0, C83.1
Patient population: B-cell indolent non-Hodgkin Lymphoma (iNHL)
Prevalence of condition: 150 patients per year (estimate)
Level of Care: Tertiary and Quaternary Hospital Level
Prescriber level: Specialist (oncologist, haematologist)
Current Standard of Care/ Comparator(s): cyclophosphamide, vincristine, and prednisone (CVP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).
Efficacy estimates: (preferably NNT) NNT = 28 to prevent 1 death at 2 years. NNT 16 to prevent 1 death at 4 years. NNT 3 to be free from progression at 4 years.

Key findings

- This is a review of the published evidence associated with the addition of rituximab in combination with either CVP (cyclophosphamide, vincristine, and prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) in the management of indolent lymphomas.
- One Cochrane Systematic Review and one randomized phase III study were identified for inclusion.
- The Cochrane systematic review demonstrated that the addition of rituximab to either CVP or CHOP improved overall survival at 2 years [HR = 0.65, 95% CI 0.54 to 0.78. (Heterogeneity: p=0.62, I2 = 0%). The NNT to prevent one death at 2 years was 28.
- The randomized controlled trial, not included in the systematic review described above, demonstrated that the addition of rituximab to CVP improved time to treatment failure by 20 months (CVP = 7 months vs R-CVP = 27 months; p < 0.0001). Four-year overall survival was 83% for R-CVP versus 77% for CVP alone (p = 0.029); NNT = 17.
- The addition of rituximab to either CHOP or CVP did not result in a clinically significant increase in the number of adverse events than either CHOP or CVP alone.
- Based on a cost-effectiveness analysis performed, the base case analysis resulted in an incremental cost-effectiveness ratio (ICER) of R 178 402. At the current acquisition cost, rituximab is not deemed to be cost-effective.

TERTIARY AND QUATERNARY EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

It is recommended that rituximab not be added onto the EML at the current contract price but be considered for inclusion if a future cost reduction of 66% - 80% of the contract price is achieved. *Rationale: Despite Rituximab-chemotherapy combination having shown to improve response rates and progression free survival in patient with indolent lymphomas compared to chemotherapy alone, at its current price its inclusion is unaffordable.*

(Refer to appendix 2 for the evidence to decision framework)

Presented at NEMLC: 3 December 2020 NEMLC referred this review back to technical Committee as, although it seemed this agent would be of clinical value for this indication, this value versus cost needed to be investigated. NEMLC recommended that the value be compared against other rituximab indications.
June 2022 – Review update and costing analysis (current document and annexure) Updated review and costing analysis to address NEMLC concerns

BACKGROUND

Non-Hodgkin's lymphoma (NHL) is broadly categorised into aggressive (e.g. diffuse large B cell lymphoma, Burkitt's lymphoma) and indolent subtypes. For the purposes of this review only B-cell types are considered. Aggressive NHL is curable with multi-agent chemotherapy regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) and CVP (cyclophosphamide, vincristine, and prednisone). The addition of rituximab to these regimens has led to significant improvement in outcomes including overall survival in aggressive lymphoma.

Indolent Non-Hodgkin's Lymphoma (iNHL) constitutes 70% of NHL diagnoses in first world countries with the most common form being follicular lymphoma (FL). Other subtypes include, lymphoplasmacytic lymphoma (LPL), Waldenströhm macroglobulinemia (WM), and marginal zone lymphoma (MZL).

Early stage (Ann Arbor stage I or II) iNHL is often treated with radiotherapy alone and approximately 50% of patients can experience long term disease free survival. Advanced stage iNHL (Ann Arbor stage III and IV) is not curable with current therapies and treatment is generally only started once a patient is symptomatic as treatment of asymptomatic patients is not associated with improved survival.. Initial treatment of iNHL is associated with high response rates, but is followed by continual relapse. The median overall survival of iNHL is 8 to 10 years.

Mantle cell lymphoma (MCL) is often grouped with iNHL, but also has features of aggressive lymphoma. Due to this, treatment is started at diagnosis, and a watch-and-wait approach is not followed. Median overall survival is 3 to 5 years.

