PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bendamustine (Treanda) for Non-Hodgkin Lymphoma

November 29, 2012

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is to evaluate the effect of bendamustine, either as a single agent or in combination with other chemotherapeutic agents on patient outcomes compared to appropriate comparators in the treatment of patients with:

1. Previously untreated indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL).
2. iNHL or MCL that has relapsed following or is refractory to treatment that included rituximab.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

1.2.1 A) Previously Untreated Indolent NHL or MCL

One open-label multicentre randomized trial (Study StiL NHL1) was identified that compared the use of the bendamustine and rituximab (B-R) to cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R) in patients with previously untreated indolent NHL or MCL.[1] The trial was designed to evaluate non-inferiority of B-R compared to CHOP-R with a primary outcome of progression-free survival.[2] A total of 549 patients were randomized in a 1:1 ratio to receive B-R (Bendamustine 90 mg/m^2 d1+2 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles (n randomized= NR; n evaluable=260) or CHOP-R (cyclophosphamide 750 mg/m^2 d1 + doxorubicin 50 mg/m^2 d1 + vincristine 1.4 mg/m^2 d1 + prednisone 100 mg orally d1-5 + rituximab 375 mg/m^2 d1 every 3 weeks for 6 cycles (n randomized=NR; n evaluable=253)).

A statistically significant difference in progression-free survival was demonstrated for B-R (median 54.8 months) compared to CHOP-R (median 34.8 months), with a HR of 0.58, 95% confidence interval (95% CI) of 0.43-0.77, p=0.0002.[1] The rate of complete response was statistically significantly higher in the B-R compared to the CHOP-R arm (40.1% versus [vs.] 30.8%, p=0.0323).[1]

A higher proportion of patients in the CHOP-R arm than in the B-R arm experienced peripheral neuropathy (28.9% vs. 6.9%) and stomatitis (18.6% vs. 6.2%).[1] The following occurred in a statistically significantly higher proportion of patients in the B-R arm than in the CHOP-R arm, erythema (16.2% vs. 9.1%) and allergic reaction in the skin (15.4% vs. 5.9%). A higher proportion of patients experienced Grade 3 or 4 neutropenia and leukopenia in the CHOP-R arm (69% and 72%) than in the B-R arm (29% and 37%); however, more patients in the B-R arm experienced Grade 3 or 4 lymphopenia (74%) than in the CHOP-R arm.[3] Similar rates of Grade 3 or 4 anemia and thrombocytopenia were reported for both arms.[3]

The BRIGHT study, an open-label randomized phase III trial, comparing bendamustine hydrochloride and rituximab (B-R) with R-CVP or R-CHOP in the first-line treatment of patients with advanced indolent NHL or MCL is currently ongoing.[4]

1.2.1 B) Previously Treated Indolent NHL or MCL

One randomized, multicentre, open-label trial (Study StiL NHL2) was identified that compared the use of B-R to fludarabine plus rituximab (F-R) in patients with previously treated relapsed follicular, indolent and mantle cell lymphomas.[5] The study was designed to evaluate whether B-R was non-inferior to F-R, with a non-inferiority margin of 15% for event-free survival.[6] The manufacturer confirmed that the study was designed as a non-inferiority study, but that the primary outcome was progression-free survival and not event-free survival.

A total of 219 patients were randomized in a 1:1 ratio to receive either B-R (bendamustine 90 mg/m^2 d1+2 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles maximum) or F-R (fludarabine 25 mg/m^2 d1-3 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles maximum). No data were available on the number of patients randomized to each arm but the final analysis reported that the analysis included 208 evaluable patients. The StiL NHL2 study has been reported in abstract form only and thus many details regarding the study quality are not publicly available.

A statistically significant difference in progression-free survival was demonstrated for B-R (median 30 months) compared to F-R (median 11 months), with a HR of 0.51, 95% confidence interval (95% CI) of 0.34-0.67, p<0.0001.[5] The rate of complete response was statistically significantly higher in the B-R arm compared to the F-R arm (38.5% vs. 16.2%, p=0.0004).[5] In addition, a statistically significant difference in the rate of overall response was observed in the B-R arm compared to the F-R arm (83.5% vs. 52.5%, p<0.0001).[5] No quality of life data were reported for the StiL NHL2 study.

The rates of the following adverse events were similar in both study arms serious adverse events (17.4% for B-R vs. 22.2% for F-R), grade 3/4 neutropenia (8.9% vs. 9.1%), and grade 3/4 leukopenia (11.8% vs. 12.4%).[5] No further data on adverse events were reported.

The ROBIN study, an open-label randomized phase III trial, investigating the efficacy of bendamustine in patients with indolent non-Hodgkin's lymphoma (NHL) refractory to rituximab is currently ongoing.[7]

1.2.2 Additional Evidence

pCODR received input on bendamustine from the following patient advocacy group The Leukemia and Lymphoma Society of Canada and Lymphoma Foundation Canada. Provincial Advisory group input was obtained from the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

1.2.3 Interpretation and Guidance

Advanced stage iNHL is a relatively common illness which is incurable and associated with reduced life expectancy. Currently available drug treatments for iNHL can induce temporary remissions but do not control iNHL indefinitely and cause adverse effects. Therefore, new treatments that can improve the depth and duration of remission with acceptable or improved toxicity profiles are needed.

Bendamustine hydrochloride is a purine analogue/alkylator hybrid that has shown activity in various cancers and has been shown to have a unique mechanism of action in comparison to other alkylating agents such as cyclophosphamide or chlorambucil.

For patients with previously untreated iNHL in the rituximab era Study STiL NHL1, comparing bendamustine plus rituximab (B-R) to CHOP plus rituximab (CHOP-R), demonstrated a dramatic difference in PFS in favour of B-R. Although cross-trial comparisons are difficult, given the dramatic increase in PFS with B-R in STiL NHL1 it can be reasonably concluded from the available body of evidence that B-R is more efficacious than either CVP-R or CHOP-R. Results of the BRIGHT study, which include a randomized comparison between B-R and either CHOP-R or CVP-R, will add further information regarding the place of B-R in the initial treatment of iNHL. In STiL NHL1 B-R was generally less toxic than CHOP-R, with similar or lower rates of most reported toxicities for B-R apart from rash which was more prevalent in B-R treated patients.

For patients with relapsed iNHL Study STiL NHL2, comparing B-R to F-R, was the only available randomized control trial demonstrating a highly significant difference in PFS in favour of B-R. Whether B-R is superior to the other available treatments for relapsed iNHL is unclear. The efficacy of bendamustine treatment for rituximab-refractory iNHL is currently limited to non-randomized single arm study data. The ongoing ROBIN randomized study comparing bendamustine to physician's choice of therapy should provide high quality data regarding the utility of bendamustine in the rituximab-refractory setting. As well, there are no high-quality studies specifically examining the use of bendamustine retreatment in iNHL. Bendamustine-containing regimens demonstrate that the drug is relatively well tolerated in the treatment of relapsed/refractory iNHL.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to bendamustine in the treatment of previously untreated iNHL or MCL, based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival for B-R compared with CHOP-R. Adverse event profiles were generally more favourable for B-R compared to CHOP-R apart from rash.

It is recognized that in Canada CVP-R is the standard first-line regimen for many iNHL patients, and that CVP-R is less toxic than CHOP-R. While B-R and CVP-R have not been directly compared (pending the ongoing BRIGHT study), the body of evidence to date suggests that CVP-R is unlikely to be superior to B-R in terms of either efficacy or toxicity and that B-R is likely to be superior to CVP-R in terms of efficacy. Caution is advised in comparing B-R directly to CVP-R until the BRIGHT study results are reported.

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to bendamustine in the treatment of relapsed/refractory iNHL. The uncertainty of the Panel's conclusion was due to the following: (1) there is data from one randomized controlled trial demonstrating improved PFS for B-R compared to F-R, but no comparisons with other standard regimens for relapsed/refractory iNHL; (2) pending the ongoing ROBIN study, there is currently single-arm study data only for bendamustine alone in rituximab-refractory patients that, while

promising, do not clearly demonstrate the equivalence or superiority of bendamustine over other treatment options. There are no data on the efficacy and safety of bendamustine retreatment in patients who received the drug as part of frontline therapy.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding bendamustine for non-Hodgkin lymphoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website,www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding bendamustine for non-Hodgkin lymphoma conducted by the Lymphoma Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background Clinical Information provided by the CGP, a summary of submitted Patient Advocacy Group Input on bendamustine for non-Hodgkin lymphoma and a summary of submitted Provincial Advisory Group Input on bendamustine for non-Hodgkin lymphoma are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Non-Hodgkin's lymphoma is the fifth most common malignancy in Canada, with 7800 new cases and 2800 deaths from this diagnosis expected in 2012. The Canadian incidence and death rates from non-Hodgkin's lymphoma rose steadily over a 30-year period until 1998 but have stabilized since then.[8,9]

Indolent Non-Hodgkin's Lymphoma (iNHL) is a term used to encompass a histologically and clinically heterogeneous group of lymphomas. The clinical hallmarks of indolent lymphoma include a long natural history, a continuous relapse rate despite initial responsiveness to therapy, and a significant subset of patients who can be managed for extended periods without therapy. Advanced stages (Ann Arbor stage III-IV) are characterized by widespread lymphadenopathy with or without bone marrow, spleen or other visceral organ involvement.

Selected patients with stage I or II iNHL are treated with external beam radiotherapy alone, even if asymptomatic, as this has been shown to lead to durable remissions. Symptomatic patients with stage I-II iNHL who are not candidates for radiotherapy alone are usually treated in a similar manner as patients with stage III-IV iNHL.

Patients with stage III-IV iNHL who require treatment generally have symptoms attributable to the lymphoma, and/or evidence of haematological or other organ dysfunction. The mainstay of front line therapy for patients with stage III-IV iNHL is combination drug therapy. The combination generally includes chemotherapy and the anti-CD20 monoclonal antibody, rituximab. In the pre-rituximab era, several chemotherapy regimens were compared in randomized controlled trials and found to yield similar long term outcomes, including chlorambucil, fludarabine, and combination therapies such as CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). A large randomized trial by Marcus et al. demonstrated improved response rates and significantly prolonged progression-free survival by adding rituximab to the CVP regimen (RCVP) as compared to CVP alone for previously untreated patients with follicular lymphoma.[10,11] Similar results have been obtained in a large randomized trial by Hiddemann

et al. when adding rituximab to the CHOP regimen (RCHOP).[12] Consequently, RCVP and RCHOP have become the most commonly used front line chemotherapy regimens for follicular lymphoma. In Canada, RCVP seems to be the more frequently prescribed regimen for follicular lymphoma, given the lack of randomized trials showing superiority of RCHOP over RCVP and the desire to defer the use of doxorubicin over toxicity concerns.

A number of randomized trials have evaluated the use of rituximab maintenance therapy following a course of chemotherapy plus rituximab for iNHL. These studies have consistently shown a significant improvement in progression free survival with the use of rituximab maintenance dosing every 2-3 months for up to two years following the completion of first-line chemotherapy. Some studies have shown an overall survival advantage with this approach. Consequently, most patients in Canada with iNHL who respond to front line therapy receive rituximab maintenance therapy.

Mantle cell lymphoma is usually treated immediately rather than starting out with a period of observation, because of its significantly poorer prognosis relative to other types of iNHL. A commonly used regimen is RCHOP initial therapy followed by rituximab maintenance therapy. Selected patients are offered even more dose-intensive chemotherapy, such as the hyper-CVAD regimen or high dose chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation, as first line treatment.

Improvements in the front-line therapy of iNHL and mantle cell lymphoma would potentially include one or more of the following characteristics: reduced treatment toxicity, improved progression free and/or overall survival, and improved quality of life.

