pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Bendamustine (Treanda) for Chronic Lymphocytic Leukemia

November 29, 2012

Please note that sections pertaining to the use of Bendamustine (Treanda) for First Line Chronic Lymphocytic Leukemia in this report are superceded by the Clinical Guidance Report on Bendamustine (Treanda) for First Line Chronic Lymphocytic Leukemia which can be found at: Bendamustine (Treanda) First Line CLL

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FUNDING

The pan-Canadian Oncology Drug Review is funded collectively by the provinces and territories, with the exception of Quebec, which does not participate in pCODR at this time.

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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 chronic lymphocytic leukemia (CLL) and
2. CLL that has relapsed following or is refractory to previous therapy.

1.2 Key Results and Interpretation

Systematic Review Evidence

1.2.1 A) Previously Untreated (First Line) Chronic Lymphocytic Leukemia

One open-label multicentre randomized control trial, Study 02CLLIII, was identified that met the inclusion criteria for this review.[1-9] The trial was designed to evaluate superiority of bendamustine compared to chlorambucil for two primary outcomes: progression-free survival and overall response rate in previously untreated CLL. A total of 319 patients (Age ≤75 years, WHO PS/ECOG 0-2) were randomized in a 1:1 ratio to receive bendamustine monotherapy 100 mg daily on day 1 and 2 given i.v. over 30 minutes, every 4 weeks (n=162) or to chlorambucil CLB 0.8 mg/kg (Broca's normal weight in kg) on days 1 and 15 orally, every 4 weeks (n=157).

Study 02CLLIII had two primary endpoints, progression-free survival and overall response rate.[1] Progression-free survival based on the independent review committee assessments demonstrated a statistically significant difference for bendamustine (median 21.6 months) compared to chlorambucil (median 8.3 months), with HR=0.214, p<0.0001.[1] A statistically significant difference in overall response rates was demonstrated for bendamustine (68% of 162 patients) compared to chlorambucil (31% of 157 patients; p<0.0001), based on the independent review committee assessments.[1] No data was reported to support quality of life statements.

A higher proportion of patients in the bendamustine arm than in the chlorambucil arm experienced neutropenia (any grade or Grade 3/4), leukopenia (any grade or Grade 3/4), vomiting (any grade), pyrexia (any grade), infection (any grade) or rash (any grade).[1] None of the study reports indicated whether any of these differences were statistically different. A total of 72 patients (31 in the bendamustine arm and 41 in the chlorambucil arm) have died during the follow-up period.

1.2.1 B) Previously Treated Chronic Lymphocytic Leukemia

One randomized controlled trial was identified that compared bendamustine to fludarabine in patients with Rai stage II-IV or Binet stage B or C relapsed or refractory B-cell CLL.[10,11] A total of 96 patients (ECOG PS/ECOG 0-3, Age ≥18 years) were randomized to receive either bendamustine (100 mg/m^2/d on days 1 and 2 every 4 weeks) or to receive fludarabine (25 mg/m^2/d on days 1-5 every 4 weeks). Patient in both arms continued until best response or a maximum of eight cycles.

No significant differences were observed for overall survival (HR=0.82, 95% CI 05.1-1.30, p=0.48) or progression-free survival (HR=0.87, 95% CI 0.59-1.28, p=0.27) for the bendamustine arm compared to the fludarabine arm.[10] Grade 3 or 4 infections occurred in 13% of 49 patients in the bendamustine arm and in 15% of the 43 patients in the fludarabine arm. No further adverse event data were reported. The study has so far only been reported in abstract form and no information was available on the required sample size, randomization methods, masking of allocation, primary or secondary outcomes, or the statistical methods used in the analysis.

Five single-arm studies of bendamustine in relapsed or refractory CLL were identified with number of patients ranging from 4-78.[12-16] The studies demonstrated overall response rates ranging from 51 – 100%, with the majority of patients achieving only a partial response. Most of these studies do not report harms.

1.2.2 Additional Evidence

pCODR received input on bendamustine from the following patient advocacy groups: The Leukemia and Lymphoma Society of Canada and The CLL Patient Advocacy Group. 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

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the western world, and affects 4.2 people/100 000 population per year. Cure of this disease is not a reasonable expectation and most affected patients will eventually die as a result of their disease with the median survival from the time patients require treatment for CLL being approximately 4 years.

The majority of patients with CLL are older and so are not considered suitable candidates for modalities such as intensive chemotherapy regimens and stem cell transplantation. Having fewer options, older patients usually receive treatment with single agents, occasionally in combination with rituximab. The two classes of drugs most often used to treat CLL are nucleoside analogues and alkylating agents. As none of these treatments is expected to be curative and all are expected to be associated with significant side effects, there is a need for new drugs to treat CLL in both untreated and previously treated patients.

Bendamustine is a novel bifunctional alkylating agent with a similar mechanism of action and side effect profile as chlorambucil making it an appropriate comparator in front-line therapy. As many older patients are treated with alkylating agents initially, fludarabine is an appropriate comparator for patients being treated for relapsed disease.

Study 02CLLIII comparing bendamustine and chlorambucil in untreated patients with CLL demonstrated a clinically-significant improvement in progression-free survival among patients treated with bendamustine. The overall and complete response rates were significantly higher with bendamustine than they were with chlorambucil. Although statistically not significant, rates of grade 3 / 4 cytopenias were higher among patients treated with bendamustine compared with chlorambucil.

Megdenberg et al 2009, comparing bendamustine with fludarabine for patients with previously treated chronic lymphocyte leukemia failed to demonstrate a difference in overall survival or progression-free survival between the two arms. Complete and overall

response rates were similar between the two groups, as were rates of serious infection. No further adverse event data were reported.

Overall response rates in five single-arm studies of bendamustine in relapsed or refractory CLL ranged from 51 – 100%, with the majority of patients achieving only a partial response (CR rate 6.7 – 30%). Most of these studies do not report harms.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall clinical benefit to bendamustine in the treatment of previously-untreated patients with CLL who are not suitable candidates for more intensive regimens. This conclusion is based on the results of one high-quality randomized, active control study comparing bendamustine with chlorambucil (Study 02CLLIII) that demonstrated a clear clinically- and statistically-significant improvement in progression-free survival. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Study 02CLLIII showed a clear benefit to untreated patients with Binet stage B or C CLL who were under the age of 75 and had ECOG performance status 0 – 2.
- While patients with CLL may initially be observed, most eventually require treatment for their disease. Treatment options for older or unfit patients are limited.
- The frequency and severity of adverse events observed with bendamustine are consistent with the adverse events seen with other front-line regimens for CLL. Physicians who treat CLL are comfortable managing patients with grade 3 / 4 cytopenias. Extramedullary toxicity was generally mild.

The Clinical Guidance Panel concluded that there may not be an overall clinical benefit to bendamustine in the treatment of patients with CLL who have relapsed or are refractory to chemotherapy. This conclusion is based on the results of a randomized, active control study (n=92) comparing bendamustine and fludarabine that failed to demonstrate a clear-cut benefit to bendamustine. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Medgenberg et al. demonstrated similar PFS and OR rates when previously-treated patients received bendamustine or fludarabine. This study has only been presented in abstract form and requires further clarifications regarding study design.
- Several single-arm studies demonstrate that bendamustine has activity in relapsed or refractory CLL, although the small numbers of patients studied and use of other active agents in some of these studies makes drawing firm conclusions difficult.
- As patients with CLL become more extensively treated, myelosuppression is likely to become more pronounced. The adverse event profile associated with the use of bendamustine in heavily pretreated patients requires further study.

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 (Treanda) for CLL. 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 (Treanda) for CLL conducted by the Leukemia 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 (Treanda) for CLL and a summary of submitted Provincial Advisory Group Input on Bendamustine (Treanda) for CLL are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

With an age-adjusted incidence rate of 4.2 cases/100 000 population, CLL represents the most common leukemia in western countries. CLL is a disease of the elderly, with a median age at diagnosis of 72 years, and its long natural history (median survival from diagnosis is 10+ years) reflects an extended period of watchful waiting in most patients.[17] Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities.

Common indications to treat patients with CLL include the development of cytopenias (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< 3 months). Treatment is individualized based on patients' suitability for intensive chemotherapy. The combination of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care for young, otherwise healthy patients given the results of a recent German CLL Study Group study showing improved PFS (51.8 vs. 32.8 months, p<0.0001) and OS (87% vs. 83%, p=0.012) with the addition of rituximab to FC.[18] Significant and prolonged neutropenia and leucocytopenia and frequent extramedullary toxicity make this regimen unsuitable for older and less fit individuals.

Patients who are not considered fit enough to receive FCR but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Chlorambucil, an alkylating agent, has been in use for more than 30 years and can be given in daily, weekly, biweekly and monthly schedules. Extramedullary toxicity is generally mild and transient. Other alkylator-based regimens, such as cyclophosphamide and prednisone or CVP have been described in CLL (see Table 2). The nucleoside analog fludarabine was compared with chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS.[19] Patients treated with fludarabine in this study had higher rates of severe infection and neutropenia, and the combination of fludarabine and chlorambucil has been associated with unacceptably high rates on severe infection.[20] The addition of monoclonal antibodies to induction regimens for less fit patients is an area of active research, but appears promising in early-phase studies. Novel agents such as lenalidomide[21] and new

monoclonal antibodies such as ofatumumab[22] have been evaluated in CLL but have yet to find their place in the therapeutic arsenal for this disease.

In contrast to initial treatment, there is no established treatment for patients with relapsed or refractory disease. While the disease may respond to regimens similar to those used for induction, responses are generally of lesser quality and duration in previously treated patients. CLL that is refractory to both nucleoside analogues and alkylating agents has an especially poor prognosis. Alemtuzumab has been used successfully as a bridge to allogeneic stem cell transplantation in this setting. Responses are generally brief and are frequently associated with opportunistic infection as a result of the intense immunosuppression associated with this agent. While survival from diagnosis in CLL may exceed 10 years, survival from the onset of treatment is only 4 years and contrary to widely held belief, 70% of patients with CLL die of causes related to their disease. New, more effective treatments for patients with this disease are desperately needed.

Bendamustine hydrochloride was developed in East Germany in the 1960's.[23] It is a purine analogue/alkylator hybrid that has shown activity in various cancers.[24] 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.[24] 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.[25,26]

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 chronic lymphocytic leukemia (CLL).
2. CLL that has relapsed following or is refractory to previous therapy.

See Table 8 in Section 6.2.1 for outcomes of interest and appropriate comparators.

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 (First-Line) Chronic Lymphocytic Leukemia

Trial Characteristics

One open-label multicentre RCT (02CLLIII) was identified that met the inclusion criteria for this review. [1-9] The study investigated the use of bendamustine compared to chlorambucil in patients less than 75 years old with previously untreated Binet stage B or C CLL. A summary of key trial characteristics can be found in Table 1.

The trial was designed to evaluate superiority of bendamustine compared to chlorambucil for two primary outcomes: progression-free survival and overall response rate. [1-9] The trial used a group sequential design with planned interim analyses. The investigators estimated that approximately 350 patients would be required if a fixed sample design was

used. After the third interim analysis including 305 patients, the Independent Data Monitoring Committee recommended that patient recruitment be stopped after 319 patients were enrolled. The analyses of the primary outcomes were to be stratified by Binet stage.