Rituximab is a chimeric mouse/human monoclonal antibody that binds specifically to the transmembrane antigen CD20. CD20 is expressed on > 95 % of all B-cell non-Hodgkin's lymphomas (NHLs). Rituximab binds to the CD20 antigen on B lymphocytes and initiates immunologic reactions that mediate B-cell lysis. In-vitro studies have demonstrated that rituximab sensitises drug-resistant human B-cell lymphoma lines to the cytotoxic effects of some chemotherapeutic agents. (MabThera Package Insert)

Since early 2000's, rituximab added to standard chemotherapy regimens has been an accepted treatment option for B-cell iNHL expressing CD20, however not routinely available for this indication in the South African public sector. This review seeks to assess the published peer-reviewed data associated with the addition of rituximab to standard chemotherapy as well as its affordability within the South African context.

RESEARCH QUESTION:

Should rituximab be used in addition to chemotherapy (CHOP) in the management of newly diagnosed and relapsed patients with indolent B cell non-hodgkins lymphoma?

METHODS

Eligibility criteria for review

Population: Indolent B cell non-hodgkins lymphoma. Newly diagnosed and relapsed
Intervention: Rituximab + chemotherapy
Comparators: Chemotherapy alone: CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone)
Outcomes: Response rate, progression free survival, overall survival; adverse effects
Study designs: Randomised controlled trials (RCTs), meta-analyses, systematic reviews

RESULTS

Identification of studies (results of the search with PRISMA flowchart)

Pubmed

a. Search strategy: MESH terms search: (((rituximab[MeSH Terms]) AND (indolent lymphomas[MeSH Terms]))) NOT (bendamustine[MeSH Terms])
(Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review)

- 44 results (see table below)
- Inclusion: 2 RCTs, Meta-analyses and systematic reviews included.
- Exclusion: 42 excluded:
  - Did not meet PICO
    - » Rituximab in combination with alternative agent
    - » Rituximab dose/regimen finding study
    - » Different chemotherapy regimen (not CHOP or CVP)
    - » One meta-analysis and systematic review excluded [included same studies as Cochrane 2007, Schulz et.al. 2007, JNCI]
    - » One systematic review and practice guideline excluded [not specific to indolent lymphomas, Cheung et.al. 2007]
    - » One RCTs excluded as included in 2007 Cochrane review [Herold et.al. 2004]
    - » One RCT excluded as evaluating sequential vs concurrent therapy [Tobinai 2010]

(see appendix 1)

Epistemonikos: no additional studies

Reference search: 3 studies

- Marcus et. al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. 2008. [include]

- Bachy et al. Long-term follow up of the FL2000 study comparing CHVP-interferon to CHVP-interferon plus rituximab in follicular lymphoma. 2013. [exclude: R-chemo and chemo duration of regimens different]
- Marcus et.al. 2005. CVP chemotherapy plus rituximab compared with CVP as first-line treatment for advanced follicular lymphoma. [exclude: included in 2007 Cochrane review]

Included studies:

Author, year	Study type	Title
Schulz et.al. 2007[1]	Cochrane Systematic Review	Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma.
Marcus et. al. 2008[2]	Randomised Phase III study	Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma

Effects of Interventions

Comparison: R-chemo versus chemotherapy alone

- **Schulz et.al:**
  - Seven RCTs included (n = 1943)
  - Follicular lymphoma, mantle lymphoma or other indolent lymphomas
  - Overall survival: R-chemo had better overall survival [hazard ratio for mortality 0.65, 95% CI 0.54 to 0.78. *(Heterogeneity: p=0.62, I2 = 0%)*
  - Overall response: R-chemo had better overall response [relative risk tumour response, 1.21, 95% CI 1.16 to 1.27] *(large heterogeneity: p<0.0001, I2 = 81%)*
  - Disease control: R-chemo had better overall response [hazard ratio of disease event 0.62, 95% CI 0.55 to 0.71] *(Heterogeneity: p=0.56, I2 = 0%)*
  - Overall survival for specific lymphomas:
    - Follicular lymphoma: R-chemo improved overall survival [hazard ratio for mortality 0.63, 95% CI 0.51 to 0.79.]
    - Mantle cell lymphoma: R-chemo improved overall survival [hazard ratio for mortality 0.60, 95% CI 0.37 to 0.98] *(large heterogeneity in trial, p=0.07)*