Patients who experience symptomatic progression of iNHL, including mantle cell lymphoma, are treated with a variety of regimens, including but not limited to the following:

- Re-treatment with CVP (+/- rituximab, depending on duration of first response and availability of funding for retreatment with rituximab)
- CHOP (+/- rituximab)
- Fludarabine-containing regimens (+/- rituximab)
- Anti-CD20 radioimmunoconjugates (i.e. Bexxar or Zevalin, where available)
- Oral alkylating agents (chlorambucil or cyclophosphamide)
- High dose chemotherapy with autologous hematopoietic stem cell transplantation
- Allogeneic stem cell transplantation
- Clinical trials
- Radiotherapy

No one of these various approaches has emerged as the preferred treatment for relapsed iNHL, and they are often used sequentially as patients tend to relapse repeatedly. Some patients are not considered candidates for some or all of these approaches, and are treated with supportive and palliative care alone without active anti-cancer therapy.

Patients eventually succumb to iNHL if the disease becomes progressive and resistant to available therapies, and/or if patients become unable to tolerate further therapy. Additional therapies for relapsed iNHL that would induce durable remission with acceptable toxicity would be of value.

Bendamustine hydrochloride was developed in East Germany in the 1960's.(ref-Van der Jagt 2012) It is a purine analogue/alkylator hybrid that has shown activity in various cancers.(ref-Leoni 2008) It is composed of a 2-chloroethylamine group, a benzimidazole ring, and a

butyric acid side chain and has been shown to have a unique mechanism of action in comparison to other alkylating agents such as cyclophosphamide or chlorambucil.(ref-Leoni 2008) Bendamustine is approved by Health Canada for the following indications: 1) indolent non-Hodgkin lymphoma that has progressed during or shortly following treatment with a rituximab regimen; and, 2) previously untreated CLL.[13,14]

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of bendamustine, either as a single agent or in combination with other chemotherapeutic agents on patient outcomes compared to appropriate comparators in the treatment of patients with:

1. Previously untreated indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL).
2. iNHL or MCL that has relapsed following or is refractory to treatment that included rituximab.

See Table 1 in Section 6.2.1 for outcomes of interest and appropriate comparators and for additional details.

See Section 6.2.1 for more details on the pCODR systematic review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

This section describes highlights of evidence in the systematic review. Refer to section 2.2 for the clinical interpretation of this evidence and section 6 for more details of the systematic review.

2.1.3 A) Previously Untreated Indolent NHL or MCL

Trial Characteristics

One open-label multicentre randomized trial (StiL NHL1) was identified that compared the use of the bendamustine and rituximab (B-R) to cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab (CHOP-R) in patients with previously untreated indolent NHL or MCL.[1,15] A summary of key trial characteristics can be found in Table 1.

The ClinicalTrials.gov record reported that the primary outcome was progression-free survival, event-free survival was a secondary outcome, and that the trial was designed to determine if bendamustine and rituximab was non-inferior to CHOP-R with respect to progression-free survival.[2] The primary outcome was changed to progression-free survival through a protocol amendment; however, the details of this change are not available in the public domain.[16] The change of primary outcome did not require a change to the initial sample size.[16]

The Ann Arbor stage and histologies were balanced between the treatment arms. The mean age was 64 years in the B-R arm and 63 years in the CHOP-R arm.[1]

A total of 549 patients were randomized in a 1:1 ratio to receive B-R (n=274) or CHOP-R (n=275). The final analysis presented at ASH 2009 reported that 513 patients were evaluable: 260 patients in the B-R arm and 253 patients in the CHOP-R arm.[1] In an updated analysis presented at ASCO 2012, 514 evaluable patients were include in the

analysis: 261 patients in the B-R arm and 253 patients in the CHOP-R arm.[3,15] A total of 35 patients were excluded from that analysis.

The StiL NHL1 study has been reported in abstract form only and thus many details regarding the study quality are not publicly available. The final and updated analyses appeared to exclude 36 patients and 35 patients, respectively. Of note, in the updated analysis, one patient in the B-R arm and seven patients in the CHOP-R arm withdrew consent immediately after randomization. This could reflect a potential for bias, given that neither the patients nor investigators were blinded to treatment assignment. In addition, the tumour assessments were conducted by the study investigators and not by a blinded and independent body. This has the potential to introduce bias to the outcome measurements. The StiL NHL1 study was not funded by industry.

Table 1. Summary of StiL NHL1 study.[1-3,15]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
StiL NHL1 Multicenter study: 81 sites in Germany Study start date: October 2003; Study completion: August 2009 Enrolled: n=549 Randomized: n=549 Evaluable: n=513 Open-label, RCT Randomized in a 1:1 ratio (B-R:CHOP-R) Study Sponsor: University of Giessen(ref StiL NHL1 on ClinicalTrials.gov)	Patients with histologically verified CD20-positive B-cell lymphomas: grade 1 and 2 FL, LP-IC, MZL (nodal and generalized), MCL, lymphocytic lymphoma (CLL without leukemic characteristics), nonspecified/classified lymphomas of low malignancy. No prior therapy with cytotoxics, interferon, or monoclonal antibodies. Age ≥18 years WHO PS ≤2	Two arms: B-R: Bendamustine 90 mg/m^2 d1+2 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles (n randomized=NR; n evaluable=260) Or CHOP-R: cyclophosphamide 750 mg/m^2 d1 + doxorubicin 50 mg/m^2 d1 + vincristine 1.4 mg/m^2 d1 + prednisone 100 mg orally d1-5 + rituximab 375 mg/m^2 d1 every 3 weeks for 6 cycles (n randomized=NR; n evaluable=253)	<u>Primary</u> Progression-free survival <u>Secondary</u> Remission rates Overall survival Event-free survival Time-to-next treatment Adverse events including infectious complications

Notes: B-R=bendamustine-rituximab; CHOP-R=cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; LP-IC=lymphoplasmocytic lymphoma/immunocytoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; n=number of patients; NR=not reported; RCT=randomized controlled trial; WHO PS=World Health Organization Performance Status.

Outcome Data and Summary of Outcomes

The final efficacy and safety analysis appeared to include 513 patients (B-R arm, n=260; CHOP-R arm, n=253) out of 549 randomized patients.[1] The updated efficacy analysis included 514 patients (B-R arm, n=261; CHOP-R arm, n=253).[3,15] A summary of key efficacy and harms outcomes can be found in Table 2 below. Outcomes that were reported as important to patients included disease control and quality of life.

Table 2. Summary of Key Trial Outcomes From the StiL NHL1 Study.[1,3,15]

Efficacy	Analysis	Intervention	Median [months] (95% CI)	HR (95% CI)	p-value	Median follow-up [months]
Progression-free Survival	Final analysis ASH 2009	B-R (n=260) CHOP-R (n=253)	54.8 34.8	0.5765 (0.4292-0.7683)	p=0.0002	32
	Updated analysis ASCO 2012	B-R (n=261) CHOP-R (n=253)	69.5 31.2	0.58 (0.44-0.74)	P<0.001	45
Efficacy		**Intervention**		**Rate (%)**	**p-value**	
Response	CR (final analysis)	B-R (n=257) CHOP-R (n=249)		40.1 30.8	p=0.0323	
	OR (final analysis)	B-R (n=257) CHOP-R (n=249)		93.8 93.5	p=NR	

Harms	B-R (n=260)	CHOP-R (n=253)
Deaths from AE (%)	NR	NR
Any AE (%)	NR	NR
SAE (%)	NR	NR
Erythema (%)	16.1	9.1, p=0.0122
Allergic reaction, skin (%)	15.4	5.9, p=0.0003
Peripheral neuropathy (%)	6.9	28.9, p<0.0001
Alopecia (%)	15	62, p=NR
Stomatitis (%)	6.2	18.6, p<0.0001
Infection (%)	36.8	50.2, p=0.0025
Febrile neutropenia-Grade 4[†] (%)	[redacted]	[redacted]
Neutropenia-Grade 3/4 (%)	29	69
Leukopenia-Grade 3/4 (%)	37	72
Lymphopenia-Grade 3/4	74	34
Anemia-Grade 3/4	3	5
Thrombocytopenia-Grade 3/4	5	6

Notes: AE=adverse event; B-R=bendamustine-rituximab; CHOP-R=cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab; CI=confidence interval; HR=hazard ratio; NR=not reported; SAE=serious adverse event.

[†]Data for Grade 4 febrile neutropenia is not publicly available. Data were obtained from the submission by the manufacturer to pCODR.[14]

(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).

The final analysis presented at ASH in 2009, demonstrated a statistically significant difference in progression-free survival for B-R (median 54.8 months) compared to CHOP-R (median 34.8 months), with a HR of 0.58, 95% confidence interval (95% CI) of 0.43-0.77, p=0.0002.[1] Median follow-up was 32 months.

The updated analysis presented at ASCO in 2012, demonstrated a statistically significant difference in progression-free survival for B-R (median 69.5 months) compared to CHOP-R (median 31.2 months), with a HR of 0.58, and 95% CI of 0.44-0.74, p<0.001.[15] Median follow-up was 45 months.

The final analysis also reported that the rate of complete response was statistically significantly higher in the B-R compared to the CHOP-R arm (40.1% versus [vs.] 30.8%, p=0.0323).[1] No statistically significant difference was observed in the overall response rates.

The following adverse events occurred in a statistically significant higher proportion of patients in the CHOP-R arm than in the B-R arm (Table 2): peripheral neuropathy (28.9% vs. 6.9%), stomatitis (18.6% vs. 6.2%), and infection (50.2% vs. 36.8%).[1] The following occurred in a statistically significantly higher proportion of patients in the B-R arm than in the CHOP-R arm (Table 2): erythema (16.1% vs. 9.1%) and allergic reaction in the skin (15.4% vs. 5.9%).[1]

No statistical comparisons were reported for the proportion of patients who experienced any specific hematological adverse event. A higher proportion of patients experienced Grade 3 or 4 neutropenia and leukopenia in the CHOP-R arm (69% and 72%) than in the B-R arm (29% and 37%); however, more patients in the B-R arm experienced Grade 3 or 4 lymphopenia (74%) than in the CHOP-R arm (34%).[3] Similar rates of Grade 3 or 4 anemia and thrombocytopenia were reported for both arms (Table 2).[3]

No quality of life data were reported for the StiL NHL1 study.

2.1.3 B) Previously Treated Indolent NHL or MCL

Trial Characteristics

One randomized, multicentre, open-label trial (StiL NHL2) was identified that compared the use of B-R to fludarabine plus rituximab (F-R) in patients with previously treated relapsed follicular, indolent and mantle cell lymphomas.[5] A Summary of key trial characteristics can be found in Table 3.

The ClinicalTrials.gov record reported that the study was designed to evaluate whether B-R was non-inferior to F-R, with respect to event-free survival.[6] The manufacturer confirmed that the study was designed as a non-inferiority study, but that the primary outcome was progression-free survival and not event-free survival.[16] No information is available on when the change to the primary outcome occurred. In addition, no information is available on the required sample size.

The Ann Arbor stage and histologies were balanced between the treatment arms. The median age was 68 years with a range of 38 years to 87 years for all patients.[5] Patients had received a median of one prior therapy (range 1-7).[5]

A total of 219 patients were randomized in a 1:1 ratio to receive either B-R or F-R. No data were available on the number of patients randomized to each arm. The final analysis presented at ASH 2010 reported that the analysis included 208 evaluable

patients and that 11 patients were excluded due to protocol violations—those patients were not followed further.[5]

The StiL NHL2 study has been reported in abstract form only and thus many details regarding the study quality are not publicly available.[5] The final analysis excluded 11 patients. Tumour assessments were conducted by the study investigators and not by a blinded and independent body. This has the potential to introduce bias to the outcome measurements. The StiL NHL2 study was not funded by industry.