A total of 319 patients were randomized in a 1:1 ratio to receive bendamustine monotherapy (100 mg/m^2/d on days 1 and 2 of a 4-week cycle; n=162) or to chlorambucil (0.8 mg/kg, Broca's normal weight in kg; n=157). Patients received up to a maximum of six cycles of therapy. A median of six treatment cycles were administered in both treatment arms. The mean number of cycles was 4.9 (standard deviation, 1.7).

The two arms were balanced for a number of baseline demographic and disease characteristics, including; World Health Organization (WHO) performance status, B symptoms, lactate dehydrogenase, and time from initial diagnosis to enrolment. A similar number of female patients were enrolled in each arm (37.0% in the bendamustine arm and 39.5% in the chlorambucil arm). Of 162 patients in the bendamustine arm 71.6% had Binet stage B disease and 28.4% had Binet stage C. Similarly, of 157 patients in the chlorambucil arm, 70.7% had Binet stage B disease and 29.3% had Binet stage C. The mean ages of patients in each arm were similar (bendamustine arm, 63.0 years; chlorambucil arm 63.6 years) as was the median age (bendamustine, 63.0 years; chlorambucil arm 66.0 years).

Of 319 randomized patients, 18 patients had protocol violations: 11 did not meet the diagnostic confirmation required in the protocol, and seven did not receive the allocated intervention (one in the bendamustine arm and six in the chlorambucil arm). No patients were lost to follow-up in the bendamustine arm and only one patient was lost to follow-up in the chlorambucil arm.

Neither the investigators nor the patients were blinded to treatment assignment; however, the trial protocol was amended to include independent and blinded tumour assessments, thus reducing the risk of bias in the assessments of response and progression-free survival. The 18 patients with protocol violations also represented, at most, 5.6% of the study population and therefore likely had little impact on the study results.

Table 1. Summary of Included Studies in Study 02CLLIII.[1]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study 02CLLIII Multicenter study: 45 sites in 8 countries in Europe* Study start date: November 2002; Study completion: November 2006 Open-label, active control RCT Randomized in a 1:1 ratio (BEN:CLB) stratified by center and Binet	Patients with previously untreated CLL with Binet stage B (≥3 lymph node regions involved including hepatomegaly and splenomegaly) or Binet stage C (anemia and/or thrombocytopenia regardless of the number of lymph node regions) with coexpression of CD5, CD23 and either CD19, or CD20, or both. Age ≤75 years WHO PS 0-2 Life expectancy >3	Two arms: BEN 100 mg/m^2/d d1,2 i.v. over 30 minutes, every 4 weeks *Or:* CLB 0.8 mg/kg (Broca's normal weight in kg) on days 1 and 15 orally, every 4 weeks. Prophylactic use of hyperuricemia treatment was recommended to prevent uric acid-induced nephropathy.	<u>Co-Primary</u> Overall response rate Progression-free survival <u>Secondary</u> Time-to-progression Duration of remission Overall survival Adverse events Infection

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
stage Randomized: n=319 Analysis ITT: n=319 Funded by: Ribosepharm GmbH, Germany and Mundipharma International, U.K.	months		

Notes: BEN=bendamustine; CLB=chlorambucil; ITT=intention-to-treat; i.v.=intravenous; RCT=randomized controlled trial; WHO PS=World Health Organization performance status.
*Countries included Austria, Bulgaria, France, Germany, Italy, Spain, Sweden, and the United Kingdom.

Outcome Data and Summary of Outcomes

The final efficacy intent-to-treat analysis included all 319 randomized patients (bendamustine arm, n=162; chlorambucil arm, n=157).[1] The safety analysis included all 312 treated patients (161 patients in the bendamustine arm and 151 patients in the chlorambucil arm).[1] A summary of key efficacy and harms outcomes can be found in Table 2 below.

Table 2. Summary of Key Trial Outcomes From Study 02CLLIII.[1]

Efficacy	Analysis	Intervention	Median [months]	HR (95% CI)	p-value	Median follow-up [months]
Progression-free Survival	Analysis using Independent Review Committee Assessments[A]	Bendamustine (n=162) Chlorambucil (n=157)	21.6 8.3	0.214 (NR)	p<0.0001	35
	Sensitivity analysis using strictly applied NCI-WG criteria[B]	Bendamustine (n=162) Chlorambucil (n=157)	17.6 5.7	0.269 (0.169-0.428)	p<0.0001	35
Efficacy		**Intervention**		**Rate (%)**	**p-value**	
Response	CR	Bendamustine (n=162) Chlorambucil (n=157)		31 2	p=NR	
	OR	Bendamustine (n=162) Chlorambucil (n=157)		68 31	p<0.0001	

Harms	Bendamustine (n=161)	Chlorambucil (n=151)
Withdrew due to AE (%)	11.2	3.3
At least one AE (%)	89	81
At least one Grade 3 or 4 AE (%)	55[C]	32[C]
Neutropenia		
Any Grade (%)	27.3	13.9
Grade 3/4 (%)	23.0	10.6
Thrombocytopenia		
Any Grade (%)	24.8	20.5
Grade 3/4 (%)	11.8	7.9
Anemia		
Any Grade (%)	21.7	13.9
Grade 3/4 (%)	2.5	0
Leukopenia		
Any Grade (%)	17.4	3.3
Grade 3/4 (%)	14.3	1.3
Nausea (any Grade, %)	19.3	13.9
Vomiting (any Grade, %)	15.5	6.6
Pyrexia (any Grade, %)	24.8	5.3
Infection (any Grade, %)	6.2	1.3
Rash (any Grade, %)	9.3	4.6

Notes: AE=adverse event; CI=confidence interval; CR=complete response; HR=hazard ratio; NCI-WG=National Cancer Institute-Working Group; NR=not reported; OR=overall response; SAE=serious adverse event.
[A]Data obtained from primary publication.[1]
[B]Data obtained from FDA Medical Review.[27]
[C]Data obtained from Product Monograph.[26]

Progression-free survival based on the independent review committee assessments demonstrated a statistically significant difference for bendamustine (median 21.6 months) compared to chlorambucil (median 8.3 months), with HR=0.214, p<0.0001.[1] The FDA Medical review reported a sensitivity analysis of progression-free survival where a computer algorithm was used to strictly apply the NCI-WG criteria. That analysis also demonstrated a statistically significant difference in progression-free survival for bendamustine (median 17.6 months) compared to chlorambucil (median 5.7 months), with HR=0.269, 95% confidence interval (CI) 0.169-0.428, p<0.0001.[27] Median follow-up was 35 months.

A total of 72 patients (31 in the bendamustine arm and 41 in the chlorambucil arm) died during the follow-up period. At the time of the final analysis, there were insufficient data to comment on overall survival.[1] In 2012, Knauf et al reported updated results for the 02CLLIII study.[2] The analysis was conducted in May 2010 on the final intent-to-treat population (N=319). After a median follow-up of 54 months, with a total of 132 deaths, no statistically significant difference in overall survival was observed for the bendamustine arm (median not yet reached) compared to the chlorambucil arm (median 78.8 months; HR 0.77 95% CI 0.52-1.12).[2]

A statistically significant difference in overall response rate was demonstrated for bendamustine (68% of 162 patients) compared to chlorambucil (31% of 157 patients; p<0.0001), based on the independent review committee assessments.[1].

Although some qualitative statements regarding the quality of life study accompanying the 02CLLIII study were reported at ASH in 2010 and in the Health Canada review, no data were reported to support the statements.[3,25]

Rates of harms outcomes can be found in Table 2; however, none of the study reports indicated whether any of the differences were statistically different. Of note, more patients in the bendamustine arm than in the chlorambucil arm withdrew due to an adverse event.[1] In addition, 55% of patients in the bendamustine arm experienced a Grade 3 or 4 adverse event compared to 32% of patients in the chlorambucil arm.[26] A higher proportion of patients in the bendamustine arm than in the chlorambucil arm experienced neutropenia (any grade or Grade 3/4), leukopenia (any grade or Grade 3/4), vomiting (any grade), pyrexia (any grade), infection (any grade) or rash (any grade).[1] Tumour lysis syndrome occurred in two patients in the bendamustine arm after the first cycle—neither was fatal and both patients continued treatment. [1]

2.1.3 B) Previously Treated Chronic Lymphocytic Leukemia

Trial Characteristics

Randomized Controlled Trials

One randomized controlled trial was identified that compared bendamustine to fludarabine in patients with Rai stage II-IV or Binet stage B or C relapsed or refractory B-cell CLL.[10,11] A summary of the key trial characteristics can be found in Table 3.

A total of 96 patients were randomized to receive either bendamustine (100 mg/m^2/d on days 1 and 2 every 4 weeks) or to receive fludarabine (25 mg/m^2/d on days 1-5 every 4 weeks). Patient in both arms continued until best response or a maximum of eight cycles.[10] The two treatment arms were balanced for sex, Binet stage, and B symptoms. The median age was 68 years in the bendamustine arm and 69 years in the fludarabine arm.

The study has been reported in only a single abstract report by Medgenberg et al.[10] No information was available on the required sample size, randomization methods, masking of allocation, primary or secondary outcomes, or the statistical methods used in the analysis. Without further information, the quality of this study cannot be determined.

Single Arm Trials

A total of five single-arm trials investigating the efficacy of bendamustine in patients with previously treated CLL were identified.[12-16] A summary of the key characteristics from each trial can be found in Table 3.

Koppler et al enrolled 59 CLL patients who had received at least one prior chemotherapy regimen with Binet stage C or symptomatic stage A or B with active disease.[12] Patients were administered bendamustine 50 mg/m^2/d on days 1-3 plus mitoxantrone 10 mg/m^2 on day 1, every 28 days, up to 4 cycles. The median age was 67 years.

Fischer et al enrolled 83 patients with relapsed or refractory CLL who had received 1-3 prior treatments.[13] Patients were administered bendamustine 70 mg/m^2/d on days 1 and 2 plus rituximab 375 mg/m^2 on day 0 for the first course then 500 mg/m^2 on day 1 for subsequent courses, every 28 days, up to 6 cycles. The median age was 66.5 years.