- **Marcus et.al:**
  - Phase III, randomised study
  - Previously untreated CD20-positive stage III/IV patients with follicular lymphoma randomly received either eight cycles of R-CVP (n = 159) or CVP alone (n = 162)
  - Median follow up was 53 months.
  - Primary end-point: time to treatment failure (TTF), *including patients without a response after 4 cycles as an event*
  - TTF was prolonged in patients receiving R-CVP versus CVP (CVP = 7 months vs R-CVP = 27 months; p < 0.0001)
  - Improvements in all other endpoints were seen in R-CVP versus CVP alone:
    - 4-year overall survival: 83% versus 77% (p=0.029).
    - Overall response rates (CVP = 57% vs R-CVP = 81%; p < 0.0001)
    - Complete response rate (CVP = 10% vs R-CVP = 41%; p < 0.0001)

- Time to progression (CVP = 15 months vs R-CVP = 34 monthsp < 0.0001)
- Response duration (CVP = 14 months vs R-CVP = 38 months; p < 0.0001)

COST ANALYSIS

See CEA for rituximab in indolent non-Hodgkins lymphoma.

CONCLUSION

Rituximab-chemotherapy combination has been shown to improve response rates and progression free survival in patient with indolent lymphomas compared to chemotherapy alone, however it not deemed to be cost-effective at its current acquisition cost. It is proposed that a reference price (66 – 80% price reduction of current contract price – June 2022) be set for this agent in this indication.

REVIEWER(S):

Reviewers: Jacques Malherbe, Roger Wiseman, Kim MacQuilkan, Jane Riddin.

AUTHOR AFFILIATION AND CONFLICT OF INTEREST DETAILS:

JM: Conference sponsorship and payment for scientific talk (Janssen, Roche); Conference sponsor (Key Oncologics, Novartis, Shire, Astellas). Assessed as potentially significant, all decisions made by committee as a collective and not the lead reviewer. RW: employed by Liberty Health (Pty) Ltd, ad hoc consulting for Aligned (Pty) Ltd. KM (Better Health Programme South Africa, Right to Care) and JR (National Department of Health, Essential Drugs Programme) have no interests to declare.

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Table 1. Characteristics of included studies

Meta-analyses/Systematic Reviews

Citation	Study design	Population (n)	Treatment	Main findings	Risk of Bias
Schulz 2007	Meta-analysis of 7 RCT's (Cochrane)	Adults with iNHL (5 trials untreated advanced iNHL, 2 trials relapsed/ refractory FL/MCL)	R-chemo vs chemo (various chemo regimens included CHOP, CHOP, CVP, FCM and MCP) Cycles varied from 4 to 8	HR for death **Pooled 0.65** (95% CI = 0.54 to 0.78) in favour of R-chemo. **In FL 0.63** (95% CI = 0.51 to 0.76) **In MCL 0.60** (95% CI = 0.37 to 0.98) NNT to prevent one death at 2 years = 28 Disease Control **Pooled HR 0.62** (95% CI = 0.55 to 0.71) in favor of R-chemo Toxicity comparable between two groups. Only fever (HR 3.79) and leukocytopenia (HR 1.31) more frequent in rituximab arm. Infection rate (HR 1.05), thrombocytopenia (HR 1.14) and granulocytopenia (HR 1.18) equal.	Median observation 24 months. Patients with HIV, Hep B or C was excluded. Significant to show survival benefit for generally slowly progressive disease in median 24 months observation Toxicity comparable between two groups. Only fever (HR 3.79) and leukocytopenia (HR 1.31) more frequent in rituximab arm. Infection rate (HR 1.05), thrombocytopenia (HR 1.14) and granulocytopenia (HR 1.18) equal