Table 3. Summary of Stil NHL2 Study.[5]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Previously Treated Indolent Lymphomas			
Stil NHL2 Multicentre RCT Study start date: September 2003; Study completion: August 2010 Enrolled: n=NR Randomized: n=219 Evaluable: n=208 Open-label, RCT Randomized in a 1:1 ratio (B-R:F-R) Study Sponsor: University of Giessen	Patients with histologically confirmed CD20-positive B-cell lymphomas: grade 1 and 2 FL, MCL, LP-IC, MZL, lymphocytic leukemia (CLL without leukemic characteristics), nonspecified/classified lymphomas of low malignancy. Patients had recurrent disease (remission duration minimum of 3 months), independent of type or quantity of prior therapies, except of rituximab containing regimens, or if remission duration is >1 year after rituximab containing regimen, or refractory to prior therapy (progression under therapy or during 3 months after competion), expect refractory disease to purine analogs or bendamustine. Patients refractory to rituximab were excluded. Age ≥18 years WHO PS ≤2	Two arms: B-R: bendamustine 90 mg/m^2 d1+2 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles maximum Or F-R: fludarabine 25 mg/m^2 d1-3 + rituximab 375 mg/m^2 d1 every 4 weeks for 6 cycles maximum	<u>Primary</u> Progression-free survival <u>Secondary</u>[†] Overall response rate Complete response rate Overall survival Toxicity

Notes: B-R=bendamustine-rituximab; CLL=chronic lymphocytic leukemia; FL=follicular lymphoma; F-R=fludarabine, rituximab; LP-IC=lymphoplasmocytic lymphoma/immunocytoma; MCL=mantle cell lymphoma; MZL=marginal zone lymphoma; n=number of patients; NR=not reported; RCT=randomized controlled trial; WHO PS=World Health Organization Performance Status.

[†]The secondary outcomes were not explicitly reported as such for this trial. The outcomes listed are those reported in addition to the primary outcome in the abstract publication by Rummel et al.[5]

Outcome Data and Summary of Outcomes

The final efficacy and safety analysis included 208 patients (B-R arm, n=109; F-R arm, n=99) out of 219 randomized patients.[5] A summary of key efficacy and harms outcomes can be found in Table 4 below. Outcomes that were reported as important to patients included disease control and quality of life.

Table 4. Summary of Key Trial Outcomes From the StiL NHL2 Study.[5]

Efficacy	Intervention	Median [months] (95% CI)	HR (95% CI)	p-value	Median follow-up [months]
Progression-free Survival	B-R (n=109) F-R (n=99)	30 11	0.51 (0.34-0.67)	P<0.0001	33

Efficacy	Intervention	Rate (%)	p-value
CR	B-R (n=109) F-R (n=99)	38.5 16.2	p=0.0004
OR	B-R (n=109) F-R (n=99)	83.5 52.5	p<0.0001

Harms	B-R (n=109)	F-R (n=99)
Deaths from AE (%)	NR	NR
Any AE (%)	NR	NR
SAE (%)	17.4	22.2
Febrile neutropenia (%)	NR	NR
Neutropenia-Grade 3/4 (%)	8.9	9.1
Leukopenia-Grade 3/4 (%)	11.8	12.4

Notes: AE=adverse event; B-R=bendamustine-rituximab; CI=confidence interval; F-R=fludarabine, rituximab; HR=hazard ratio; NR=not reported; SAE=serious adverse event.

The final analysis presented at ASH in 2010, demonstrated a statistically significant difference in progression-free survival for B-R (median 30 months) compared to F-R (median 11 months), with a HR of 0.51, 95% confidence interval (95% CI) of 0.34-0.67, p<0.0001.[5] Median follow-up was 33 months.

The final analysis also reported that the rate of complete response was statistically significantly higher in the B-R arm compared to the F-R arm (38.5% vs. 16.2%, p=0.0004).[5] In addition, a statistically significant difference in the rate of overall response was observed in the B-R arm compared to the F-R arm (83.5% vs. 52.5%, p<0.0001).[5]

The rates of the following adverse events were similar in both study arms (Table 4): serious adverse events (17.4% for B-R vs. 22.2% for F-R), grade 3/4 neutropenia (8.9% vs. 9.1%), and grade 3/4 leukopenia (11.8% vs. 12.4%).[5] No further data on adverse events were reported.

No quality of life data were reported for the StiL NHL2 study.

2.1.4 Comparison with Other Literature

The pCODR Clinical Guidance Panel and the pCODR Methods Team did not identify other relevant literature providing supporting information for this review.

2.1.5 Summary of Supplemental Questions

No supplemental issues were identified during the development of this report.

2.1.6 Other Considerations

Patient Advocacy Group Input

PAG Input

Other

The product monograph for Treanda (bendamustine hydrochloride) provided by the manufacturer (Lundbeck Canada Inc.) provides the following serious warnings and precautions:[13]

- ***Clinically Significant Adverse Events:***

  Myelosuppression

  Patients treated with Treanda are likely to experience myelosuppression. In the NHL study, 98% of patients had Grade 3-4 myelosuppression. Three patients (2%) died from myelosuppression-related adverse reactions; one each from neutropenic sepsis, diffuse alveolar hemorrhage with Grade 3 thrombocytopenia, and pneumonia from an opportunistic infection. Hematologic nadirs were observed predominantly in the third week of therapy. In the clinical trials, blood counts were monitored every week initially.

  In the event of treatment-related myelosuppression, monitor leukocytes, platelets, hemoglobin (Hgb) and neutrophils closely. Hematologic nadirs may require dose delays if recovery to the recommended values have not occurred by the first day of the next scheduled cycle. Prior to the initiation of the next cycle of therapy, the absolute neutrophil count [ANC] should be $\geq 1 \times 10^9$/L and the platelet count should be $\geq 75 \times 10^9$/L.

  Infections, Including Fatalities

  Cytomegalovirus (CMV) infections were reported in 3% of patients in the NHL study and were responsible for at least one death. CMV testing should be considered in patients with fever of unknown origin. The use of live attenuated vaccines should be avoided.

Herpes zoster was reported in 12% of patients in the NHL study (Grade 3: 4%; Grade 4; 0%).

Patients should be informed about early signs and symptoms of herpes zoster and should seek treatment as early as possible.

Second Malignancies

Pre-malignant and malignant diseases have developed in patients treated with Treanda including myelodysplastic syndrome, myeloproliferative disorders, acute myeloid leukemia and bronchial carcinoma. Bendamustine is mutagenic, genotoxic and carcinogenic with cancers reported following subcutaneous and oral delivery of the drug to mice.

- ***Treanda should not be used in patients with serious infections:***

  Treanda should not be administered to patients with serious infections, including patients with HIV. Infections, including pneumonia and sepsis, have been reported in patients in clinical trials and in post-marketing reports. Infections have been associated with hospitalization, septic shock and death. Patients with myelosuppression following treatment with Treanda are more susceptible to infections and should be advised to contact a physician if they have symptoms or signs of infection.

- ***Treanda should be administered under the supervision of a qualified health professional who is experienced in oncology.***

2.2 Interpretation and Guidance

Burden of illness and need

Advanced stage iNHL is a relatively common illness which is incurable and associated with reduced life expectancy. Currently available drug treatments for iNHL can induce temporary remissions but do not control iNHL indefinitely and cause adverse effects. Therefore, new treatments that can improve the depth and duration of remission with acceptable or improved toxicity profiles are needed. In the front line setting, there is high quality evidence of improved efficacy compared to current standard treatment with comparable (or potentially a more favourable) safety profile for B-R. In the relapsed setting, there is evidence that bendamustine-based regimens are well tolerated and active.

<u>Previously Untreated iNHL</u>

Efficacy

For patients with previously untreated iNHL in the rituximab era there is only one relevant randomized controlled trial (STiL NHL1), comparing bendamustine plus rituximab (B-R) to CHOP plus rituximab (CHOP-R), demonstrating a dramatic difference in PFS in favour of B-R. In Canada, CHOP-R is a standard front line regimen for mantle cell lymphoma and is sometimes used for other subtypes of iNHL. For iNHL other than mantle cell lymphoma, the most commonly used Canadian front line standard regimen, CVP-R, is generally felt to be of comparable efficacy to CHOP-R for many subtypes of iNHL. In the pre-rituximab era,

CVP and CHOP were found to have equivalent efficacy for iNHL. Although cross-trial comparisons are difficult, given the dramatic increase in PFS with B-R in STiL NHL1 it can be reasonably concluded from the available body of evidence that B-R is more efficacious than either CVP-R or CHOP-R. The BRIGHT study has completed accrual and results are pending; this study includes a randomized comparison between B-R and either CHOP-R or CVP-R. The results of that study will add further information regarding the place of B-R in the initial treatment of iNHL.

Maintenance Rituximab is effective after both RCVP and RCHOP and the magnitude of benefit is significant. As there is no biological rational to think R maintenance would not work after B-R, it is likely that maintenance rituximab would routinely be offered following first line B-R.

Safety

In STiL NHL1 B-R was generally less toxic than CHOP-R, with similar or lower rates of most reported toxicities for B-R apart from rash which was more prevalent in B-R treated patients. For the majority of iNHL patients in Canada CVP-R is the usual initial therapy, and CVP-R is also less toxic than CHOP-R. The body of evidence regarding the toxicity of bendamustine-containing regimens for iNHL, including the COP versus BOP study of Herold et al[17], suggests that bendamustine-based chemotherapy is unlikely to be dramatically more toxic than CVP-R. The BRIGHT study should provide high quality evidence regarding the toxicity comparison of B-R to CVP-R.

Previously treated NHL

Efficacy

For patients with relapsed iNHL, there is only one relevant randomized controlled trial in the rituximab era (STiL NHL2), comparing B-R to F-R, demonstrating a highly significant difference in PFS in favour of B-R. Although F-R is a relevant comparator regimen commonly used Canada, there are numerous additional options for the treatment of relapsed iNHL and no one option can be considered as a standard against which to compare B-R. STiL NHL2 is a smaller study than STiL NHL1, but still shows a significant PFS advantage to B-R. Whether B-R is superior to the other available treatments for relapsed iNHL is unclear.

The evidence for the efficacy of bendamustine treatment for rituximab-refractory iNHL is currently limited to non-randomized single arm study data. The ongoing ROBIN randomized study comparing bendamustine to physician's choice of therapy should provide high quality data regarding the utility of bendamustine in the rituximab-refractory setting. Although there is no formal definition for rituximab-refractory, currently accepted standard of rituximab-refractory disease is someone whose lymphoma has failed to respond to rituximab-containing therapy, or has progressed while on rituximab or within 6 months of completing a rituximab-containing regimen, or intolerance of rituximab. Clinicians have generally debated the 6-12 month time-frame in some jurisdictions, but would definitely consider those patients whose disease returns after 1 year of previously completing a rituximab-containing regimen to still have rituximab sensitive disease.

The evidence for the efficacy of bendamustine in relapsed/refractory iNHL has generally been obtained from patients who have not previously been treated with bendamustine. There are no high-quality studies specifically examining the use of bendamustine retreatment in iNHL. As such based on expert opinion, bendamustine, alone or as part

of B-R, will likely be requested by physicians for patients who have relapsed after R maintenance, particularly if those patients had no prior exposure to bendamustine or had a good response to prior bendamustine.

Bendamustine alone would be desired as an option by clinicians for patients with rituximab-refractory disease. This is based on expert clinical opinion, extrapolating results from the single arm phase II data showing significant anti-lymphoma activity in this setting, as well as the evidence of bendamustine superiority in STiL 1 and 2 relative to other standard drugs when combined with rituximab.

Safety

The body of evidence regarding the toxicity of bendamustine-containing regimens demonstrate that the drug is relatively well tolerated in the treatment of relapsed/refractory iNHL.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is a net overall clinical benefit to bendamustine in the treatment of previously untreated iNHL, based on one high-quality randomized controlled trial that demonstrated a clinically and statistically significant benefit in progression-free survival for B-R compared with CHOP-R. Adverse event profiles were generally more favourable for B-R compared to CHOP-R apart from rash.

It is recognized that in Canada CVP-R is the standard first-line regimen for many iNHL patients, and that CVP-R is less toxic than CHOP-R. While B-R and CVP-R have not been directly compared (pending the ongoing BRIGHT study), the body of evidence to date suggests that CVP-R is unlikely to be superior to B-R in terms of either efficacy or toxicity and that B-R is likely to be superior to CVP-R in terms of efficacy. Caution is advised in comparing B-R directly to CVP-R until the BRIGHT study results are reported. As there is no biological rational to think R maintenance would not work after B-R, it is likely that maintenance rituximab would routinely be offered following first line B-R.