The remaining three trials enrolled 15 patients or less who had previously treated CLL. Bremer et al administered bendamustine alone (60 mg/m^2/d on days 1-5, every 4 weeks) to 15 patients with previously treated CLL.[14] Weide et al administered bendamustine (80 mg/m^2/d on days 1-3) plus mitoxantrone (10 mg/m^2/d on day 1) plus rituximab (375

mg/m^2 during weeks 2-5) every 35 days to a total of four patients with previously treated CLL.[15] Kath et al administered bendamustine alone (70 years and older: 50 mg/m^2/d on days 1-5; younger than 70 years: 60 mg/m^2/d on days 1-5; every 28 days) to 10 patients with previously treated CLL.[16]

Table 3. Summary of Included Studies in Patients with Previously Treated CLL.[10-16]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Randomized Controlled Trials			
Medgenberg 2009[10,11] Number of study sites: NR Start date: September 2001; Enrolment end date: 2006; Completion: May 2009 Open-label, active control RCT Randomized in a 1:1 ratio (BEN:F) stratification: NR Randomized: n=96 Analysis: n=92 Funded by: WiSP Wissenschaftlicher Service Pharma GmbH	Patients with relapsed or refractory B-CLL requiring treatment after 1 previous systemic regimen (not including F or BEN) Disease stage Rai II-IV or Binet B-C ECOG PS 0-3 Age ≥18 years	Two arms: BEN 100 mg/m^2/d d1,2 i.v., every 4 weeks *Or:* Fludarabine 25 mg/m^2/d d1-5 i.v., every 4 weeks Both treatments until best response or maximum of 8 cycles	Primary Progression-free survival Secondary NR
Single-arm Trials			
Koppler 2012[12] Multicenter study: 16 sites, in Germany Start date: July 2004 Completion date: November 2007 Enrolled: n=59 Analysis, ITT: n=59 Funded by: Mundipharma GmbH, Ribosepharm GmbH, and Lederle	Patients with previously treated B-CLL. Binet stage C or symptomatic A/B and active disease as defined by NCI-WG guidelines. At least 1 prior chemotherapy regimen. ECOG PS 0-2 Age ≥18 years	BEN 50 mg/m^2/d d1-3 + mitoxantrone 10 mg/m^2 d1, every 28 days, up to 4 cycles	Primary Objective response rate Secondary Time to progression Overall survival

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Fischer 2011[13] Multicenter study: 32 sites in Germany Start date: March 2006 Completion date: June 2007 Enrolled: n=83 Analysis, ITT: n=83 Funded by: F. Hoffmann-La Roche and Mundipharma.	Relapsed or refractory[A] CLL in need of treatment according to NCI-WG guidelines. 1-3 prior treatments. Age ≥18 years WHO PS 0-2 Life expectancy ≥12 weeks	BEN 70 mg/m^2/d d1,2 + rituximab 375 mg/m^2 d0 (first course) then 500 mg/m^2 d1 (subsequent courses), every 28 days, up to 6 cycles	Primary Objective response rate Secondary Toxicity Duration of response Event-free survival Minimal residual disease
Bremer 2002[14] Number of sites: NR Start date: 1993 Completion date: 1998 Enrolled: n=102 CLL enrolled: n=15 Funded by: NR	NHL including CLL, MM, immunocytoma, FL, MCL, other lymphomas Binet stage B or C for CLL Relapsed or refractory disease	BEN 60 mg/m^2/d d1-5 i.v., every 4 weeks until complete or partial response. Treatment discontinued if progressive disease. Antiemetic prophylaxis with 8 mg dexamethasone or 50mg of metoclopramide.	Primary NR Outcomes reported Duration of response Overall survival Response
Weide 2002[15] Number of sites: NR Start date: March 1999 Completion date: December 2000 Enrolled: n=20 CLL enrolled: n=4 Funded by: NR	Patients with advanced relapsed or refractory indolent lymphoma or relapsed/refractory CLL Rai stage IV or Binet stage C CLL WHO PS 0-3 Age ≥18 years	BEN 80 mg/m^2/d d1-3 + mitoxantrone 10 mg/m^2/d d1 + rituximab 375 mg/m^2 during weeks 2-5; every 35 days until best response (complete or partial)	Primary NR Outcomes reported Response
Kath 2001[16] Number of sites: NR Start date: May 1995 Completion date: February 2000 Enrolled: n=23 Previously treated CLL enrolled: n=10 Funded by:	B-CLL Rai stage III or IV Previously untreated or relapsed/refactory Age ≥18 years PS ≤2 or life expectancy ≥3 months	Benda 60 mg/m^2/d d1-5 (up to 70 years old) or 50 mg/m^2/d d1-5 (70 years and older), every 28 days. Treatment until complete or best response, progressive disease, unacceptable toxicity, or poor performance status. Routine antimicrobial	Primary NR Outcomes reported Response Overall survival Toxicity

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
		prophylaxis was not given at the start of the trial; however a routine prophylactic treatment with trimethoprim/ sulfamerazine was started in the second half of the study.	

Notes: B-CLL=B-cell chronic lymphocytic leukemia; BEN=bendamustine; ECOG PS=Eastern Cooperative Oncology Group performance status; F=fludarabine; FL=follicular lymphoma; i.v.=intravenous; MCL=mantle cell lymphoma; MM=multiple myeloma; NCI-WG=National Cancer Institute-Working Group; NHL=non-Hodgkin lymphoma; NR=not reported; RCT=randomized controlled trial; WHO PS=World Health Organization performance status.
[A]Refractory CLL defined as no complete or partial response after therapy or progression within 6 months.

Outcome Data and Summary of Outcomes

Randomized Controlled Trials

The analysis reported in the abstract by Medgenberg et al included 92 evaluable patients of 96 randomized patients (bendamustine arm, n=49; fludarabine arm, n=43).[10] The abstract did not report whether this analysis was final. A summary of key efficacy outcomes can be found in Table 4. Key harms outcomes can be found in Table 5.

No significant differences were observed for overall survival (HR=0.82, 95% CI 05.1-1.30, p=0.48) or progression-free survival (HR=0.87, 95% CI 0.59-1.28, p=0.27) for the bendamustine arm compared to the fludarabine arm.[10] Median progression-free survival was 20.0 months in the bendamustine arm compared to 15.6 months in the fludarabine arm with median follow-up times of 44 months and 41 months, respectively.[10] No significant differences in complete or overall response rates were reported by the authors.[10]

Grade 3 or 4 infections occurred in 13% of 49 patients in the bendamustine arm and in 15% of the 43 patients in the fludarabine arm.[10] No further adverse event data were reported.

Table 4. Efficacy outcomes in Trials of Bendamustine in Relapsed or Refractory CLL.[10,12-16]

Study	Interventions	N	OS, mdn (mos)	PFS, mdn (mos)	CR (%)	PR (%)	OR (%)	Follow-up, mdn (mos)
Randomized Controlled Trials								
Medgenberg 2009[10]	B	49	Deaths: 24	20.0	29	NR	78	44
	F	43	Deaths: 28 HR 0.82, 90% CI 0.51-1.30, p=0.48	15.6 HR 0.87, 90% CI 0.59-1.28, p=0.27	10	NR	65	41
Single-arm Trials								
Koppler 2012[12]	B+M	59	27	22	8	42	51	20
Fischer 2011[13]	B+R	78	33.9 95% CI 25.5-42.1	15.2 95% CI 12.5-17.9	9.0	50.0	59.0 95% CI 47.3-70.0	24.0
Bremer 2002[14]	B	15	32	Not reached[A]	6.7	86.7	93.4	NR
Weide 2002[15]	B+M+R	4	NR	NR	25	75	100	NR
Kath 2001[16]	B	10	NR	NR	30	30	60	NR

Notes: B=bendamustine monotherapy; B+M=bendamustine and mitoxantrone; B+R=bendamustine and rituximab;
[A]Estimated from Kaplan-Meier survival curve for progression-free survival in Bremer et al.(ref-Bremer 2002)

Table 5. Grade 3 or 4 Adverse Events Reported in Trials of Bendamustine in Relapsed or Refractory CLL.[10,12-16]

Study	Interventions	N	Leukopenia (%)	Neutropenia (%)	Thrombocytopenia (%)	Anemia (%)	Infection (%)	Tumour lysis syndrome (%)	Hyper-uraemic syndrome (%)
Randomized Controlled Trials									
Megdenberg 2009[10]	B	49	NR	NR	NR	NR	13	NR	NR
	F	43	NR	NR	NR	NR	15	NR	NR
Single-arm Trials									
Koppler 2012[12]	B+M	59	42	NR	12	NR	12	1.7	5
Fischer 2011[13]	B+R	78	NR	23.1	28.2	16.6	12.8	0	NR
Bremer 2002[14]	B	15	NR	NR	NR	NR	NR	NR	NR
Weide 2002[15]	B+M+R	4	NR	NR	NR	NR	NR	NR	NR
Kath 2001[16]	B	10	NR	NR	NR	NR	NR	NR	NR

Notes: B=bendamustine; F=fludarabine; M=mitoxantrone; N=number included in analysis; NR=not reported; R=rituximab.

Single Arm Trials

Koppler et al reported an efficacy and safety analysis that included all 59 enrolled patients.[12] Fischer et al reported an efficacy and safety analysis of 78 patients who received at least one dose of study drug out of 83 enrolled patients.[13] Bremer et al[14], Weide et al[15], and Kath et al[16] all reported separate data for all enrolled patients with previously treated CLL. A summary of key efficacy outcomes can be found in Table 4. Key harms outcomes can be found in Table 5.

Koppler et al reported median overall survival of 27 months in 59 patients who received bendamustine plus mitoxantrone after a median follow-up of 20 months.[12] Median progression-free survival was 22 months for 59 patients who received bendamustine plus mitoxantrone.[12] The rates of complete, partial and overall response were 8%, 42%, and 51%, respectively. Grade 3/4 leukopenia, thrombocytopenia, infection, tumour lysis syndrome, and hyper-uremic syndrome occurred in 42%, 12%, 12%, 1.7%, and 5% of 59 patients.

Fischer et al reported median overall survival of 33.9 months (95% CI 25.5-42.1 months) after a median follow-up of 24.0 months for 78 patients who received bendamustine plus rituximab.[13] Median progression-free survival was 15.2 months (95% CI 12.5-17.9 months).[13] The authors reported similar response rates to those in the Koppler et al study: complete response, 9.0%; partial response, 50.0%; and overall response, 59.0% (95% CI 47.3% to 70.0%). Grade 3/4 neutropenia, thrombocytopenia, anemia, and infection occurred in 23.1%, 28.2%, 16.6%, and 12.8% of 78 patients. No patients experienced tumour lysis syndrome.

Bremer et al reported median overall survival of 32 months and that median progression-free survival had not yet been reached for 15 patients who received bendamustine alone.[14] The amount of follow-up time was not reported. The rates of complete, partial, and overall response were 6.7%, 86.7%, and 93.4%. The authors did not report separate adverse event data for the 15 previously treated CLL patients.

Kath et al also treated patients with bendamustine monotherapy (n=10); however, the authors did not report on overall or progression-free survival.[16] The rates of complete, partial and overall response were 30%, 30%, and 60%. The authors did not report separate data for the 10 previously treated CLL patients.

Weide et al reported data for only four patients (Tables 4 and 5).[15]

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:[26]

- ***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 Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) represents the most common leukemia in the western world, and affects 4.2 people/100 000 population per year. Although the disease has an indolent course and most patients can be safely observed without treatment for many years, cure of this disease is not a reasonable expectation and most affected patients will eventually die as a result of their disease. Young patients may benefit from intensive chemotherapy regimens and possibly from stem cell transplantation, but the majority of patients with CLL are older and so are not considered suitable candidates for these modalities. Older patients have few options and usually receive treatment with single agents, occasionally in combination with rituximab. Most patients will receive multiple lines of chemotherapy and will experience shorter remissions after each cycle as the disease becomes more resistant to treatment. The median survival from the time patients require treatment for CLL is approximately 4 years.