Randomised Studies

Citation	Study design	Population (n)	Treatment	Main findings	Risk of Bias
Marcus 2008	Phase III RCT. Updated results from trial included in Schulz meta-analysis	Adults with previously untreated stage III/IV FL	R-CVP (n = 159) Vs. CVP (n = 162) 8 cycles Median Follow up was 53 months	Time to treatment failure (TTF) R-CVP = 27m vs CVP = 7m (p < 0.0001) Time to progression: R-CVP = 34m vs CVP 15m (p < 0.0001) Overall Survival at 48 months R-CVP = 83% vs CVP = 77% (p = 0.029) NNT = 17 All in favor of R-CVP	

Appendix 1: Search strategy

MESH terms search: (((rituximab[MeSH Terms]) AND (indolent lymphomas[MeSH Terms]))) NOT (bendamustine[MeSH Terms])
(Filters applied: Meta-Analysis, Randomized Controlled Trial, Systematic Review)

Included studies

5	2007	Schulz et.al.	Chemotherapy plus Rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma.	Include	Meets PICO
Ref search	2008	Marcus et. al.	Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma	Include	Meets PICO

Excluded studies

	Year	Authors	Title	Include/ exclude	Reason
1	2019	Leonard et.al	AUGMENT: A Phase III Study of Lenalidomide Plus Rituximab Versus Placebo Plus Rituximab in Relapsed or Refractory Indolent Lymphoma.	Exclude	Does not meet PICO
2	2018	Morschhauser et.al.	Rituximab plus Lenalidomide in Advanced Untreated Follicular Lymphoma.	Exclude	Does not meet PICO
3	2021	Matasar et.al.	Copanlisib plus rituximab versus placebo plus rituximab in patients with relapsed indolent non-Hodgkin lymphoma (CHRONOS-3): a double-blind, randomised, placebo-controlled, phase 3 trial.	Exclude	Does not meet PICO
4	2003	Plosker et. al.	Rituximab: a review of its use in non-Hodgkin's lymphoma and chronic lymphocytic leukaemia.	Exclude	Narrative review
6	2020	Poddubnava et.al.	Proposed rituximab biosimilar BCD-020 versus reference rituximab for treatment of patients with indolent non-Hodgkin lymphomas: An international multicenter randomized trial.	Exclude	Does not meet PICO
7	2007	Cheung	Rituximab in lymphoma: a systematic review and consensus practice guideline from Cancer Care Ontario.	Exclude	Not specific for indolent lymphomas
8	2021	Buske	Long-term efficacy and safety of CT-P10 or rituximab in untreated advanced follicular lymphoma: a randomized phase 3 study.	Exclude	Does not meet PICO
9	2003	Hiddermann	Rituximab plus chemotherapy in follicular and mantle cell lymphomas.	Exclude	Vs fludarabine/mitoxantrone/cyclophosphamide
10	2007	Schultz et.al.	Immunochemotherapy with rituximab and overall survival in patients with indolent or mantle cell lymphoma: a systematic review and meta-analysis.	Exclude	Includes same studies as Cochrane
11	2002	Sarris et.al.	Quantitative real-time polymerase chain reaction for monitoring minimal residual disease in patients with advanced indolent lymphomas treated with rituximab, fludarabine, mitoxantrone, and dexamethasone	Exclude	Does not meet PICO
12	2009	Vidal et.al.	Rituximab as maintenance therapy for patients with follicular lymphoma.	Exclude	Does not meet PICO
13	2017	Natoupil et.al.	High ten-year remission rates following rituximab, fludarabine, mitoxantrone and dexamethasone (R-FND) with interferon maintenance in indolent lymphoma: Results of a randomized Study.	Exclude	Fludarabine/ mitoxantrone/ dexamethasone
14	2012	Schaaf et.al.	High-dose therapy with autologous stem cell transplantation versus chemotherapy or immuno-chemotherapy for follicular lymphoma in adults.	Exclude	Does not meet PICO