The Clinical Guidance Panel concluded that there may be a net overall clinical benefit to bendamustine in the treatment of relapsed/refractory iNHL. The uncertainty of the Panel's conclusion was due to the following: (1) there is data from one randomized controlled trial demonstrating improved PFS for B-R compared to F-R, but no comparisons with other standard regimens for relapsed/refractory iNHL; (2) pending the ongoing ROBIN study, there is currently only single-arm study data only for bendamustine alone in rituximab-refractory patients that, while promising, do not clearly demonstrate the equivalence or superiority of bendamustine over other treatment options. There are no data on the efficacy and safety of bendamustine retreatment in patients who received the drug as part of frontline therapy, bendamustine, alone or as part of B-R, will likely be requested by physicians for patients who have relapsed after R maintenance, particularly if those patients had no prior exposure to bendamustine or had a good response to prior bendamustine. Access to rituximab re-treatment is limited in some jurisdictions; so whether rituximab would be added to the regimen will depend on the individual jurisdictional parameters for retreatment.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Lymphoma and Myeloma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

3.1 Description of the Condition

Non-Hodgkin's lymphoma is the fifth most common malignancy in Canada, with 7800 new cases and 2800 deaths from this diagnosis expected in 2012. The Canadian incidence and death rates from non-Hodgkin's lymphoma rose steadily over a 30-year period until 1998 but have stabilized since then. [8,9]

Indolent Non-Hodgkin's Lymphoma (iNHL) is a term used to encompass a histologically and clinically heterogeneous group of lymphomas. The clinical hallmarks of indolent lymphoma include a long natural history, a continuous relapse rate despite initial responsiveness to therapy, and a significant subset of patients who can be managed for extended periods without therapy. Advanced stages (Ann Arbor stage III-IV) are characterized by widespread lymphadenopathy with or without bone marrow, spleen or other visceral organ involvement.

Collectively, iNHL accounts for approximately 40% of non-Hodgkin lymphomas.[18] The list of histological subtypes of lymphoma that are considered to be indolent varies by author, but often includes follicular, small lymphocytic, marginal zone and lymphoplasmacytoid lymphomas. Follicular lymphoma is the most extensively studied of these subtypes of iNHL, therefore the treatment of other iNHLs is often patterned after the treatment of follicular lymphoma.

Mantle cell lymphoma is sometimes also called an indolent lymphoma, although this disease often leads to a much shorter survival than most other indolent lymphomas. Mantle cell lymphoma is sometimes treated more like an aggressive lymphoma rather than an indolent lymphoma.

All of the lymphomas listed above are B-cell lymphomas, and the vast majority express the B-cell antigen CD20.

3.2 Accepted Clinical Practice

Patients with iNHL are sometimes managed with a period of careful observation, rather than immediate initiation of treatment. Patients who are candidates for an observation approach generally have few or no symptoms attributable to lymphoma, preserved organ and bone marrow function, and no signs of rapid disease growth or imminently life threatening complications. There is as yet no evidence that treatment of the asymptomatic patient prolongs survival, although this is a topic under active investigation. Conventional chemotherapy has not been shown to be beneficial in this setting.

Selected patients with stage I or II iNHL are treated with external beam radiotherapy alone, even if asymptomatic, as this has been shown to lead to durable remissions. Symptomatic patients with stage I-II iNHL who are not candidates for radiotherapy alone are usually treated in a similar manner as patients with stage III-IV iNHL.

Patients with stage III-IV iNHL who require treatment generally have symptoms attributable to the lymphoma, and/or evidence of haematological or other organ dysfunction. The mainstay of front line therapy for patients with stage III-IV iNHL is combination drug therapy. The combination generally includes chemotherapy and the anti-CD20 monoclonal antibody, rituximab. In the pre-rituximab era, several chemotherapy regimens were compared in randomized controlled trials and found to yield similar long term outcomes, including chlorambucil, fludarabine, and combination therapies such as CVP (cyclophosphamide, vincristine, prednisone) or CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). A large randomized trial by Marcus et al. demonstrated improved response rates and significantly prolonged progression-free survival by adding rituximab to the CVP regimen (RCVP) as compared to CVP alone for previously untreated patients with follicular lymphoma.[10,11] Similar results have been obtained in a large randomized trial by Hiddemann et al. when adding rituximab to the CHOP regimen (RCHOP).[12] Consequently, RCVP and RCHOP have become the most commonly used front line chemotherapy regimens for follicular lymphoma. In Canada, RCVP seems to be the more frequently prescribed regimen for follicular lymphoma, given the lack of randomized trials showing superiority of RCHOP over RCVP and the desire to defer the use of doxorubicin over toxicity concerns.

A number of randomized trials have evaluated the use of rituximab maintenance therapy following a course of chemotherapy plus rituximab for iNHL. These studies have consistently shown a significant improvement in progression free survival with the use of rituximab maintenance dosing every 2-3 months for up to two years following the completion of first-line chemotherapy. Some studies have shown an overall survival advantage with this approach. Consequently, most patients in Canada with iNHL who respond to front line therapy receive rituximab maintenance therapy.

Mantle cell lymphoma is usually treated immediately rather than starting out with a period of observation, because of its significantly poorer prognosis relative to other types of iNHL. A commonly used regimen is RCHOP initial therapy followed by rituxmab maintenance therapy. Selected patients are offered even more dose-intensive chemotherapy, such as the hyper-CVAD regimen or high dose chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation, as first line treatment.

Improvements in the front-line therapy of iNHL and mantle cell lymphoma would potentially include one or more of the following characteristics: reduced treatment toxicity, improved progression free and/or overall survival, and improved quality of life.

Patients who experience symptomatic progression of iNHL, including mantle cell lymphoma, are treated with a variety of regimens, including but not limited to the following:

- Re-treatment with CVP (+/- rituximab, depending on duration of first response and availability of funding for retreatment with rituximab)
- CHOP (+/- rituximab)
- Fludarabine-containing regimens (+/- rituximab)
- Anti-CD20 radioimmunoconjugates (i.e. Bexxar or Zevalin, where available)
- Oral alkylating agents (chlorambucil or cyclophosphamide)
- High dose chemotherapy with autologous hematopoietic stem cell transplantation
- Allogeneic stem cell transplantation
- Clinical trials
- Radiotherapy

No one of these various approaches has emerged as the preferred treatment for relapsed iNHL, and they are often used sequentially as patients tend to relapse repeatedly. Some patients are not considered candidates for some or all of these approaches, and are treated with supportive and palliative care alone without active anti-cancer therapy.

Patients eventually succumb to iNHL if the disease becomes progressive and resistant to available therapies, and/or if patients become unable to tolerate further therapy. Additional therapies for relapsed iNHL that would induce durable remission with acceptable toxicity would be of value.

Bendamustine is a chemotherapy drug that is being evaluated as a treatment for iNHL. A randomized phase III trial by Rummel et al. comparing bendamustine plus rituximab (BR) to the RCHOP regimen in 549 patients with advanced stage follicular, indolent or mantle cell lymphomas has shown significantly improved complete response rates and progression free survival in the BR arm.[1] A second large phase III study comparing BR to RCVP or RCHOP is ongoing.[4] Based on the results of the Rummel study, BR is under consideration as the preferred therapy for these diseases in the front line setting.

Another randomized trial (n=219) by Rummel et al. has compared BR to fludarabine plus rituximab (FR) as second line therapy for relapsed iNHL, showing improved PFS for the BR arm.[5] A single arm study by Kahl et al. in patients whose iNHL was progressive within 6 months of receiving a rituximab-containing regimen has shown a 75% response rate and a median progression-free survival of 9.3 months.[19] Based on these and other studies, bendamustine is being considered as therapy for relapsed iNHL.

3.3 Evidence-Based Considerations for a Funding Population

Based on the available evidence, bendamustine could be considered as part of the treatment for patients with iNHL, including mantle cell lymphoma.

The drug could be considered in combination with rituximab for previously untreated patients with advanced stage disease who are not candidates for observation and require systemic therapy. One large randomized trial supports this indication.

Bendamustine could also be considered as part of the treatment for patients with relapsed or refractory iNHL, including mantle cell lymphoma, alone or in combination with other agents.

Bendamustine is approved in the US and the UK for the treatment of iNHL that has progressed within 6 months of a rituximab containing regimen. A single arm study of 100 patients supports this indication.

3.4 Other Patient Populations in Whom the Drug May Be Used

Bendamustine is approved in several countries for the treatment of chronic lymphocytic leukemia and multiple myeloma.

Bendamustine has been evaluated in clinical trials for a variety of other malignancies including breast and lung cancer, but is not yet approved in any country for those indications.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on bendamustine (Treanda) for non-Hodgkin lymphoma (NHL) and their input is summarized below:

- The Leukemia and Lymphoma Society of Canada
- Lymphoma Foundation Canada

The Leukemia and Lymphoma Society of Canada conducted an anonymous survey to gather information about patient and caregiver experiences with non-Hodgkin- lymphoma (NHL). Survey respondents could provide answers online, by phone, in writing, or in person. Additional information was gathered through printed sources.

The Lymphoma Foundation Canada (LFC) used an online survey, hosted by the Canadian Cancer Action Network, to gather information about patient and caregiver experiences with non-Hodgkin lymphoma, as well as, the drug under review. Responses were solicited via email to the LFC membership. A total of 75 patients and caregivers participated in the survey. In addition, internal LFC resources were used for contextual information on lymphoma.

From a patient perspective, additional drug therapies for the treatment of NHL which have a different mechanism of action and enable the patient to have a choice in their therapy, is an important aspect when consideration is given to treatment. In addition, patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life. Most patients indicate they would be willing to tolerate the side effects of a new therapy, even significant side effects, if the therapy was able to control their disease, if the side effects disappear after treatment is complete and if there is an improvement in their quality of life for a substantial length of time afterwards. In addition, patients also express a desire to have a treatment option that does not acquire or develop resistance, so the patient may be able to receive repeat treatments for their condition without having to worry about the therapy becoming less effective due to resistance.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences patients have with non-Hodgkin's lymphoma

Patient advocacy group input highlights that non-Hodgkin lymphoma (NHL) is the fifth most commonly diagnosed cancer and the sixth leading cause of cancer death in Canada. Input from patients indicate that approximately 30% of patients with NHL will be diagnosed with an indolent or slow-growing NHL, which tends to be a chronic, slow-progressing cancer, and patients may live with the disease for many years before they require chemotherapy or other drug treatments. However, there may also be cases where the disease progresses rapidly and patients require immediate treatment. Patient input also indicates that indolent NHL may recur many times and often times,

the cancer becomes less responsive to treatment over time, due to the development of drug resistance.

Patients report that fatigue is one of the most common symptoms that patients with indolent NHL experience and it can have a significant impact upon their quality of life. Patients may be unable to continue to work and report having to retire at an earlier age than they anticipate due to the fatigue. Patients also indicate that fatigue prevents them from being able to perform household duties, such as yard work and indoor or outdoor cleaning, and as a result, they are unable to maintain their home to the same degree as before their diagnosis. In addition, patients convey that the fatigue they experience limits their social connectivity, as they are too tired to socialize and as a result, they end up spending a lot of time alone. Patients responding to the LFC survey rank fatigue as one of the most important symptoms of NHL to control and manage.

Patients also report that swollen lymph nodes are a symptom of NHL that is important for them to control and manage. Patients indicate that watching the lymph nodes grow in size can cause both emotional and physical stress. These swollen lymph nodes can cause swelling in the legs and feet, as well as, cramping and bloating, and some patients have concerns that the swollen lymph nodes may start to interfere with more vital bodily functions.

Many patients with NHL also report that they experience feelings of depression, stemming from the knowledge that they have an unrelenting illness with a variable lifespan. Patients wish to fulfill many life goals, but express that they do not have the energy to do so, which also contributes to feelings of depression. Patients also report experiencing feelings of fear and worry, as they are uncertain of their future. Patients with NHL are cognizant of the effect that their illness has on their family and friends, and indicate that their diagnosis places a burden on others to care for them.