Treatment of Chronic Lymphocytic Leukemia

In broad terms, the two classes of drugs most often used to treat CLL are nucleoside analogues and alkylating agents. These agents were developed in the middle decades of the twentieth century, and have well known safety profiles. The pivotal trial that compared fludarabine and chlorambucil in untreated patients with CLL demonstrated a 6-month improvement in median PFS (20 vs. 14 months, $p<0.001$) with similar overall survival with both agents. Subsequent comparisons in elderly patients failed to demonstrate clinical benefit with fludarabine over chlorambucil, potentially due to increased toxicity in this population. While targeted therapy with small molecule inhibitors has not entered clinical practice, inhibitors of Bruton's tyrosine kinase (PCI-32765) and immunomodulatory drugs such as lenalidomide are in clinical trials currently. The monoclonal anti-CD20 antibody rituximab has been shown to improve overall and progression-free survival when added to regimens commonly used to treat CLL and later generation anti-CD20 antibodies such as ofatumumab and GA-101 have the potential to

change treatment for this disease. As none of these treatments is expected to be curative and all are expected to be associated with significant side effects, there is a need for new drugs to treat CLL in both untreated and previously treated patients.

Bendamustine is a novel bifunctional alkylating agent originally developed in East Germany. Given its similar mechanism of action and side effect profile, chlorambucil is an appropriate comparator in front-line therapy. As many older patients are treated with alkylating agents initially, fludarabine is an appropriate comparator for patients being treated for relapsed disease.

Previously Untreated Patients with CLL

Study 02CLLIII

The systematic review identified a single well-conducted open-label randomized, active control trial comparing bendamustine and chlorambucil in untreated patients with CLL. As the routes of administration differ for these two agents allocation concealment was not possible. Response assessments were made by a central adjudication committee blinded to treatment allocation as a way of avoiding bias. In this study, a total of 319 patients were randomly assigned to receive bendamustine (100 mg/m2/day on days 1 and 2 of a 4-week cycle, n=162) or chlorambucil (0.8 mg/kg, Broca's normal weight in kg, n=157) in a 1:1 ratio for a maximum of six cycles of treatment. Eligible patients were younger than 75 years, had Binet stage B or C CLL and had never received treatment for their disease. Groups were balanced for demographic and disease characteristics. The primary outcomes of interest were overall response rate and progression-free survival. As CLL is a sequential-treatment disease overall survival was examined as a secondary outcome, as were time-to-progression, duration of remission, and rates of adverse events.

This study demonstrated a clinically-significant improvement in progression-free survival among patients treated with bendamustine. This group of patients experienced PFS of 21.6 months, compared with 8.3 months in patients treated with chlorambucil ($p<0.0001$). The overall and complete response rates were significantly higher with bendamustine than they were with chlorambucil (OR 68% vs. 31%, $p<0.0001$; CR 31% vs. 2%, p=NR). Rates of grade 3 / 4 cytopenias were higher among patients treated with bendamustine compared with chlorambucil but withdrawals due to adverse events were infrequent in either arm (11.2% with bendamustine vs. 3.3 with chlorambucil).

Treatment of Patients with Relapsed or Refractory CLL

The systematic review identified a single randomized, active control study comparing bendamustine (100 mg/m2/day on days 1 and 2 of a 4-week cycle, n=49) with fludarabine 25 mg/m2/day on days 1 – 5 of a 4-week cycle, n=43) for patients with Binet stage B or C CLL that had relapsed and required treatment. The study has so far only been reported in abstract form, and so its quality is suspect. Among the deficiencies of this report, the lack of sample size calculation, the inadequate description of prior therapies, and the possible lack of allocation concealment suggest that the design may suffer from serious flaws.

The study failed to demonstrate a difference in overall survival (HR=0.082, 95% CI 0.51-1.30, p=0.48) or progression-free survival (HR=0.87, 95% CI 0.59-1.28, p=0.27) between the two arms. Complete and overall response rates were similar between the two groups, as were rates of serious infection (13% vs. 15% for bendamustine and fludarabine, respectively).

Five single-arm studies of bendamustine in relapsed or refractory CLL were identified. In two of these studies bendamustine was given as a single agent; in one report it was given with mitoxantrone, in another with rituximab and in the fifth report it was given with both of these agents. The administration schedules of bendamustine varied from bendamustine 70 mg/m2/d on days 1 and 2 of a 28-day cycle to bendamustine 60 mg/m2/d on days 1 – 5 of a 28-day cycle. The number of patients treated ranged from 4 – 78 patients and overall response rates ranged from 51 – 100%, with the majority of patients achieving only a partial response (CR rate 6.7 – 30%). Most of these studies do not report harms.

Summary

CLL is a common disease with a long natural history, and patients with this condition receive treatment on an intermittent basis as dictated by the activity and symptoms of their illness. Patient groups indicate that there is a need for more treatment options throughout the course of their disease. While the standard of care for young, fit patients is gradually shifting to moderately intensive combination regimens (i.e. fludarabine-cyclophosphamide-rituximab, FCR) there is no standard of care for older or less fit patients. The results of the systematic review suggest that bendamustine should have a place in the front-line management of patients not considered eligible for FCR. Although bendamustine is clearly active in later phases of the disease, its exact role is impossible to determine from the available literature and it clearly requires further study in previously treated patients.

The review raises several questions for future study:

- The Cumulative Illness Rating Scale (CIRS) score has been used to define eligibility for FCR chemotherapy. It is unclear whether this same scale can be used to define eligibility for bendamustine.
- The impact of biological risk factors such as deletions of 17p or 11q, IgH mutational status and ZAP-70 expression on outcome with bendamustine should be examined in future studies.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall clinical benefit to bendamustine in the treatment of previously-untreated patients with CLL who are not suitable candidates for more intensive regimens. This conclusion is based on the results of one high-quality randomized, active control study comparing bendamustine with chlorambucil (Study 02CLLIII) that demonstrated a clear clinically- and statistically-significant improvement in progression-free survival. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Study 02CLLIII showed a clear benefit to untreated patients with Binet stage B or C CLL who were under the age of 75 and had ECOG performance status 0 – 2.
- While patients with CLL may initially be observed, most eventually require treatment for their disease. Treatment options for older or unfit patients are limited.
- The frequency and severity of adverse events observed with bendamustine are consistent with the adverse events seen with other front-line regimens for CLL. Physicians who treat CLL are comfortable managing patients with grade 3 / 4 cytopenias. Extramedullary toxicity was generally mild.

The Clinical Guidance Panel concluded that there may not be an overall clinical benefit to bendamustine in the treatment of patients with CLL who have relapsed or are refractory to chemotherapy. This conclusion is based on the results of a randomized, active control study (n=92) comparing bendamustine and fludarabine that failed to demonstrate a clear-cut benefit to bendamustine. In reaching this conclusion, the Clinical Guidance Panel considered that:

- Medgenberg et al. demonstrated similar PFS and OR rates when previously-treated patients received bendamustine or fludarabine. This study has only been presented in abstract form and its quality is suspect.
- Several single-arm studies demonstrate that bendamustine has activity in relapsed or refractory CLL, although the small numbers of patients studied and use of other active agents in some of these studies makes drawing firm conclusions difficult.
- As patients with CLL become more extensively treated, myelosuppression is likely to become more pronounced. The adverse event profile associated with the use of bendamustine in heavily pretreated patients requires further study.

3 BACKGROUND CLINICAL INFORMATION

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

3.1 Description of the Condition

With an age-adjusted incidence rate of 4.2 cases/100 000 population, CLL represents the most common leukemia in western countries. CLL is a disease of the elderly, with a median age at diagnosis of 72 years, and its long natural history (median survival from diagnosis is 10+ years) reflects an extended period of watchful waiting in most patients.[17] Treatment is normally reserved for patients with symptomatic disease, as cure is not a realistic goal with current modalities.

A diagnosis of CLL is normally suspected when an unexplained lymphocytosis is noted on blood counts, often done for another reason. Examination of a peripheral blood film demonstrates lymphocytes that are slightly larger than normal lymphocytes, with clumped chromatin and a thin crescent of pale cytoplasm. Prolymphocytes are infrequent, and the presence of > 55% prolymphocytes suggests a diagnosis of B-cell prolymphocytic leukemia.[28] Further testing demonstrates the characteristic immunophenotype of CLL cells, which are typically kappa- or lambda-restricted CD19+, CD5+, CD23+, CD10-, CD11cdim, CD20dim, sIg dim B-cells with absent or dim expression of FMC-7 and CD79a. The 2008 WHO Classification indicates that in the absence of extramedullary involvement there must be $\geq 5 \times 10^9$ cells/L with this phenotype for a diagnosis of CLL to be made.[29] Lymph node infiltration by B-lymphocytes with a CLL phenotype may occur in the absence of peripheral lymphocytosis: when this occurs a diagnosis of small lymphocytic lymphoma (SLL) is made. CLL and SLL are generally considered to be indolent lymphomas based on the mature appearance of the malignant cells and their similarity to other mater B-cell neoplasms. It is important to distinguish CLL from other peripheralizing lymphomas, such as mantle cell lymphoma, follicular lymphoma and marginal zone lymphoma as treatment of these entities differs from that of CLL.

3.2 Accepted Clinical Practice

Two staging systems have been in use for CLL, with a strong preference for the Rai staging system in North America and for the Binet system in Europe (see Table 1).[30,31] Both staging systems reflect the gradual infiltration of CLL target organs, lymph nodes, spleen and bone marrow by disease cells, with higher stages indicating impairment of bone marrow function. Advanced CLL with bone marrow impairment (Rai stage 3 or 4, Binet stage C) has poor prognosis and is a commonly accepted indication for treatment.

A large numbers of factors have been associated with adverse prognosis in CLL. Rapid cell turnover, reflected by a short lymphocyte doubling time, is associated with an aggressive clinical course and shortened survival. Plasma factors indicating rapid turnover including LDH, ß2- microglobulin and thymidine kinase have also been confirmed to reflect adverse prognosis.[32]

Early work examining the status of the immunoglobulin domain of CLL B-cells indicated that CLL may arise from either antigen naïve (without immunoglobulin gene somatic hypermutation) or antigen exposed (with somatic hypermutation) B-cells.[33,34] These two disease subtypes have dramatically divergent clinical courses, with patients with unmutated disease having median survival of 8-9 years, compared with > 20 years for patients with mutated immunoglobulin domains. The cumbersome nature of the technology necessary to

determine the mutation status of IgH domains has limited the clinical utility of this assay and has instead led to the investigation of surrogate markers associated with these changes. Two such markers, CD38 and ZAP-70, have shown an imperfect correlation with mutational status, but nonetheless remain important and relevant prognostic factors in their own rights.[35-37]

Metaphase cytogenetics in CLL is hampered by the low mitotic rate of these cells in tissue culture. Interphase FISH has become a powerful tool in such situations, and allows the detection of clonal cytogenetic abnormalities on fixed tissue without the need to prepare metaphase spreads. Isolated 13q deletions are associated with favourable prognosis while deletions of 11q or 17p are associated with unmutated IgH and poor prognosis. Some studies have suggested that with appropriate treatment the prognosis of del (11q) cases can approach that of more favourable subgroups.[38]

Common indications to treat patients with CLL include the development of cytopenias (Rai stage 3 or 4 disease), bulky lymphadenopathy or splenomegaly, B-symptoms or rapid lymphocyte doubling (< 3 months). Treatment is individualized based on patients' suitability for intensive chemotherapy. The combination of fludarabine, cyclophosphamide and rituximab (FCR) has become the standard of care for young, otherwise healthy patients given the results of a recent German CLL Study Group study showing improved PFS (51.8 vs. 32.8 months, p<0.0001) and OS (87% vs. 83%, p=0.012) with the addition of rituximab to FC.[18] Significant and prolonged neutropenia and leucocytopenia and frequent extramedullary toxicity make this regimen unsuitable for older and less fit individuals.