15	2019	Telford et.al.	Matching-adjusted Indirect Comparisons of the Efficacy and Safety of Acalabrutinib Versus Other Targeted Therapies in Relapsed/Refractory Mantle Cell Lymphoma.	Exclude	Does not meet PICO
16	2016	Williams et.al.	Rituximab extended schedule or retreatment trial for low tumour burden non-follicular indolent B-cell non-Hodgkin lymphomas: Eastern Cooperative Oncology Group Protocol E4402.	Exclude	Does not meet PICO
18	2020	Walewski et.al.	First-line R-CVP versus R-CHOP induction immunochemotherapy for indolent lymphoma with rituximab maintenance. A multicentre, phase III randomized study by the Polish Lymphoma Research Group PLRG4.	Exclude	Does not meet PICO
19	2020	Maloney et.al.	A phase 3 randomized study (HOMER) of ofatumumab vs rituximab in iNHL relapsed after rituximab-containing therapy.	Exclude	Does not meet PICO
20	2006	Ogura et.al.	Randomized phase II study of concurrent and sequential rituximab and CHOP chemotherapy in untreated indolent B-cell lymphoma.	Exclude	Does not meet PICO (sequential vs concurrent)
21	2021	Matasar et.al.	Feasibility of Combining the Phosphatidylinositol 3-Kinase Inhibitor Copanlisib With Rituximab-Based Immunochemotherapy in Patients With Relapsed Indolent B-cell Lymphoma.	Exclude	Does not meet PICO
22	2007	Tobinai et.al.	Antibody therapy for malignant lymphoma.	Exclude	Does not meet PICO
23	2009	Hochster	Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: results of the randomized phase III ECOG1496 Study.	Exclude	Does not meet PICO
24	2020	Davies et.al.	Health-related quality of life in the phase III GALLIUM study of obinutuzumab- or rituximab-based chemotherapy in patients with previously untreated advanced follicular lymphoma	Exclude	Does not meet PICO
25	2003	Herold et.al.	Randomized phase III study for the treatment of advanced indolent non-Hodgkin's lymphomas (NHL) and mantle cell lymphoma: chemotherapy versus chemotherapy plus rituximab.	Exclude	Included in Cochrane 2007
26	2001	Brandt et.al.	A systematic overview of chemotherapy effects in indolent non-Hodgkin's lymphoma.	Exclude	Does not meet PICO
27	2015	Chen et.al.	Comparing the cost-effectiveness of rituximab maintenance and radioimmunotherapy consolidation versus observation following first-line therapy in patients with follicular lymphoma.	Exclude	Does not meet PICO
28	2002	Forstpointner et.al.	[Increased response rate with rituximab in relapsed and refractory follicular and mantle cell lymphomas -- results of a prospective randomized study of the German Low-Grade Lymphoma Study Group].	Exclude	Does not meet PICO
29	2015	Cheah et.al.	Dulanermin with rituximab in patients with relapsed indolent B-cell lymphoma: an open-label phase 1b/2 randomised study.	Exclude	Does not meet PICO
30	2020	Thanarajasingam et.al.	Longitudinal Toxicity over Time (ToxT) analysis to evaluate tolerability: a case study of lenalidomide in the CALGB 50401 (Alliance) trial.	Exclude	Does not meet PICO
31	2008	2008	Cost-effectiveness of maintenance rituximab treatment after second line therapy in patients with follicular lymphoma in Sweden.	Exclude	Does not meet PICO
32	2007	Herold et.al.	Rituximab added to first-line mitoxantrone, chlorambucil, and prednisolone chemotherapy followed by interferon maintenance prolongs survival in patients with advanced follicular	Exclude	Does not meet PICO