In addition to the symptoms noted above, patients also indicate that they may experience fever, weight loss, night sweats, hair loss, muscle stiffness, head aches and pain. Patients responding to the LFC survey also express that it is also important to control and manage these symptoms of NHL.

4.1.2 Patients' Experiences with Current Therapy for non-Hodgkin's lymphoma

Patient advocacy group input indicates that many people with a diagnosis of indolent NHL begin with an active watch and wait approach, where patients and their physicians wait for their symptoms to progress and start causing significant problems prior to starting any therapy. Patients express that this approach can be difficult to deal with, as they are used to the concept that treatment start right away after being diagnosed with cancer. Patients report that it is emotionally difficult to know that there is a cancer growing within them that must progress before they can begin to receive treatment.

Once medical interventions are required for the treatment of NHL, patients indicate that there are many different therapies available, including chemotherapy, radiation therapy, biologic therapies, bone marrow or stem-cell transplants, and other experimental treatments through clinical trials. Specific chemotherapy and biologic

agents that patients report may be used in treating NHL include vincristine, fludarabine, chlorambucil, cyclophosphamide, and rituximab, and some of these agents may be used in combination with each other.

Patients indicate that these treatments are not without side effects, some of which include extreme fatigue, nausea, hair loss, infections, anemia, depression, mouth sores, skin irritations, peripheral neuropathy, weakness, lack of mental acuity, fever, insomnia, and weight gain or loss. One patient responding in the LFC survey reports experiencing side effects so severe that hospitalization was required. Although patients report that the side effects of treatment can be awful, patients also note that they go away and patients feel much better once treatment is finished and it is successful, as they have an increase in their energy level and a better quality of life. Patients also express that they are willing to endure negative side effects if it means having more quality years of life afterwards.

Patient input reveals that many patients need to travel to receive care from specialists knowledgeable in the treatment of NHL. As a result, patients often incur additional costs to travel to treatment centers and physician appointments, and for accommodations during their travels.

In addition, patients indicate that they may have to cover the cost of medications not funded by provincial or private drug plans. This may include the costs for medications to treat the cancer, as well as, supportive medications that patients may require throughout the treatment. Patients express concern that there is unequal coverage of rituximab across the country. Patients without rituximab coverage must pay for the treatment on their own if they wish to receive it and for some patients, the cost may be prohibitory and they do not receive the treatment.

Input from the patient advocacy group also points out that many cases of indolent NHL recur. Patients can develop drug resistance to the treatments for NHL and their options for further treatments are limited. Patients express a need for more treatment options, as well as, more effective treatment options.

4.1.3 Impact of non-Hodgkin's lymphoma and Current Therapy on Caregivers

Patient advocacy group input indicates that the impact of this condition on caregivers can be significant. Caregivers may experience physical, emotional, financial, and time impact. Caregivers report that they often exhaust themselves by providing caregiving responsibilities in addition to their normal daily routines. Caregivers often are responsible for performing additional tasks around the home that were once shared or assumed completely by the patient and they may have to assume more of the financial burden as patients may have to stop working earlier than anticipated.

Caregivers report that their life is put on hold, as they have to take time to be with the patient during physician appointments and treatments. They must also be knowledgeable with the side effects of treatment and how to support the patient through the side effects. Caregivers indicate that their social support system is reduced as they choose to stay with the patient who is oftentimes not able to have the same level of social activity as in the past due to fatigue.

Caregivers also indicate that there is daily stress and worry about the wellbeing of the patient, as well as, the uncertainty of the disease and if it will progress.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Bendamustine

Input from patients without direct experience with bendamustine indicates that patients with NHL are seeking more treatment options or choices for their condition. Patients responding to the LFC survey indicate that is it very important for patients and physicians to have a choice in deciding which drug therapy the patient should receive. In addition, patients want treatment options that will control their disease and extend their life, while also allowing them to enjoy a good quality of life.

Feedback on the degree of side effects patients are willing to endure varied from medium-range effects to significant. In addition, patients would be willing to tolerate some side effects of therapy if the side effects disappear after treatment is complete and there is an improvement in their quality of life for a substantial length of time afterwards. Conversely, a few patients responding to the LFC survey indicate that they would not be willing to tolerate significant side effects with a new therapy. In addition, patients anticipate that bendamustine may have fewer side effects than some of the currently available therapies.

Patients also express a desire to have a treatment option with a differing mechanism of action, as not all treatments work the same in all patients. Patients also want therapies that do not acquire or develop resistance, such as the case with the currently available treatment options. Patients convey that they have heard reports that indicate that patients do not develop resistance to bendamustine the way they do with other treatments and this is important to those patients who require repeat treatments for their condition. Patient input highlights that for patients who have already been treated in the past, they need another treatment option now that will not have a decreased efficacy due to resistance.

Input from the Leukemia and Lymphoma Society of Canada indicates that they did not receive any feedback from patients currently using bendamustine. Input from Lymphoma Foundation Canada also indicates that it was difficult to identify many patients with bendamustine experience as there were limited clinical trials and access programs for bendamustine in Canada.

Of the two patients with direct experience with bendamustine, they indicate that treatment with bendamustine provided them good results. One patient reports that the swollen lymph nodes in his/her neck and groin were no longer palpable after two weeks of bendamustine treatment, and a subsequent scan showed a favourable response. Another patient reports that approximately 90% of his/her tumours have disappeared and they are now clinically considered to be in remission.

With respect to side effects, one patient with direct experience with bendamustine reports that they experienced dry skin and hair thinning. Another patient reports experiencing headaches and neck pain with bendamustine, although these side effects

were tolerable and not as severe as that experienced with previously treatments. When patients with direct experience with bendamustine were asked to rate their quality of life while on treatment, with 1 (low/severely impacted) to 10 (high/normal living), of the two patients who had experience with bendamustine one patient ranked QoL as 10 and the other patient ranked QoL as 4.

4.3 Additional Information

The Leukemia and Lymphoma Society of Canada indicates that they appreciate the opportunity to ensure that the patient voice is heard during the review process, but express that timelines are rather short, which can make it difficult to gather and review the necessary information. In addition, the patient group points out that it can be difficult to find patients with direct experience with the drug under review within the time constraints due to a number of factors, such as privacy or physician schedules.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for bendamustine (Treanda) for the treatment of indolent non-Hodgkin's Lymphoma (iNHL) and mantle cell lymphoma (MCL). The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the bendamustine (Treanda) review was obtained from all nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, there are relatively few treatment options available once a patient progresses on or within a short time-frame after rituximab-containing treatment and additional options are required. PAG also identified that there is a potential for bendamustine to be used in other lines of therapy for NHL, such as the first-line setting, and noted that information on the use of bendamustine in other lines of therapy would be useful.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG recognized that there are relatively few treatment options currently available for patients who progress on or within six to 12 months of a rituximab-containing protocol and additional treatment options in this clinical setting, such as bendamustine, are needed.

If it were determined that bendamustine had a favourable efficacy and toxicity profile in relation to other comparators used in this setting during the pCODR review, PAG identified that there may be significant market uptake of bendamustine, which would need to be factored into the budget impact.

5.2 Factors Related to Patient Population

As hematologic malignancies tend to be less common than solid tumors overall, PAG recognized that there may be small numbers of patients accessing bendamustine. However, it was also noted that the number of potential bendamustine funding requests for the iNHL indication is expected to be greater than that for the CLL indication.

Although the Health Canada approved indication for bendamustine is for iNHL that has progressed during or following treatment with a rituximab regimen, PAG identified that there is potential for bendamustine to be used in other treatment settings, such as the first-line setting of NHL. PAG noted that information on the use of bendamustine in other lines of therapy would be useful.

PAG also identified that there is potential for indication creep with bendamustine in the aggressive NHL setting and also as a bridge to allogeneic stem cell transplant and noted that any information on bendamustine in these clinical settings would be helpful.

5.3 Factors Related to Accessibility

PAG identified several potential accessibility issues with respect to bendamustine treatment in this indication, which are explored further in the dosing and implementation cost sections.

PAG noted that re-treatment with a rituximab-containing regimen is a standard practice in many jurisdictions if the patient does not progress on or within six to 12 months of a rituximab-containing protocol and many jurisdictions have eligibility criteria in place for rituximab in this situation. As rituximab is already funded in many jurisdictions for this indication, this would be an enabler to combination therapy with bendamustine and rituximab. However, PAG also recognized that there may be requests for rituximab to be used in combination with bendamustine that would fall outside of the current rituximab eligibility criteria which would create potential problems for accessing the rituximab portion of the combination therapy. Therefore, depending on the particular funding criteria in place for rituximab, it may become an enabler or a barrier to a funding implementation for bendamustine.

PAG noted that there may be a potential for bendamustine to be delivered in non-tertiary care areas; however, this may depend on the threshold for cost of drug wastage and toxicity may preclude bendamustine administration in some smaller centers.

PAG also recognized that treatment with bendamustine may allow for more patients to be eligible for a stem cell transplant.

5.4 Factors Related to Dosing

PAG noted that bendamustine is also indicated for the treatment of chronic lymphocytic leukemia (CLL) with a different dosage regimen than that indicated for NHL. PAG recognized that there may potentially be confusion in dosing between the two different indications which could lead to medication errors.

In addition, PAG identified that there is a more frequent dosing schedule for bendamustine in the treatment of NHL (120mg/m^2 every 21 days) compared with its use in the treatment of CLL (100mg/m^2 every 28 days). As a result of the different dosing regimens, PAG noted that there may be a requirement for more dosing adjustments and an increased use of growth factors when bendamustine is used in the NHL setting. As the additional need for growth factor support would add to the total costs of bendamustine treatment, it would be helpful if it were factored into the economic analysis.

5.5 Factors Related to Implementation Costs

PAG speculated that the cost of bendamustine is likely to be more than the costs of other therapies currently available once a patient progresses on rituximab. However, PAG also noted that the chemotherapy workload after introducing bendamustine into this salvage treatment setting would likely be neutral, as these patients would likely be receiving further therapy at any rate.

PAG noted that there may be some difficulty determining an appropriate place in therapy for bendamustine, considering it may be used in the first-line or the relapsed/progressive setting.

In addition, it was noted that jurisdictions may have difficulty determining how to implement a funding recommendation for bendamustine, given that they may already have funding criteria in place for the other currently used therapies in this clinical setting and further guidance on this matter would be helpful. Furthermore, PAG noted that if bendamustine were to be funded, there is a possibility that it would become an additional line of therapy in the treatment of iNHL, which could increase overall costs, and would need to be factored into the economic analysis.

PAG recognized that drug wastage could be an issue with bendamustine as there will likely only be two vial sizes available (25mg vial and 100mg vial as in the US) and there is no preservative. The product monograph indicates that the final admixture is stable for 24 hours under refrigeration or three hours at room temperature and partial vials are to be discarded. In some jurisdictions, hospitals are not reimbursed for wastage costs and would have to incur the additional costs of the wasted product which would be a barrier to implementation.

PAG identified that difficulties may be encountered when reconstituting bendamustine, as the product monograph indicates that it may take five minutes for complete dissolution of the particles, and this could slow down production time in the pharmacy. Also, it was noted that there may be additional drug wastage if the particles remain in the product after it has been prepared and it must be discarded.

PAG also recognized that there may be additional costs associated with bendamustine treatment, such as the cost of growth factors or hospitalization costs if a patient develops febrile neutropenia.

If it were determined that bendamustine had a favourable toxicity profile in relation to other comparators for CLL during the pCODR review, there may potentially be cost savings as a result of not having to treat those toxicities.

5.6 Other Factors

No additional input was received.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of bendamustine, either as a single agent or in combination with other chemotherapeutic agents on patient outcomes compared to appropriate comparators in the treatment of patients with:

1. Previously untreated indolent non-Hodgkin lymphoma (iNHL) or mantle cell lymphoma (MCL).
2. iNHL or MCL that has relapsed following or is refractory to treatment that included rituximab.