Patients who are not considered fit enough to receive FCR but who are still suitable to receive treatment may derive benefit from several less intensive regimens. Chlorambucil, an alkylating agent, has been in use for more than 30 years and can be given in daily, weekly, biweekly and monthly schedules. Extramedullary toxicity is generally mild and transient. Other alkylator-based regimens, such as cyclophosphamide and prednisone or CVP have been described in CLL (see Table 7). The nucleoside analog fludarabine was compared with chlorambucil in a seminal phase 3 study showing improved complete response rates and PFS but similar OS.[19] Patients treated with fludarabine in this study had higher rates of severe infection and neutropenia, and the combination of fludarabine and chlorambucil has been associated with unacceptably high rates on severe infection.[20] The addition of monoclonal antibodies to induction regimens for less fit patients is an area of active research, but appears promising in early-phase studies. Novel agents such as lenalidomide[21] and new monoclonal antibodies such as ofatumumab[22] have been evaluated in CLL but have yet to find their place in the therapeutic arsenal for this disease.

Table 6. Accepted staging systems for patients with chronic lymphocytic leukemia.

Staging System	Stage	Definition	Median OS (mo)
Rai	0	Blood/marrow lymphocytosis	126
	1	Lymphadenopathy	92
	2	Splenomegaly	53
	3	Anemia (Hb < 110)	23
	4	Thrombocytopenia (Plt < 100)	20

Staging System	Stage	Definition	Median OS (mo)
Binet	A	< 3 lymph node areas*	128
	B	≥ 3 lymph node areas	47
	C	Anemia (Hb < 100) or thrombocytopenia (Plt < 100)	24

* Lymph node areas for Binet staging are unilateral or bilateral cervical, axillary or inguinal lymph nodes, liver and spleen.

Table 7. Results of selected chemotherapy trials in chronic lymphocytic leukemia.[39-42]

Regimen	Entry Criteria	Response Rate (CR+PR)	Overall Survival
Chlorambucil vs. obs.[33]	Untreated, Stage A	76%	76% vs. 80% (5-year)
Chlorambucil vs. obs.[34]	Untreated, Stage A	68%	75% vs. 82% (5-year)
Chlorambucil vs. COP[35]	Untreated, B or C	59% vs. 61%	44% vs. 43% (5-year)
Chlorambucil vs. ChOP[36]	"Advanced"	89.5% vs. 75%	68% vs. 47% (5-year)

3.3 Evidence-Based Considerations for a Funding Population

In contrast to initial treatment, there is no established treatment for patients with relapsed or refractory disease. While the disease may respond to regimens similar to those used for induction, responses are generally of lesser quality and duration in previously treated patients. CLL that is refractory to both nucleoside analogues and alkylating agents has an especially poor prognosis. Alemtuzumab has been used successfully as a bridge to allogeneic stem cell transplantation in this setting. Responses are generally brief and are frequently associated with opportunistic infection as a result of the intense immunosuppression associated with this agent. While survival from diagnosis in CLL may exceed 10 years, survival from the onset of treatment is only 4 years and contrary to widely held belief, 70% of patients with CLL die of causes related to their disease. New, more effective treatments for patients with this disease are desperately needed.

3.4 Other Patient Populations in Whom the Drug May Be Used

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 Chronic Lymphocytic Leukemia (CLL) and their input is summarized below:

- The Leukemia and Lymphoma Society of Canada
- The CLL Patient Advocacy Group

The Leukemia and Lymphoma Society of Canada conducted an anonymous survey to gather information about patient and caregiver experiences with Chronic Lymphocytic Leukemia (CLL). The survey was divided into four components, including the patient experience with CLL, current therapies used to treat CLL, the caregiver experience, and the patient experience or expectations for bendamustine. Survey respondents provided answers online, by phone, in writing, or in person. Additional information was gathered through printed sources.

The CLL Patient Advocacy Group (CLL PAG) designed and conducted an online survey to gather information about the patient and caregiver experience with CLL and the drug under review. The online survey was promoted on the CLL Patient Advocacy Group website, the CLL Canada website, as well as, various other discussion boards and websites dedicated to CLL. A total of 177 respondents participated in the survey. Due to the rarity of CLL and difficulties in identifying Canadian patients with experience with bendamustine, participation was requested from Canadian patients, as well as, patients from other countries. Of the 177 respondents to the survey, 70 patients were from Canada, 84 patients were from the United States, 9 patients were from Australia, 8 patients were from the United Kingdom, and there was one patient each from Belgium, India, France, Brazil, New Zealand, and Germany. In addition, additional background information on CLL and CLL treatments was gathered from the CLL PAG and CLL Canada websites.

From a patient perspective, additional drug therapies for the treatment of CLL which 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 extend their life and bring about complete remission of the disease, while also allowing them to enjoy a good quality of life. Patients indicate they would be willing to tolerate the side effects of a new therapy, even significant side effects, 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 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 Chronic Lymphocytic Leukemia (CLL)

Patient advocacy group input highlights that CLL is the most commonly diagnosed leukemia in Canada, although it is still considered to be an orphan disease in other countries, such as the United States or in Europe. Input from patients indicates that CLL is generally a disease of the older population, with most patients with CLL typically being diagnosed in their 60's and 70's. However, input from patients also points out that it is possible for CLL to be diagnosed in younger patients as well.

Input from patient advocacy groups indicates that for some patients, CLL is a chronic, slow-progressing cancer, and patients may live for many years before they require any drug treatment, if they even require treatment at all. However, some patients with CLL will progress more quickly and require treatment earlier.

Patients with CLL report that fatigue is one of the most common symptoms experienced and it can have a significant impact upon their quality of life. Patients may be unable to continue with their current workload 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, 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 CLL PAG survey report that fatigue and lack of energy is the most significant symptom of CLL that they deem as being important to control and manage.

Many patients with CLL also report that they experience feelings of depression, stemming from the knowledge that they have an incurable illness with a widely variable lifespan, and the inability to fulfill many life goals due to their lack of energy. Patients also report experiencing feelings of fear and worry, as they are uncertain of their future. Patients with CLL 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. Patients responding to the CLL PAG survey report that depression, stress, and psychological stress are the second-most significant symptoms of CLL that they deem important to control and measure.

Input from the patient advocacy groups also identify that patients with CLL have an increased susceptibility to infections, such as shingles or pneumonia, as a result of having a compromised immune system. Consequently, patients express that they often have to restrict their participation in social groups due to the fear of contracting an illness and often have to restrict any travel plans. Input also reports that many patients avoid long-term planning because they never know how they will feel.

In addition to the symptoms noted above, patients with CLL also indicate they may experience low platelets, enlarged lymph nodes, increased white cell count, night sweats, unexplained fevers, low immunoglobulin levels, aches, pains, enlarged spleen, weight loss and respiratory issues. . Patients responding to the CLL PAG survey also express that it is important to control and manage these symptoms.

4.1.2 Patients' Experiences with Current Therapy for Chronic Lymphocytic leukemia (CLL)

Patient advocacy group input indicates that current treatments for CLL are life-extending, but are not curative. With the treatments that patients receive, they have a period of remission, but the disease does return. Patients report that certain treatments may be repeated, but they usually experience shorter periods of remission due to the development of resistance.

Patients note that CLL is not a cancer that is easier to treat if caught early, therefore many patients with a diagnosis of CLL begin with an active watch and wait approach, where patients 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 many patients are used to the concept that you start treatment right away after you have been 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 CLL, patients indicate there are several different therapies available, including chemotherapy agents such as fludarabine, chlorambucil, or cyclophosphamide, as well as, monoclonal antibodies, such as rituximab. The combination of fludarabine, cyclophosphamide, and rituximab, known as FCR, was noted by patient groups to be the gold standard for the treatment of CLL. However, patient input also pointed out that FCR is quite toxic and can leave patients in a greater immune-compromised state. Other side effects that patients indicate may occur with chemotherapy include hair loss, extreme fatigue, infections, nausea, and anemia. 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 they finish therapy 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 advocacy group input also indicates that some patients, such as those who are younger or high-risk, may have the option of receiving an allogeneic stem cell transplant. In addition, some patients may be eligible to participate in a clinical trial, and this is often a way for patients to receive emerging drug therapies while waiting for their province to fund a drug that has been approved by Health Canada. Unfortunately, patient input highlights that many clinical trials often restrict enrollment to those patients who meet stringent criteria and have access to a cancer center participating in the clinical trial, and therefore, not all patients can access new drug therapies via clinical trials.

Patient input reveals that patients who start to receive treatment for CLL often have to travel to the hospital for therapy administration and physician visits, which can lead to these patients incurring additional financial costs.

Many patients express feelings of frustration that there is currently no standard of practice for CLL in Canada, and the treatment that a patient will receive may depend

upon which province they reside in. In particular, 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.

Patients also express the importance of having additional choices for their treatment. In the CLL PAG survey, a majority of patients responding indicates that it would be very important to have choice in a therapy. In addition, patients feel that more treatment options need to be available for the treatment of CLL, such as bendamustine.

4.1.3 Impact of Chronic Lymphocytic Leukemia and Current Therapy on Caregivers

Patient advocacy group input indicates that the impact of this condition on caregivers can be significant, both prior to the patient receiving treatment and during the treatment itself. Caregivers may experience an emotional, financial and time impacts. Caregivers report that there can be a permanent change in how their household functions once a patient receives a CLL diagnosis.

Caregivers are often 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. In addition, caregivers have to assume the additional costs of providing care, and in particular, they may have to reduce their work hours to help provide care. Patients diagnosed with CLL who have young families are facing an additional burden of finding child care. Caregivers indicate that their social support system is reduced as they choose to stay with the patient who is often times not able to have the same level of social activity as in the past due to fatigue. In addition, caregivers must try to limit the normal activities and interactions of the patient with family and friends to try to prevent the CLL patient from developing infections.

Caregivers also indicate that they worry about the wellbeing of the patient, as well as, the uncertainty of the disease and if it will progress. Caregivers report feelings of anxiety and stress.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with bendamustine (Treanda)

Input from patients without direct experience with bendamustine for CLL indicates that patients with CLL are seeking more treatment options for their condition. Patients are aware that they have an incurable disease and that the currently available treatment options only work for a limited amount of time due to drug resistance and therefore, patients want more choices and rate more treatment options as being very important. In addition, patients want treatment options that will extend

their life and bring about complete remission of the disease, while also allowing them to enjoy a good quality of life. A majority of patients responding to the CLL PAG survey indicate that that when considering bendamustine as a treatment for CLL, it is important to bring about complete remission.

Patients indicate that they would be willing to tolerate the side effects of a new therapy, even significant side effects, 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.