			lymphoma: an East German Study Group Hematology and Oncology Study.		
33	2011	Watanabe et.al.	Phase II/III study of R-CHOP-21 versus R-CHOP-14 for untreated indolent B-cell non-Hodgkin's lymphoma: JCOG 0203 trial.	Exclude	Does not meet PICO
34	2008	Kimby et.al.	Long-term molecular remissions in patients with indolent lymphoma treated with rituximab as a single agent or in combination with interferon alpha-2a: a randomized phase II study from the Nordic Lymphoma Group.	Exclude	Does not meet PICO
35	2015	Kimby et.al.	Two courses of four weekly infusions of rituximab with or without interferon-alpha2a: final results from a randomized phase III study in symptomatic indolent B-cell lymphomas.	Exclude	Does not meet PICO
36	2015	Sehn et.al.	Randomized Phase II Trial Comparing Obinutuzumab (GA101) With Rituximab in Patients With Relapsed CD20+ Indolent B-Cell Non-Hodgkin Lymphoma: Final Analysis of the GAUSS Study.	Exclude	Does not meet PICO
37	2009	De Vos et.al.	Multicenter randomized phase II study of weekly or twice-weekly bortezomib plus rituximab in patients with relapsed or refractory follicular or marginal-zone B-cell lymphoma.	Exclude	Does not meet PICO
38	2011	Tomblyn et.al	Autologous versus reduced-intensity allogeneic hematopoietic cell transplantation for patients with chemosensitive follicular non-Hodgkin lymphoma beyond first complete response or first partial response.	Exclude	Does not meet PICO
39	2005	Hainsworth et.al.	Maximizing therapeutic benefit of rituximab: maintenance therapy versus re-treatment at progression in patients with indolent non-Hodgkin's lymphoma--a randomized phase II trial of the Minnie Pearl Cancer Research Network.	Exclude	Does not meet PICO
40	2016	Pavandeh et.al.	Phase III of Study of R-CHOP-21 vs R-CHOP-14 for Untreated Stage III and IV B-cell Non-Hodgkin's Lymphoma: a Report from Iran.	Exclude	Does not meet PICO
41	2016	Barta et.al.	Randomized phase 3 study in low-grade lymphoma comparing maintenance anti-CD20 antibody with observation after induction therapy: A trial of the ECOG-ACRIN Cancer Research Group (E1496).	Exclude	Does not meet PICO
42	2000	McLaughlin et.al.	Safety of fludarabine, mitoxantrone, and dexamethasone combined with rituximab in the treatment of stage IV indolent lymphoma.	Exclude	Does not meet PICO
43	2002	?	Rituxan delays disease progression in indolent non-Hodgkin's lymphoma.	Exclude	Only interim results released
44	2004	Williams et.al.	ECOG 4402: randomized phase III-trial comparing two different rituximab dosing regimens for patients with low tumor burden indolent non-Hodgkin's lymphoma.	Exclude	Does not meet PICO

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Large heterogeneity for certain types of indolent lymphomas.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☒ Small ☐ None ☐	Consistent advantage of addition of Rituximab to standard backbone of chemotherapy across all trials
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☒ Low ☐ Very low ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Large heterogeneity for certain types of indolent lymphomas.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large ☐ Moderate ☐ Small ☐ None ☒	Addition of rituximab does not add significantly to the well-known and routinely managed complications of chemotherapy.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☒ Favours control ☐ Intervention = Control *or* Uncertain ☐	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	
RESOURCE USE	**How large are the resource requirements?** More intensive ☒ Less intensive ☐ Uncertain ☐	**See CEA document**
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor ☒ Major ☐ Uncertain ☐ **Is the option acceptable to key stakeholders?** Yes ☒ No ☐ Uncertain ☐	

EQUITY	**Would there be an impact on health inequity?** Yes: x No: Uncertain:	Improve inequities in indolent lymphomas therapy across provinces

REFERENCES

[1] Schulz H, Bohlius J et al. Chemotherapy plus rituximab versus chemotherapy alone for B-cell non-Hodgkin's lymphoma. Cochrane Database of Systematic Reviews 2007, Issue 4

[2] Marcus R, Imrie K et al. Phase III study of R-CVP compared with cyclophosphamide, vincristine, and prednisone alone in patients with previously untreated advanced follicular lymphoma. Journal of Clinical Oncology 2007;26:4579-4586.