See Table 5 in Section 6.2.1 for outcomes of interest and appropriate comparators.

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 5. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Previously untreated iNHL/MCL				
Published or unpublished RCT	Patients with previously untreated iNHL or MCL	Bendamustine, (single agent or in combination) any dose or schedule	R-CHOP R-CVP	OS **PFS** **Response** **QOL** Adverse events Neutropenia FN Infection Rash – SJS, TENS
Relapsed or Refactory iNHL/MCL				
Published or unpublished RCT	Patients with iNHL or MCL that has progressed following or during treatment that included rituximab	Bendamustine (single agent or in combination) any dose or schedule	CHOP±R; CVP±R; FC±R; CLB+R; F±R; FCM+R; Cyclophosphamide; Rituximab; Tositumomab; Ibritumomab + R	OS **PFS** **Response** **QOL** Adverse events

CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CLB=chlorambucil; CVP=cyclophophamide, vincristine, prednisone; F=fludarabine; FCM=fludarabine, cyclophosphamide, mitoxantrone; FN=febrile neutropenia; iNHL=indolent non-Hodgkin lymphoma; MCL=mantle cell lymphoma; OS=overall survival; PFS=progression-free survival; QOL=quality of life; R=rituximab; RCT=randomized controlled trial; SJS=Stevens-Johnson Syndrome; TENS=Toxic Epidermal Necrolysis

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; EMBASE (1980-) via Ovid; The Cochrane Central Register of Controlled Trials (2012, Issue 8) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were bendamustine (Treanda) and non-Hodgkin lymphoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was limited to English language.

The search is considered up to date as of September 6, 2012.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies, clinical trial registries and relevant conference abstracts. Searches of conference abstracts were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

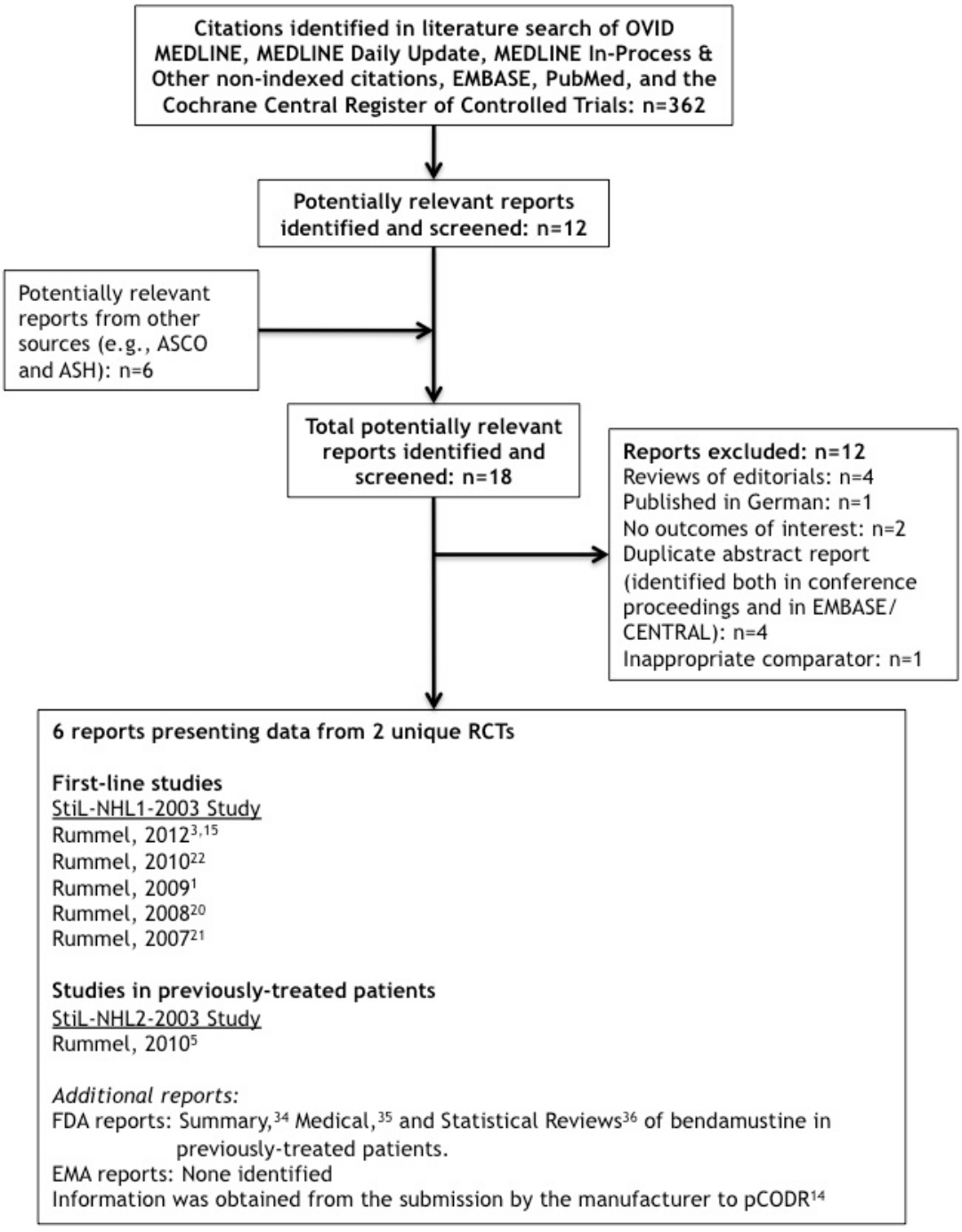
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 A) Results for Previously Untreated (First-Line) Indolent Lymphoma

6.3.1A) Literature Search Results

Of the 18 potentially relevant reports identified, six reports of two unique studies were included in the pCODR systematic review[1,3,5,15,20-22] and 12 reports were excluded. Studies were excluded because they were reviews or editorials[23-26], published in German[27], did not report on the outcomes of interest[28,29], an RCT with an inappropriate comparator[17], or they were duplicate citations of abstracts from ASH that were identified both in EMBASE or CENTRAL and through a manual search of the ASH conference proceedings.[30-33] Three reports from the United States Food and Drug Administration (US FDA),[34-36] were identified; however, none of the reports contained data on any of the included studies, and as such are not discussed further. Additional information was obtained from the submission by the manufacturer to pCODR.[14]

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies in the first-line setting and in studies of previously treated patients.



Note: Additional data related to studies StiL NHL1-2003 and StiL NHL2-2003 were also obtained through requests to the Submitter by pCODR.[16]

6.3.2 A) Summary of Included Studies (Previously Untreated)

One randomized trial was identified that investigated the use of bendamustine in patients with previously untreated indolent NHL or MCL. In the Study Group Indolent Lymphomas, Germany (StiL) NHL1-2003 study, patients with previously untreated advanced follicular, indolent and mantle cell lymphomas were randomized to receive bendamustine plus rituximab (BR) or to receive standard cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (R-CHOP).[1,3,15]

6.3.2.1 A) Detailed Trial Characteristics

a) Trials (Previously Untreated)

One trial met the inclusion criteria for this review and included patients with previously untreated indolent lymphomas (Table 1). The study was a multicenter RCT. The Stil NHL1 study was reported in abstract form only.. The study was conducted in 81 sites in Germany.[3] The trial was open-label, that is neither patients nor investigators were blinded to study treatment. Based on information forwarded by the manufacturer (via a personal communication with the lead investigator), a standard randomization method was used.[16] The sponsor for the StiL NHL1 study was the University of Giessen.[2]

The StiL NHL1 (B-R vs. CHOP-R) trial's design was unclear from the available published abstracts. The ClinicalTrials.gov record states that the trial was designed to determine if B-R was non-inferior to CHOP-R with respect to the primary outcomes, progression-free survival.[2] None of the publicly available sources reported a sample size calculation or requirement. The primary outcome was changed to progression-free survival through a protocol amendment; however, the details of this change are not available in the public domain.[16] Based on information provided by the manufacturer, revisions to the sample size occurred based on protocol amendments.[16] Event-free survival was a secondary outcome. Other secondary outcomes included remission rates, overall survival, toxicity, and infectious complications.[2] None of the secondary outcomes were defined. Event-free survival defined an event as a response less than a partial response, disease progression, relapse, or death from any cause. A standard definition of progression-free survival was was used.[16] Response was assessed following World Health Organization (WHO) criteria.[16] Tumour assessments were conducted by the investigators using World Health Organization (WHO) criteria.[16] The statistical methods used to analyze the treatment outcomes were not reported; however, progression-free survival was analyzed using a stratified log rank test.[3] The non-inferiority analyses for event-free survival or progression-free survival were not reported; however, superiority analyses of progression-free survival, overall survival, and response were reported.

b) Populations (Previously Untreated)

Table 6. Baseline patient characteristics in Study StiL NHL1.[1,3]

Characteristic	Treatment arms	
	B-R	CHOP-R
N Randomized	274	275
Sex **Male** **Female**	NR	NR
Age (years)		

Characteristic	Treatment arms	
	B-R	CHOP-R
N Randomized	274	275
Mean, SD	64	63
Ann Arbor stage **III** **IV**	 19.2% 76.9%	 18.6% 77.5%
Histology **FL** **MCL** **LP-IC** **Other**	 55% 18% N/A 27%	 56% 19% N/A 24%
WHO PS **0** **1** **2** **3**	 NR	 NR

Notes: B-R=bendamustine, rituximab; CHOP-R=cyclophophamide, doxorubicin, vincristine, prednisone, rituximab; FL=follicular lymphoma; LP-IC= lymphoplasmocytic lymphoma/immunocytoma; MCL=mantle cell lymphoma; N=number of patient; WHO PS=World Health Organization Performance status.

The StiL NHL1 trial (B-R vs. CHOP-R) randomized a total of 549 patients. A total of 274 patients were randomized to the B-R arm and 275 patients were randomized to the CHOP-R arm.[3] The trial was well balanced for Ann Arbor stage and histology (Table 6).[1] The mean age was 64 years in the B-R arm and 63 years in the CHOP-R arm. No further data regarding patient characteristics were reported.

c) Interventions (Previously Untreated)

The StiL NHL1 trial compared bendamustine plus rituximab (B-R; dose and schedule in Table 1) to cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R; dose and schedule in Table 1).[1] Rummel et al reported that the prophylactic use of antibiotics or growth factors were not generally recommended in the trial protocol.[1] A median number of six cycles was given in both treatment arms with 82% of patients in the B-R arm and 86% of patients in the CHOP-R arm receiving six cycles of therapy. No further details were reported.

d) Patient Disposition (Previously Untreated)

The StiL NHL1 trial randomized 549 patients. Rummel et al reported that 36 patients were not evaluable due to the following reasons: 10 did not receive the study medication, nine withdrew consent, 13 had an incorrect diagnosis, and four for other reasons. In total, the authors included 513 evaluable patients in the final analysis (B-R arm, n=260; CHOP-R arm, n=253).[1] The authors reported that all patients were counted for evaluation of progression-free survival, overall survival, event-free survival, and time-to-next treatment. Although it is unclear from the abstract report whether the authors were referring to the 549 randomized patients or the 513 evaluable patients, it is likely that the analysis included only the 513 evaluable patients.[1] Nine additional patients were not evaluable for response, four

in the CHOP-R arm and three in the B-R arm: five patients due to early death, three patients due to a change in therapy after severe toxicity in first cycle of CHOP-R, and one patient due to progressive disease. No further data were reported. In an abstract presented at ASCO 2012, Rummel et al reported an updated analysis with a data cut-off of October 31, 2011.[15] The analysis included 514 evaluable patients (261 in the B-R arm and 253 in the CHOP-R arm). No further details were reported in the abstract; however, the abstract presentation indicated that of 274 patients randomized to the B-R arm, only 261 were included in the analysis.[3] Thirteen patients were excluded due to incorrect histology or malignancy (n=6), withdrew informed consent immediately after randomization (n=1), allergic reaction to first rituximab treatment (n=1), received radiotherapy only (n=1), received incorrect therapy (CHOP-R, n=1), or violated inclusion/exclusion criteria (n=3). Out of 275 randomized to the CHOP-R arm, only 253 were included in the analysis, with 22 patients excluded due to incorrect histology or malignancy (n=6), withdrew informed consent immediately after randomization (n=7), allergic reaction to first rituximab treatment (n=2), received radiotherapy only (n=1), received incorrect therapy (B-R, n=1), violated inclusion/exclusion criteria (n=3), received no therapy (n=1), or died prior to receiving any therapy (n=1).[3]

e) Limitations/Sources of Bias (Previously Untreated)

The StiL NHL1 trial has only been reported in abstract form and it is difficult to determine the quality of the trial from the very limited information reported in the abstract.