Patients also express a desire to have a treatment option that does 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 were previously treated, they need another treatment option that will not have a decreased efficacy due to resistance.

Input from the Leukemia and Lymphoma Society of Canada indicates feedback was not received from patients currently using bendamustine. Input from CLL PAG indicates that 18 patients who responded to their survey report having direct experience with bendamustine.

Approximately half of patients with direct experience with bendamustine indicate that the infusion schedule was easier to manage with bendamustine in comparison to the administration of other IV treatments for CLL, while the other half of patients indicate that that the infusion schedule was about the same as the administration of other IV treatments for CLL.

When patients with direct experience with bendamustine were asked in the CLL PAG survey which symptoms have shown a great improvement with bendamustine in comparison to other treatments for CLL, eleven of the 14 patients who answered this question report having greater symptomatic improvement with bendamustine in comparison to other treatments. Two patients report having a similar symptomatic improvement, and one patient reports that bendamustine was not effective in treating his/her CLL. When patients were asked in the CLL PAG survey what the effects of bendamustine have been on their CLL, eleven of the 13 patients who answered this question report a positive response to bendamustine with respect to white blood cell counts, and/or a reduction in node size, and/or a reduction in fatigue, whereas two patients report that bendamustine was not effective in treating their CLL.

When patients were asked to rate their quality of life (QoL) on a scale of 1 (low QoL/ severely impacted) to 10 (high Q0L/normal living) while receiving bendamustine, responses were mixed. Fifteen patients with with bendamustine experience responded to this question in which five patients rank their QoL as 8 or higher; six patients rank their QoL between 5 and 7 and four patients ranking their QoL as 3 or 4 while receiving bendamustine. However, a majority of patients responding to the CLL PAG survey indicate that they would consider receiving bendamustine again for that second-line treatment of CLL after receiving it for the first-line treatment.

Overall, most patients in the survey would rank their experience with bendamustine the same as, or better, than other treatments for CLL. A minority of patients would rank their experience with bendamustine as worse than that with other treatments.

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 Chronic Lymphocytic Leukemia (CLL). This input was collected at the outset of the pCODR review.

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, the combination of rituxmab, fludarabine and cyclophosphamide was identified as the main comparator to bendamustine and comparative information between the two treatments with respect to side effect profile or treatment outcomes would be important to know. PAG also identified that there is a potential for bendamustine to be used in other lines of therapy for CLL, such as the relapsed or refractory setting. PAG noted that information on the use of bendamustine in these other lines of therapy (i.e. relapsed/refractory setting) would be useful.

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

5.1 Factors Related to Comparators

PAG recognized that chlorambucil was previously the standard of care for the first-line treatment of CLL when the pivotal trial for bendamustine was designed and as such, was the most appropriate comparator at that time.

PAG noted that the combination of rituximab, fludarabine and cyclophosphamide (FC-R) is the current first-line treatment option for medically fit patients with CLL; however, if there are no comparative trials between bendamustine and this comparator, this may pose as a barrier to implementation of a funding decision for bendamustine. It was noted that rituximab is currently funded in some jurisdictions for this indication. PAG identified that any available comparative data with respect to side effect profile or treatment outcomes for these two treatments (i.e. FC-R and bendamustine) would be helpful. In addition, PAG recognized that bendamustine is a single agent treatment, which would likely be less complicated to administer compared to a multiple drug regimen such as FC-R.

PAG noted that chlorambucil would likely be the other main comparator to bendamustine in situations where FC-R treatment cannot be used.

If it were determined that bendamustine had a favourable efficacy and toxicity profile in relation to other comparators for CLL 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

jurisdictions may see more patients requesting bendamustine than anticipated due to its assumed improved tolerability compared with the FC-R regimen.

Although the Health Canada approved indication for bendamustine is in the first-line setting of CLL, PAG identified that there is potential for use in later lines of therapy, such as the relapsed or refractory setting. PAG noted that information on the use of bendamustine in other lines of therapy would be useful.

5.3 Factors Related to Accessibility

PAG identified several potential accessibility issues with respect to bendamustine treatment. It was noted that bendamustine is administered intravenously and as such, specialized chemotherapy centers would be likely be required for appropriate administration, which would not be required with an oral agent such as chlorambucil. In addition, bendamustine is administered on two consecutive days out of a 28-day cycle. Compared to orally administered chlorambucil, patients will have to travel for treatment and spend two days at specialized treatment centers to receive bendamustine, which may pose as a barrier to funding implementation.

PAG recognized that wastage is a potential concern with bendamustine as it only comes in two different vial formats with no preservative. It was noted that some hospitals may not be willing to administer bendamustine if wastage is thought to be a significant problem as they would not be reimbursed for wastage costs and would have to incur the additional costs of the wasted product.

5.4 Factors Related to Dosing

PAG noted that bendamustine is also indicated for the treatment of indolent non-Hodgkin's lymphoma (iNHL) with a different dosage regimen than that indicated for CLL (i.e. 120mg/m^2 every 21 days for NHL versus 100mg/m^2 every 28 days for CLL). PAG recognized that there may potentially be confusion in dosing between the two different indications which could lead to errors.

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. Although it was noted that toxicity may preclude bendamustine administration in some smaller centers, it was also noted that bendamustine appeared to be well tolerated in the pivotal trial and approximately 90% of patients were given the planned dose of medication.

5.5 Factors Related to Implementation Costs

PAG anticipated that the price of bendamustine would be higher than that of chlorambucil, which would pose as a barrier to the implementation of funding this therapy.

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.

As bendamustine is an intravenously administered product, PAG noted that there would be chemotherapy chair utilization, increased pharmacy preparation time and an increased need for various resources. 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 the allotted five minute waiting period passes.

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 developed 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:

3. Previously untreated chronic lymphocytic leukemia (CLL).
4. CLL that has relapsed following or is refractory to previous therapy.

See Table 8 in Section 6.2.1 for outcomes of interest and appropriate comparators.

Note: Supplemental Questions most relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in section 7.

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. In addition, data on subgroup analyses by age, performance status, or CIRS score for the outcomes of interest were to be included in this review, if available.

Table 8. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Previously untreated CLL				
Published or unpublished RCT	Patients with previously untreated CLL	Bendamustine 60-100 mg/m^2 on days 1 and 2, every 28 days	FC-R Chlor +/- R Cyclo + pred CVP Cyclo+pred+dex +R	**OS** **PFS** **Response** **QOL** Adverse events Neutropenia FN Infection Rash – SJS, TENS Tumour lysis syndrome

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Relapsed or refactory CLL				
Published or unpublished RCT. Or Fully published single-arm trials investigating efficacy of bendamustine. Exclude reports of trials with only a dose-escalation design. Reports of trials with a mixed design† were to be included only if separate data were reported for the cohort of patients who received the study intervention.	Patients with relapsed or refactory CLL	Bendamustine 60-100 mg/m^2 on days 1 and 2, every 28 days	For RCTs: Any treatment approved to treat relapsed or refractory CLL in Canada For single-arm trials: N/A	**OS** **PFS** **Response** **QOL** Adverse events Neutropenia FN Infection Rash – SJS, TENS Tumour lysis syndrome
[Abbreviations] Chlor=chlorambucil; CLL=chronic lymphocytic leukemia; CVP=cyclophosphamide, vincristine; prednisone; cyclo=cyclophophamide; dex=dexamethasone; FC=fludarabine, cyclophosphamide; N/A=not applicable; OS=overall survival; PFS=progression-free survival; pred=prednisone; QOL=quality of life; R=rituximab.				

**Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*
†A mixed design was defined as a trial with a dose-escalation phase followed by an efficacy-determining phase in which the study intervention was administered at the same dose and schedule to all patients (generally the maximum tolerated dose determined in the dose-escalation phase).

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 CLL.

Methodological filters were not applied to limit retrieval to specific trial designs. Retrieval was not limited by publication year. Retrieval was not limited by language.

The search is considered up to date as of September 10, 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:

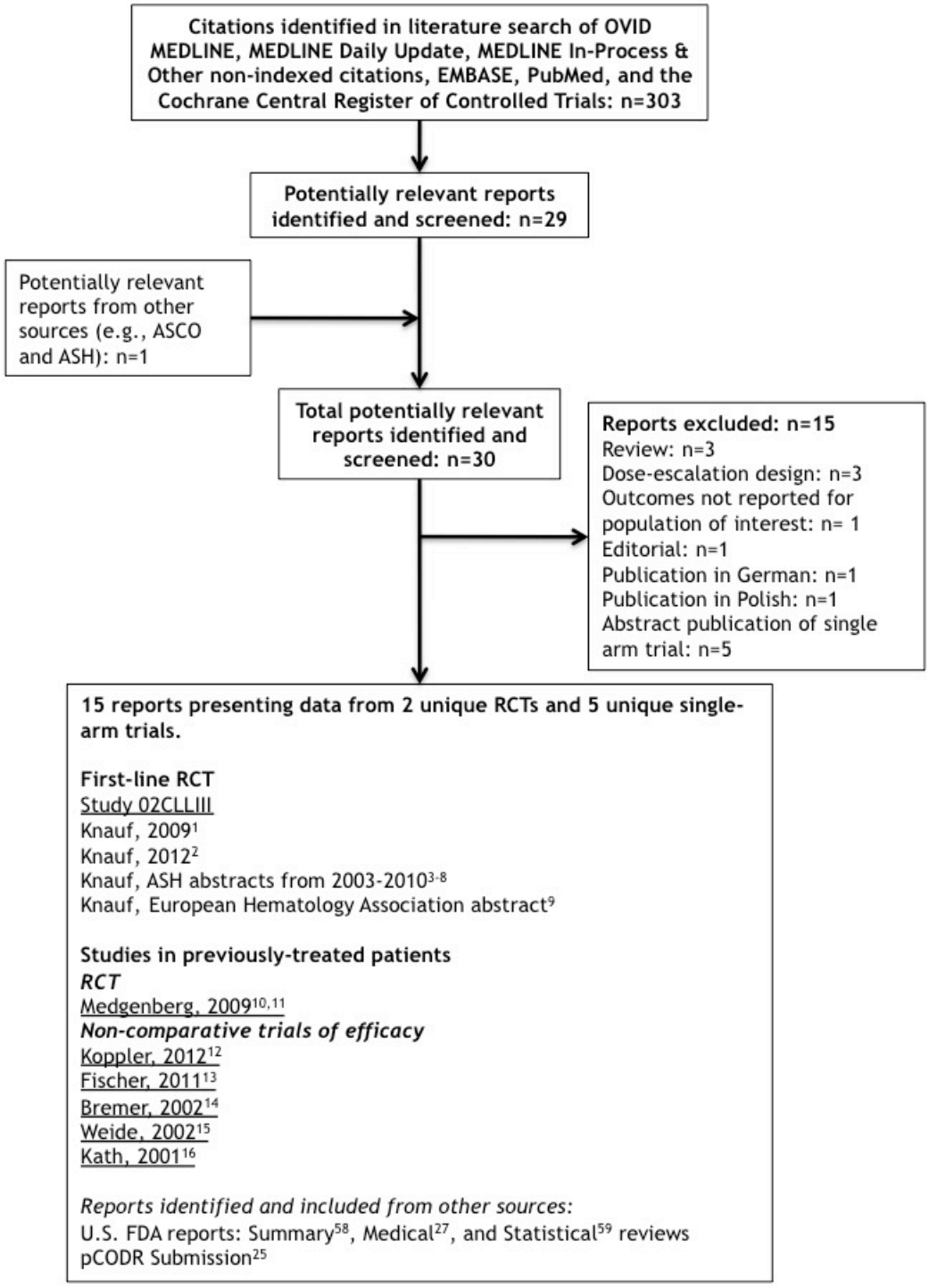
- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions 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 – Previously Untreated Chronic Lymphocytic Leukemia

6.3.1 A) Literature Search Results

Of the 30 potentially relevant reports identified, 15 reports of seven unique studies were included in the pCODR systematic review that investigated the use of bendamustine in patients with CLL[1-10,12-16] and 15 articles were excluded (Figure 1). Studies were excluded because they were reviews[43-45], editorials[46], the outcomes were not reported for the population of interest[47], the trial utilized only a dose-escalation design[48-50], abstract publications of single-arm trials[51-55], or they were published in German[56] or Polish[57]. Of the 15 reports included in the pCODR systematic review, nine reports of one study pertained to the use of bendamustine in patients with previously untreated CLL and were included in this subsection. Three reports on bendamustine in patients with previously untreated CLL from the United States Food and Drug Administration (US FDA) were identified.[27,58,59] Additional information was obtained from the submission by the manufacturer to pCODR.[25] Information on the trial design was also obtained from the ClinicalTrials.gov record.[11]

Figure 1. QUOROM Flow Diagram for Included and Excluded Studies of Bendamustine in CLL.