The required sample size, as reported by the manufacturer at the Checkpoint Meeting, was met. The final analysis presented at ASH in 2009 appeared to exclude 36 patients (549 randomized patients with 513 evaluable for the final analysis) and adverse event data were also limited.[1] In addition, an updated analysis presented at ASCO 2012 reported that only 514 patients were evaluable and included in the updated analysis.[3,15] It is unclear what effect excluding 36 patients from the final analysis and 35 patients from the updated analysis would have on the trial results. Of note, one patient withdrew consent immediately after randomization to the B-R arm, whereas seven patients in the CHOP-R withdrew consent. As the trial was open-label, there exists a potential for bias.

Ideally, for an unblinded trial, tumour assessments should be conducted in a blinded fashion by an independent clinician or committee. The StiL NHL1 study was unblinded and tumour assessments were conducted by the study investigators. There exists a potential for bias in the outcomes (such as progression-free survival, event-free survival, tumour response) that were based on the tumour assessments.

6.3.2.2 A) Detailed Outcome Data and Summary of Outcomes (Previously Untreated)

Efficacy Outcomes (Previously Untreated)

Table 7 summarizes the key efficacy outcomes for the StiL NHL1 Study.

Table 7. Summary of Key Trial Efficacy Outcomes for RCT of B-R vs. CHOP-R in Previously Untreated Indolent Lymphoma: StiL NHL1 Study.[1,3,15]

Analysis	Intervention	N (rand;eval)	OS, mdn	PFS, mdn	Response		Mdn follow-up
					CR (%)	OR (%)	
Previously Untreated Indolent Lymphoma							
Final analysis presented at ASH 2009 (Rummel 2009 ASH405)	B-R	274:260	Deaths: n=34	54.8 mos	40.1[A]	93.8[A]	32 mos
	CHOP-R	275:253	Deaths: n=33 p=ns	34.8 mos HR 0.5765, 95% CI 0.4292-0.7683; p=0.0002	30.8[A] p=0.0323	93.5[A] p=NR	
Updated analysis presented at ASCO 2012 (Rummel 2012 ASCO#3)	B-R	274:261	Deaths: n=43	69.5 mos	39.8	92.7	45 mos
	CHOP-R	275:253	Deaths: n=45 p=ns;NR	31.2 mos HR 0.58, 95% CI 0.44-0.74; p<0.001	30.0 p=0.021	91.3	

Notes: B-R=bendamustine, rituximab; CHOP-R=cyclophophamide, doxorubicin, vincristine, prednisone, rituximab; CI=confidence interval; CR=complete response; eval=evaluable and included in analysis; Mdn=median; mos=months; N=number of patients in analysis; NR=not reported; ns=not significant; OR=overall response; OS=overall survival; PFS=progression-free survival; rand=randomized; TTP=time-to-progression;
[A]Response was evaluable in only 257 patients in the B-R arm and in 249 patients in the CHOP-R arm.

Overall Survival

No statistically significant difference in overall survival was detected for the B-R arm compared to the CHOP-R control arm (see Table 7) in the final analysis presented at ASH in 2009[1] or in the updated analysis presented at ASCO in 2012[15]; however, overall survival was not the primary outcome of the StiL NHL1 study.

Progression-free Survival

In the final analysis, the StiL NHL1 trial reported median progression-free survival of 54.8 months in the B-R arm compared to 34.8 months in the CHOP-R arm, with a hazard ratio (HR) of 0.5765 and a 95% confidence interval (CI) of 0.4292-0.7683, p=0.0002.[1] In the updated analysis presented at ASCO 2012, median progression-free survival was 69.5 months in the B-R arm and 31.2 months in the CHOP-R arm, with a HR of 0.58 and a 95% CI of 0.44-0.74 with p<0.001 (stratified log rank).[3,15] Progression-free survival was the primary outcome for the trial.

The updated analysis reported that the progression-free survival benefit for B-R compared to CHOP-R was independent of age (patients aged ≤60 years, HR 0.52,

p=0.002, n=199; patients aged >60 years, HR 0.62, p=0.002, n=315).[15] No further details were reported.

In the final analysis, Rummel et al also reported that event-free survival and time-to-next treatment were statistically significantly different in the B-R arm compared to the CHOP-R arm: event-free survival median 54 months for B-R versus (vs.) 31 months for CHOP-R, HR 0.6014, 95% CI 0.4515-0.7845, p=0.0002; time-to-next treatment median not reached for B-R vs. 40.7 months for CHOP-R, HR 0.5416, 95% CI 0.3897-0.7491, p=0.0002.[1]

Response

The StiL NHL1 trial reported a statistically significant difference in the rate of complete response (40.1% of 257 response evaluable patients on B-R arm vs. 30.8% of 249 response evaluable patients on the CHOP-R arm; p=0.0323).[1] The rate of overall response was similar in both treatment arms (93.8% in B-R arm vs. 93.5% in the CHOP-R arm); however the authors did not report a p-value. The presentation of the updated analysis at ASCO 2012 reported similar values for complete and overall response as those reported in the original final analysis presented at ASH 2009 (Table 7).[3]

Harms Outcomes (Previously Untreated)

Table 8. Summary of Key Trial Harms Outcomes for RCT of B-R vs. CHOP-R in Previously Untreated Indolent Lymphoma: Proportion of Patients with Adverse Events in StiL NHL1 Study.[1,3,15]

Intervention	N	Neutropenia Gr 3/4 (%)	Leukopenia Gr 3/4 (%)	Lymphopenia Gr 3/4 (%)	Anemia Gr 3/4 (%)	Thrombocytopenia Gr 3/4 (%)	Infection (%)	Erythema (%)	Allergic reaction, skin (%)	Peripheral neuropathy (%)	Alopecia (%)	Stomatitis (%)
B-R	260	29	37	74	3	5	36.8	16.1	15.4	6.9	15	6.2
CHOP-R	253	69 p=NR	72 p=NR	43 p=NR	5 p=NR	6 p=NR	50.2 p=0.0025	9.1 p=0.0122	5.9 p=0.0003	28.9 p<0.0001	62 p=NR	18.6 p<0.0001

Notes: B-R=bendamustine, rituximab; CHOP-R=cyclophophamide, doxorubicin, vincristine, prednisone, rituximab; N=number of patients in analysis; NR=not reported; ns=not significant; SAE=serious adverse events;

Table 8 summarizes the key harms outcomes for the StiL NHL1 study of bendamustine in previously untreated indolent lymphoma.

Hematological

No statistical comparisons were reported for the proportion of patients with any specific haematological adverse event; therefore, it is unknown if the differences in the following haematological adverse events were statistically significant.

The proportion of patients with Grade 3 or 4 neutropenia was higher in the CHOP-R arm (69% of 253 patients) compared to the B-R arm (29% of 260 patients).[3]

The proportion of patients with Grade 3 or 4 leukopenia was also higher in the CHOP-R arm than in the B-R arm (72% vs. 37%).[3]

The proportion of patients with Grade 3 or 4 lymphopenia was lower in the CHOP-R arm than in the B-R arm (43% vs. 74%).[3]

The proportion of patients with Grade 3 or 4 thrombocytopenia and anemia was similar in both arms (see Table 8).

Febrile Neutropenia

Grade 4 febrile neutropenia occurred in [redacted] ([redacted]%) patients in the CHOP-R arm and in [redacted] of the patients in the B-R arm.[16] *(Non-disclosable information was used in this pCODR Guidance Report and the manufacturer requested this information not be disclosed pursuant to the pCODR Disclosure of Information Guidelines. This information will remain redacted until notification by manufacturer that it can be publicly disclosed).*

Infection

The rate of infection in the StiL NHL1 study was statistically significantly different for the B-R arm (36.8% of 260 patients) compared to the CHOP-R arm (50.2% of 253 patients; p=0.0025).[3] Sepsis occurred in one patient in the B-R arm and in eight patients in the CHOP-R arm (p=0.0190).[3]

Rash

The StiL NHL1 study reported that the rate of erythema was statistically significantly different for the B-R arm (16.1% of 260 patients) compared to the CHOP-R arm (9.1% of 253 patients; p=0.0122).[1] No data were reported on the occurrence of SJS or TENS.[1] An allergic reaction in the skin occurred in 15.4% of patients in the B-R arm and in 5.9% of patients in the CHOP-R arm (p=0.0003).[3]

Other Adverse Events

The StiL NHL1 study reported a statistically significant difference in peripheral neuropathy for the B-R arm compared to the CHOP-R arm (6.9% vs. 28.9%; p<0.0001).[1]

A statistically significant difference in the rate of stomatitis was reported for the B-R arm compared to the CHOP-R arm (6.2% vs. 18.6%; p<0.0001).[1]

A higher rate of alopecia was reported in the bendamustine arm (see Table 8); however, the authors did not report whether the difference was statistically significant.[1]

The number of treatment-related deaths was not reported for the StiL NHL1 study.[1]

Twenty secondary malignancies were observed in the B-R arm compared with 23 in the CHOP-R arm, including one occurrence of myelodysplastic syndrome in the B-R arm and 1 occurrence acute myeloid leukemia in the CHOP-R arm.[1]

Quality of Life

No quality of life data were reported for the StiL NHL1 study.

6.3 B) Results for Previously Treated Indolent Lymphoma

6.3.1 B) Literature Search Results

See section 6.3.1A for literature search results

6.3.2 B) Summary of Included Studies (Previously Treated)

One randomized trial, StiL NHL2-2003, was identified that compared the use of bendamustine plus rituximab (BR) to fludarabine plus rituximab (FR) in patients with previously treated relapsed follicular, indolent and mantle cell lymphomas.[5]

6.3.2.1 B) Detailed Trial Characteristics (Previously Treated)

a) Trials (Previously Treated)

One trial met the inclusion criteria for this review and included patients with previously treated indolent lymphoma. Key trial characteristics can be found in Table 3. The StiL NHL2 trial has only been reported in abstract form and limited details regarding the study design are available. The study was a multicentre RCT; however details regarding the number and location of study sites are not available. Neither patients nor investigators were blinded to study treatment. Details regarding the methods used to randomize patients and masking of treatment allocation were not reported. The sponsor for the StiL NHL2 study was the University of Giessen.[6] The ClinicalTrial.gov record states that the trial was designed to determine if B-R is non-inferior to F-R with respect to event-free survival; however, an abstract reported by Rummel et al reported that the primary outcome was progression-free survival.[5] The manufacturer confirmed, in a personal communication with the lead investigator, that a standard power calculation for non-inferiority was used to determine the sample size.[16] Based on the results published in the abstract report, secondary outcomes may have included overall response rate, complete response rate, overall survival, and toxicity.[5] A standard definition of progression-free survival was used.[16] Response was assessed by the investigators using WHO criteria.[16]

b) Populations (Previously Treated)

Table 9. Baseline patient characteristics in StiL NHL2 study.[5]

Characteristic	Treatment arms	
	B-R	F-R
N Randomized	Total: 219[A]	
Sex **Male** **Female**	NR	NR
Age (years) **Mean, SD**	Mdn: 68 (range: 38-87)	
Ann Arbor stage **III** **IV**	 21.1% 71.6%	 25.3% 60.6%
Histology **FL**	 45.9%	 47.5%

Characteristic	Treatment arms	
	B-R	F-R
MCL	20.2%	21.2%
LP-IC	11.9%	11.1%
Other	23%	20.2%
WHO PS		
0	NR	NR
1		
2		
3		

Notes: B-R=bendamustine, rituximab; F-R=fludarabine, rituximab; FL=follicular lymphoma; LP-IC= lymphoplasmocytic lymphoma/immunocytoma; MCL=mantle cell lymphoma; N=number of patient; WHO PS=World Health Organization Performance status.

[A]Data on the number of patients randomized to each treatment arm were not reported.

The StiL NHL2 trial (B-R vs. F-R) randomized a total of 219 patients. The number of patients randomized to each arm was not reported. The trial was well balanced for Ann Arbor stage and histology (Table 9).[5] The median age was 68 years with a range of 38-87 years. Median or mean age for each arm was not reported. Patients had received a median of 1 prior therapy (range 1-7).[5] No further data regarding patients characteristics were reported.

c) Interventions (Previously Treated)

The StiL NHL2 trial compared bendamustine plus rituximab (B-R; dose and schedule in Table 3) to fludarabine plus rituximab (F-R; dose and schedule in Table 3).[5] Rummel et al reported that the prophylactic use of antibiotics or growth factors were not generally recommended in the trial protocol; however in the case of severe granulocytopenia, the use of G-CSF was permitted.[5] Patients received a median number of six cycles of therapy in both treatment arms, with 75.2% of patients in the B-R arm and 53.4% of patients in the F-R arm receiving six cycles of therapy. No further details were reported.

d) Patient Disposition (Previously Treated)

The StiL NHL2 trial randomized 219 patients. A total of 11 patients were not evaluable due to protocol violations and were not followed further.[5] The final analysis included 208 patients. No further data were reported.

e) Limitations/Sources of Bias (Previously Treated)

Similarly to the StiL NHL1 trial, the StiL NHL2 trial has only been reported in abstract form and it is difficult to determine the quality of the trial from the very limited information reported in the abstract. The required sample size was not reported, 11 patients appeared to be excluded from the final analysis (219 randomized patients with 208 evaluable for the final analysis) and adverse event data were also limited.[5] In addition, no details were available regarding the method used for randomization or on masking of treatment allocation.

Ideally, for an unblinded trial, tumour assessments should be conducted in a blinded fashion by an independent clinician or committee. The StiL NHL2 study was unblinded and tumour assessments were conducted by the study investigators. There exists a potential for bias in the outcomes (such as progression-free survival, event-free survival, tumour response) that were based on the tumour assessments.

6.3.2.2 B) Detailed Outcome Data and Summary of Outcomes (Previously Treated)

Efficacy Outcomes (Previously Treated)

Table 10 summarizes the key efficacy outcomes for the StiL NHL2 Study.

Table 10. Summary of Key Trial Efficacy Outcomes in the StiL NHL2 study.[5]

Trial	Intervention	N	OS, mdn	PFS, mdn	Response		Mdn follow-up
					CR (%)	OR (%)	
StiL NHL2 Rummel 2010 ASH856	B-R	109	Deaths: n=42	30 mos	38.5%	83.5%	33 mos
	F-R	99	Deaths: n=46 p=ns	11 mos HR 0.51, 95% CI 0.34-0.67; p<0.0001	16.2% p=0.0004	52.5% p<0.0001	

Notes: B-R=bendamustine, rituximab; CI=confidence interval; COP=cyclophosphamide, vincristine, prednisone; CR=complete response; F-R=fludarabine, rituximab; Mdn=median; mos=months; N=number of patients in analysis; NR=not reported; ns=not significant; OR=overall response; OS=overall survival; PFS=progression-free survival; TTP=time-to-progression;

Overall Survival

The Stil NHL2 trial (B-R vs. F-R) reported 42 deaths of 109 patients in the B-R arm and 46 deaths of 99 patients in the F-R arm. The authors of the abstract publication reported that no statistically significant difference in overall survival was detected at the time of the analysis; however, no further data were reported.[5]

Progression-free Survival

The StiL NHL2 trial reported a statistically significant difference in median progression-free survival for the B-R arm (30 months) compared to the F-R arm (11 months), with HR 0.51, 95% CI 0.34-0.67, p<0.0001.[5]

Response

In the StiL NHL2 study, both the rate of complete response (38.5% vs. 16.2%, p=0.0004) and overall response (83.5% vs. 52.5%, p<0.0001) demonstrated a statistically significant difference for the B-R arm compared to the F-R arm.[5]

Harms Outcomes (Previously Treated)

Table 11. Summary of Key Trial Harms Outcomes for the StiL NHL2 Study.[5]

Trial	Intervention	N	SAE (%)	Neutropenia Gr 3/4 (%)	Leukopenia Gr 3/4 (%)	Infection (%)	Rash (%)	Peripheral neuropathy (%)	Alopecia (%)	Stomatitis (%)
StiL NHL2 Rummel 2010 ASH856	B-R	109	17.4	8.9	11.8	NR	NR	NR	NR	NR
	F-R	99	22.2	9.1	12.4	NR	NR	NR	NR	NR

Notes: B-R=bendamustine, rituximab; F-R=fludarabine, rituximab; N=number of patients in analysis; NR=not reported; ns=not significant; SAE=serious adverse events;

Table 11 summarizes the key harms outcomes for the StiL NHL2 study. Of note, Rummel et al reported that no significant differences in alopecia, stomatitis, erythema, allergic reactions, peripheral neuropathy, or infections were detected between the B-R arm compared to the F-R arm in the StiL NHL2 study.[5] The authors did not report any data for those harms outcomes.

Grade 3/4 Neutropenia

Grade 3 or 4 neutropenia was reported to occur in a similar proportion of patients in the B-R arm (8.9% of 109 patients) compared to the F-R arm (9.1% of 99 patients). No statistical comparison was reported.

Febrile Neutropenia

No data were available on the rate of febrile neutropenia for the StiL NHL1 study.

Infection

No data were available on the rate of infection for the StiL NHL1 study.

Rash

No data were available on the rates of rash, SJS, or TENS for the StiL NHL1 study.

Other Adverse Events

Serious adverse events occurred in 17.4% of 109 patients in the B-R arm and in 22.2% of 99 patients in the F-R arm.[5] No statistical comparisons were reported.

Grade 3 or 4 leukopenia occurred in 11.8% of 109 patients in the B-R arm and in 12.4% of 99 patients in the F-R arm.[5] No statistical comparisons were reported.

Quality of Life

No quality of life data were reported for the StiL NHL2 study.

6.4 Ongoing Trials

Two ongoing RCTs were identified investigating the use of bendamustin in patients with indolent lymphoma through a search of clinical trial registries: NCT00877006 and NCT01289223. Details of the trials can be found in Tables 12 and 13.

Table 12. Study NCT00877006: Study of bendamustine hydrochloride and rituximab (BR) compared with R-CVP or R-CHOP in the first-line treatment of patients with advanced indolent non-Hodgkin's lymphoma (NHL) or mantle cell lymphoma (MCL) – BRIGHT study.[4]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00877006 Open-label, randomized phase III trial. Start date: April 2009 Expected completion date: March 2012 Estimated enrolment: 447 Study Sponsor: Teva Pharmaceutical Industries (Cephalon)	Patients with CD20-positive B-cell NHL: grade 1 or 2 follicular lymphoma, immunoplasmacytoma/ immnocytoma, splenic marginal zone B-cell lymphoma, extra-nodal marginal zone lymphoma of mucosa associated lymphoid tumour, nodal marginal zone B-cell lymphoma, mantle cell lymphoma. No prior treatment ECOG PS ≤3	**Two arms:** Bendamustine 90 mg/m^2 d1+2 + rituximab 375 mg/m^2 d1 every 28 days for 6 cycles ***Or*** R-CVP: rituximab 375 mg/m^2 d1 + vincristine 1.4 mg/m^2 d1 + prednisone 100 mg d1-5 + cyclophosphamide at either 750 mg/m^2 d1 or 1000 mg/m^2 d1 every 21 days R-CHOP: rituximab 375 mg/m^2 d1 + cyclophosphamide at either 750 mg/m^2 d1 + doxorubicin 50 mg/m2 d1 + vincristine 1.4 mg/m^2 d1 + prednisone 100 mg d1-5 every 21 days	<u>Primary outcomes:</u> Complete response rate <u>Secondary outcomes:</u> Overall response rate Progression-free survival Quality of life Duration of response

Available from:
http://clinicaltrials.gov/ct2/show/record/NCT00877006?term=bendamustine+AND+randomized&rank=12

Table 13. Study NCT01289223: A trial to investigate the efficacy of bendamustine in patients with indolent non-Hodgkin's lymphoma (NHL) refractory to rituximab: ROBIN study[7]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01289223 Open-label, randomized phase III trial. Start date: February 2011	Patients with indolent B-cell lymphoma: grade 1-3a follicular, small lymhocytic, lymphoplasmacytic, and marginal zone	**Two arms:** Bendamustine in one arm—no further details available ***Or***	<u>Primary outcomes:</u> Progression-free survival <u>Secondary outcomes:</u> Overall response rate Duration of response

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Expected completion date: October 2014 Estimated enrolment: 125 Study Sponsor: Mundipharma Research Limited	lymphoma. Stage III-IV or bulky disease stage II Disease that remains stable or unresponsive during or within 6 months of treatment with rituximab or a rituximab-containing regimen. ECOG PS ≤3	Treatment of physician's choice (without bendamustine	

Available from: http://clinicaltrials.gov/ct2/show/NCT01289223?term=bendamustine+AND+randomized&rank=17

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Lymphoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on bendamustine for Non-Hodgkin Lymphoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the *pCODR Disclosure of Information Guidelines*. The manufacturer, as the primary data owner, did not agree to the disclosure of some clinical information, which was provided to pERC for their deliberations, and this information has been redacted in this publicly available Guidance Report.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report.

The Lymphoma Clinical Guidance Panel is comprised of three oncologists .The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. (bendamustine: or treanda: or ribomustin: or sdx-105: or hsdb 7763:).ti,ab,rn,nm,sh,hw,ot.
2. 3543-75-7.rn,nm.
3. 16506-27-7.rn,nm.
4. Or/1-3
5. Exp lymphoma, non-hodgkin/
6. NHL:.ti,ab,sh,hw,ot.
7. Non Hodgkin: lymphoma:.ti,ab,sh,hw,ot.
8. Mantle cell lymphoma:.ti,ab,sh,hw,ot.
9. Mcl:.ti,ab,sh,hw,ot.
10. or/5-9
11. 4 and 10

Ovid EMBASE

1. exp *bendamustine/
2. (bendamustine: or treanda: or ribomustin: or sdx-105: or hsdb 7763:).ti,ab.
3. 1 or 2
4. Exp *nonhodgkin lymphoma/
5. Nonhodgkin: lymphoma:.ti,ab.
6. Non Hodgkin: lymphoma:.ti,ab.
7. Nhl:.ti,ab.
8. Mantle cell lymphoma:.ti,ab.
9. Mcl:.ti,ab.
10. Or/4-9
11. 3 and 10

2. Literature Search via PubMed

PubMed

1. bendamustine* or treanda* or ribomustin* or sdx-105* or hsdb7763*
2. publisher[sb]
3. 1 and 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Issue 8, 2012
NN results for: bendamustine* or treanda* or ribomustin* or sdx-105* or hsdb 7763* AND breast cancer* in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: bendamustine, treanda, ribomustin, sdx-105, hsdb 7763

Select International Agencies:

Food and Drug Administration (FDA):
www.fda.gov

European Medicines Agency (EMA):
www.ema.europa.eu

Search terms: bendamustine, treanda, ribomustin, sdx-105, hsdb 7763

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the Journal of Clinical Oncology search portal: http://jco.ascopubs.org/search

American Society of Hematology (ASH)
via Blood (Journal of the American Society of Hematology) search portal:
http://bloodjournal.hematologylibrary.org/search

Search terms: bendamustine, treanda, ribomustin, sdx-105, hsdb 7763

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