Note: Additional data related to studies 02CLLIII were also obtained through requests to the Submitter by pCODR.[60]

6.3.2 A) Summary of Included Studies

One randomized trial (study 02CLLIII) was identified that randomized patients with previously untreated CLL to either bendamustine or to chlorambucil.[1-9]

6.2.6.1 A) Detailed Trial Characteristics

a) Trials

Only one study, 02CLLIII, met the inclusion criteria for this section of the review focused on previously untreated CLL (see Table 1).[1] Study 02CLLIII enrolled adult patients less than 75 years of age with previously untreated, Binet stage B or C CLL, confirmed by coexpression of CD5, CD23, and either CD19, CD20, or both. The study was conducted in 45 centers in eight countries in Europe and was industry-sponsored. The study was open-label: neither the patients nor the investigators were blinded to treatment assignment. The primary publication did not report the method used for randomization or masking of treatment allocation; however, the Health Canada review included in the pCODR submission noted that, an appropriate method of randomization was utilized.[25] This was confirmed by the manufacturer at the Checkpoint Meeting.[60]

The study had two co-primary outcomes. The first was overall response rate and the second was progression-free survival. Response assessment was conducted after three cycles of treatment using the criteria of the National Cancer Institute Working Group (NCI-WG) guidelines for CLL and had to be met for at least eight weeks. Patients were monitored at three-month intervals following the last treatment cycle. The original protocol required the investigators to conduct the response evaluations; however, these were inconsistently managed and an independent response assessment committee was established to assess response for all patients included in the third interim analysis as well as the final analysis (protocol change).[27] The final assessment of best response was conducted in a blinded fashion by the independent response assessment committee and classified as complete response, partial response, partial response with nodular involvement, stable disease, or progressive disease based on the NCI-WG criteria.[1] The definition of progression-free survival was not reported in the primary publication[1]; however, the FDA medical and statistical reviews[27,59] and the Product Monograph[26] reported that progression-free survival was defined as the time from randomization to progressive disease or death from any cause. Secondary outcomes included time-to-progression, duration of remission, overall survival, rate of infections, and adverse events.

The 02CLLIII study investigators assumed overall response rates of 60% for the bendamustine arm and 30% for the chlorambucil arm, and median progression-free survival of 20 months in the bendamustine arm and 14 months in the chlorambucil arm. To obtain a power of 80% with a 2-tail test at alpha=0.05, 42 patients per arm would be required for overall response and 326 patients total for progression-free survival. The sample size for a fixed sample design was estimated to be 350 patients.[1] The study investigators used a five-stage adaptive group sequential design with Pocock cut-offs of alpha=0.16, with four planned interim analyses. At each interim analysis, overall response rate was tested first, and if significant, progression-free survival was then tested. At the second analysis, the prespecified stopping criteria had been reached; however, it was recommended that the study continue until 300 patients had been enrolled with no further interim analyses. The third interim analysis was conducted after 305 had been enrolled. The

Independent Data Monitoring Committee recommended that patient recruitment be stopped and a final analysis be conducted. Enrolment ceased in November 2006 with 319 patients enrolled.

Overall response was analyzed by Fisher's exact test, stratified by Binet stage.[1] Progression-free survival was analyzed by the log-rank test stratified by Binet stage and combined across study groups, as described by Lehmacher and Wassmer.[59] Kaplan-Meier curves were used to estimate progression-free survival statistics.

b) Populations

A total of 162 and 157 patients were randomized to bendamustine and chlorambucil, respectively. No notable differences in baseline patient characteristics were observed between the two treatment groups (see Table 9).

Table 9. Baseline Patient Characteristics in Study 02CLLIII[1]

Characteristic	Bendamustine	Chlorambucil
n	162	157
Sex (%)		
Female	37.0	39.5
Male	63.0	60.5
WHO PS (%)		
Missing	1.9	3.2
0	69.8	65.0
1	26.5	28.7
2	1.9	3.2
Age (years)		
Mean	63.0	63.6
Standard deviation	7.5	8.8
Median	63.0	66.0
Minimum-maximum	45.0-77.0	35.0-78.0
Binet stage (%)		
B	71.6	70.7
C	28.4	29.3
B symptoms (%)		
Yes	49.4	50.3
No	50.0	47.1
Unknown	0.6	2.5
Lactate dehydrogenase (%)		
Normal	51.9	51.0
Out of normal ranges	45.1	42.0
Not done	3.1	3.8
Time from initial diagnosis to enrolment (months)		
Mean	18.8	24.6
Standard deviation	32.3	33.9

Notes: n=number of patients randomized; WHO PS=World Health Organization performance status.

c) Interventions

One hundred sixty-two patients were randomized to receive bendamustine at a dose of 100 mg/m^2/d on days 1 and 2 of a 4-week cycle. One hundred fifty-seven patients were randomized to receive chlorambucil at a dose of 0.8 mg/kg (Broca's normal weight in kg: body weight being the height of patient in centimetres minus 100) on days 1 and 15 of a 4-week cycle. In individual cases the doses of chlorambucil could be divided on days 1 to 2 and days 15 to 16.[1]

Patients were assessed for response at three weeks. Patients with no change were allowed to receive additional cycles at the discretion of the investigator to a maximum of 6 cycles. Patients with complete response or partial response received additional cycles up to a maximum of 6 cycles. Patients with progressive disease were withdrawn from the study.[1]

Treatment was interrupted if platelet counts <20x10^9/L, hemoglobin counts <7 g/dL, or the absolute neutrophil counts <0.5x10^9/L. Doses were modified according to the NCI-WG guidelines if hematologic toxicities developed. For Common Toxicity Criteria grade 3 nonhematologic toxicities other than nausea and vomiting or alopecia, the dose was reduced by 50% or the patient withdrawn from the study at the invesigator's discretion. If any grade 4 toxicity developed, the patient was withdrawn.[1]

The median number of treatment cycles was six in both treatment arms. The mean number of cycles per patient was 4.9 cycles (standard deviation, 1.7) in both the bendamustine arm and the chlorambucil arm. At least one dose reduction was required in 54 (34%) of patients in the bendamustine arm and in 46 (31%) of patients in the chlorambucil arm. The primary reason for dose reductions in both treatment groups were neutropenia and thrombocytopenia. Adherence to the dosing schedule was high with 90% of the planned bendamustine dose and 95% of the planned chlorambucil dose administered.[1]

d) Patient Disposition

The primary publication by Knauf et al 2009, reported that of 319 randomized patients, seven were not treated (six in the chlorambucil arm and one in the bendamustine arm).[1] That publication reported no further data on patient disposition.

The pCODR submission provided details of patient disposition for all 319 randomized patients (see Table 10).[25]

Table 10. Patient Disposition in Study 02CLLIII Obtained From pCODR Submission.[25]

	Bendamustine (n)	Chlorambucil (n)
N Randomized	162	157
Received allocated intervention	161	151
Discontinued intervention	39	23
Protocol violation	1	1
Unacceptable toxicity	15	5
Investigator's decision	2	5
Subject refusal	9	6
Lack of compliance	1	1
Death	1	3
Risk/benefit assessment no longer acceptable	3	0
Other reasons	7	2

	Bendamustine (n)	Chlorambucil (n)
Lost to follow-up	0	1

Notes: n=number of patients.

The U.S. FDA Medical Review noted that eight patients in the bendamustine arm and three in the chlorambucil arm were lacking a phenotypic confirmation of diagnosis.[27] Out of all 319 randomized patients, one patient in the bendamustine arm and six patients in the chlorambucil arm did not receive the allocated intervention.[25] The disposition of the seven patients who did not receive the allocated intervention is not publicly available.

e) Limitations/Sources of Bias

Neither the investigators nor the patients were blinded to treatment assignment, likely due to the different routes of administration of the two agents, bendamustine (i.v.) and chlorambucil (oral). Importantly, the investigators amended the trial protocol to include blinded tumour assessments conducted by an independent tumour assessment committee[1], therefore the risk of bias in the outcome assessments (response and progression-free survival) is likely low.

A total of up to 18 patients had protocol violations: eleven patients did not meet the diagnostic confirmation required in the protocol, and seven patients did not receive the allocated intervention. As these patients represent, at most, 5.6% of the study population, they most likely had little impact on the study results.

6.2.6.2 A) Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

A total of 319 patients (162 patients in the bendamustine arm and 157 patients in the chlorambucil arm) were included in the ITT efficacy analysis.[1] Table 2 summarizes the key efficacy outcomes for the 02CLLIII Study.

Overall Survival

In the initial 2009 full publication, Knauf et al reported that additional follow-up time would be required in order to comment on overall survival.[1] A total of 72 of 319 patients (31 in the bendamustine arm and 41 in the chlorambucil arm) died during follow-up. Median follow-up was 35 months (minimum-maximum, 1-68 months).[1] Death due to CLL was reported for 13 patients in the bendamustine arm and 21 patients in the chlorambucil arm.

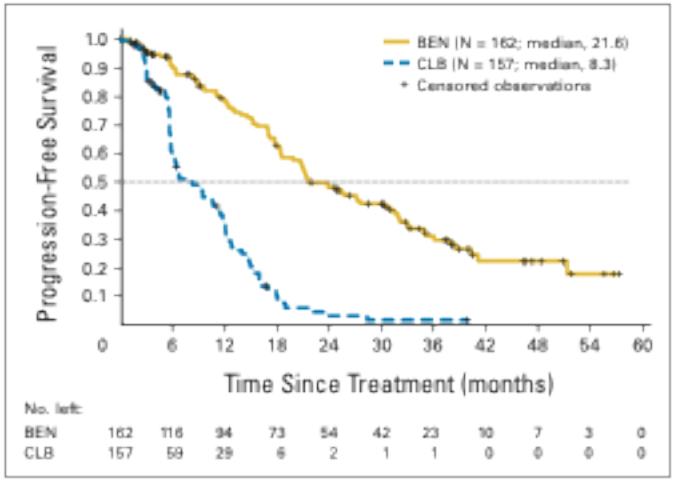
In 2012, Knauf et al published updated results from the 02CLLIII study.[2] The analysis was conducted in May 2010 on the final intent-to-treat population (N=319). After a median follow-up of 54 months, a total of 132 patients had died, with the date of death unknown for 26 patients (bendamustine, n=15; chlorambucil, n=11). The date of death for the 26 patients was censored using the date of the last contact upon which the patient was last documented to be alive. No statistically significant difference in overall survival was observed between the two treatment groups: median overall survival had not yet been reached in the bendamustine group and was 78.8 months in the chlorambucil group, with a HR of 0.77 (95% CI 0.52-1.12).[2] In addition, the authors reported no statistically significant differences in overall survival for the bendamustine

arm compared to the chlorambucil arm for the following subgroup analyses: Binet stage B or C, age (>65 years or ≤65 years), and response (objective response, stable disease or progressive disease).[2]

Progression-free Survival

Median progression-free survival was 21.6 months in the bendamustine arm compared to 8.3 months in the chlorambucil arm (p<0.0001); no hazard ratio data were reported in the primary publication.[1] However, the Product Monograph reported a hazard ratio (HR) of 0.26, p<0.0001 for the progression-free survival analysis.[25] See Figure 2 for the Kaplan-Meier survival curves for progression-free survival reported in the primary publication. There were a total of [redacted] events ([redacted] in the bendamustine arm and [redacted] in the chlorambucil arm) at the date of the analysis.[25] (*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.)*

Figure 2. Progression-free Survival Based on the Independent Tumour Assessment and as Reported in the Primary Publication of Study 02CLLIII.[1]



Knauf et al also reported that the difference in progression-free survival was observed in the subgroup of patients with Binet stage B (bendamustine arm, median 21.4 months vs. chlorambucil arm, median 9.0 months) and Binet stage C (benamustine, median 25.4 months vs. chlorambucil, 6.3 months), although no p-values or hazard ratios were reported.[1] A 2009 ASH abstract reported by Knauf et al noted that a consistent effect in favour of bendamustine compared to chlorambucil was observed for progression-free survival in both Binet stage B and C disease, and in patients older than 65 years and in those younger than 65 years.[4] No data were reported.

A sensitivity analysis of progression-free survival was conducted using a computer algorithm to rigorously apply the NCI-WG criteria to the entire data study set.[27,59] Progression-free survival based on this analysis resulted in a median progression-free survival of 17.6 months in the bendamustine arm compared to 5.7 months in the chlorambucil arm, HR=0.269, 95% CI 0.169 to 0.428, p<0.0001.[27,59]

Knauf et al reported that the progression-free survival analysis was relatively unchanged in the May 2010 analysis from the original final analysis.[2] Median progression-free survival was 21.2 months in the bendamustine arm compared to 8.8 months in the chlorambucil arm (HR adjusted for Binet stage was 0.35, 95% CI 0.27-0.46; p<0.0001).[2]

Response

The overall response rate was statistically significantly different for bendamustine compared to chlorambucil (68% vs. 31%; p<0.0001).[1] Higher rates for complete response and nodular partial response were observed in the bendamustine arm than in the chlorambucil arm (no-p-values were reported; see Table 11).

Table 11. Proportion of Patients with Response in Study 02CLLIII.[1]

Response Type	Binet Stage B		Binet Stage C		Total	
	BEN	CLB	BEN	CLB	BEN	CLB
N rand	116	111	46	46	162	157
Response Rate by Independent Tumour Assessment (%)						
CR	35	3	20	0	31	2
nPR	12	4	7	0	11	3
OR	71	34	61	22	68*	31*
Response Rate by Computer Algorithm (%)						
CR	NR	NR	NR	NR	9	<1
OR	NR	NR	NR	NR	68*	32*

Notes: BEN=bendamustine; CLB=chlorambucil; CR=complete response; N=number of patients; nPR=nodular partial response; NR=not reported; OR=overall response; rand=randomized.
*Statistically significant difference, p<0.0001.

A sensitivity analysis of response rates was conducted using a computer algorithm to apply the NCI-WG criteria for response. The analysis led to almost no change in the rates of overall response; however, the rate of complete response decreased from 31% to only 9% in the bendamustine arm.[26] The most common reason for downgrading of a complete response was a missing, indeterminate, or premature bone marrow assessment.

Knauf et al reported in abstract for that the overall response rate for patients aged less than 65 years was not statistically significantly different than patients aged more than 65 years: bendamustine arm, 71.6% vs. 63.5%; p>0.3; chlorambucil arm, 28.4% vs. 32.5%; p>0.6.[4]

Quality of Life

Quality of life was not reported in detail.[1] The Health Canada review within the pCODR submission[25] and an ASH abstract reported by Knauf et al[3] reported some quality of life details regarding study 02CLLIII.

Quality of life was measured using the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-30 instrument.

[redacted]

[redacted] (*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.)* No data were reported.

Knauf et al[3] reported that no differences in baseline quality of life scores were observed between the treatment arms and that after completion of study treatment, no differences were observed with respect to physical, social, emotional, and cognitive functioning. Self-assessment of global health status showed no differences. No data were reported.

Harms Outcomes

The safety population includes all 312 treated patients (161 patients in the bendamustine arm and 151 patients in the chlorambucil arm).[1] Table 2 summarizes the key harms outcomes.

Hematological adverse events can be found in Table 12. The rates of any grade and grade 3/4 neutropenia, anemia, leucopenia, and lymphopenia were all higher in the bendamustine arm than in the chlorambucil arm. It was not reported whether those differences were statistically significant. G-CSF was used at the discretion of the investigator in 23 of 783 (2.9%) bendamustine cycles and in 2 of 733 (0.3%) chlorambucil cycles.[1] Erythropoietin was administered in 0.5% of bendamustine cycles and in 0.3% of chlorambucil cycles.

Table 12. Proportion of Patients with Hematological Adverse Events in Study 02CLLIII.[1]

Intervention	n	Neutropenia		Thrombocytopenia		Anemia		Leukopenia		Lymphopenia	
		any	G 3/4	any	G 3/4	any	G 3/4	any	G 3/4	any	G 3/4
BEN	161	27.3	23.0	24.8	11.8	21.7	2.5	17.4	14.3	6.2	6.2
CLB	151	13.9	10.6	20.5	7.9	13.9	0	3.3	1.3	0.7	0

Notes: BEN=bendamustine; CLB=chlorambucil; n=number of patients.

The rates of non-hematological adverse events of any grade that occurred in more than 10% of patients can be found in Table 13. Eight-nine percent of patients in the bendamustine arm and 81% of patients in the chlorambucil arm experienced at least one adverse event of any Grade.[1] The rates of nausea, vomiting, pyrexia, rash and infections were higher in the bendamustine arm than in the chlorambucil arm. Rash and infection were included as they were identified a priori in the pCODR clinical guidance report review protocol as adverse events of interest. The rates of grade 3 or 4 non-hematological adverse events were similar in both treatment arms (see Table 14). Of note, 55% of patients in the bendamustine arm experienced at least one Grade 3 or 4 adverse event compared to 32% of patients in the chlorambucil arm (see Table 2); however, no information is available on whether the difference is statistically significant.[26]

Table 13. Proportion of Patients with Non-Hematological Adverse Events of Any Grade in Study 02CLLIII.[1]

Intervention	n	Nausea	Vomiting	Pyrexia	Rash	Nasopharyngitis	Infection
BEN	161	19.3	15.5	24.8	9.3	6.8	6.2
CLB	151	13.9	6.6	5.3	4.6	7.3	1.3

Notes: BEN=bendamustine; CLB=chlorambucil; n=number of patients.

Table 14. Proportion of Patients with Grade 3 or 4 Non-Hematological Adverse Events in Study 02CLLIII.[1]

Intervention	N	Nausea	Vomiting	Diarrhea	Pyrexia	Fatigue	Hyper-sensitivity	Infection	Hyper-uricemia	Cough	Rash
BEN	161	0.6	1.2	1.2	1.9	1.2	1.2	1.9	1.9	0.6	2.5
CLB	151	0.7	0	0	1.3	0	0	0	0	0.7	2.0

Notes: BEN=bendamustine; CLB=chlorambucil; n=number of patients.

Tumour lysis syndrome occurred in two patients in the bendamustine arms after the first cycle. Neither was fatal and both patients continued treatment. [1-9]

The rates of febrile neutropenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis were not reported in the publicly available literature. The manufacturer indicated that no events were reported for Stevens-Johnson syndrome or toxic epidermal necrolysis.[60] The manufacturer also indicated that febrile neutropenia, defined as pyrexia (any grade) coincident with a period of grade 3 or 4 neutropenia without clinical or microbiological documentation of infection, occurred in [redacted] ([redacted]) in the chlorambucil arm and in [redacted] ([redacted]) in the bendamustine arm.[60] (*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.)*

The U.S. FDA medical review reported that four patients died within 30 days of taking the study drug, one patient in the bendamustine arm and three in the chlorambucil arm.[27] The review noted that the one death in the bendamustine arm was unlikely due to bendamustine.

6.3 B) Results – Previously Treated Chronic Lymphocytic Leukemia

6.3.1B) Literature Search Results

Of the 30 potentially relevant reports identified, 15 reports of seven unique studies were included in the pCODR systematic review that investigated the use of bendamustine in patients with CLL[1-10,12-16] and 15 articles were excluded (Figure 1). Studies were excluded because they were reviews[43-45], editorials[46], the outcomes were not reported for the population of interest[47], the trial utilized only a dose-escalation design[48-50], abstract publications of single-arm trials[51-55], or they were published in German[56] or Polish[57]. Of the 15 reports included in the pCODR systematic review, six reports of six studies pertained to the use of bendamustine in patients with previously treated CLL and were included in this subsection.

6.3.2 B) Summary of Included Studies

One open-label randomized trial[10] and five single-arm trials investigating the efficacy of bendamustine[12-16] in patients with previously treated CLL.

6.3.2.1 B) Detailed Trial Characteristics

a) Trials

Randomized Controlled Trials

Medgenberg et al reported, in abstract form only, a randomized controlled trial of bendamustine compared to fludarabine in patients with relapsed or refractory B-cell CLL.[10] Additional information was obtained from the ClinicalTrials.gov record.[11] The study included patients with Rai stage II-IV or Binet stage B or C disease. Patients had to have ECOG performance status of 3 or better and be 18 years of age or older. The randomization method and masking of treatment allocation appeared appropriate; however, information was limited. The primary outcome of the study was progression-free survival. No secondary outcomes were reported. The study sample size requirement was not provided, and the abstract publication did not report whether the analysis was final or interim. Table 3 summarized the key trial characteristics.

Single-arm Trials

Five single-arm trials investigating the efficacy of bendamustine in patients with previously treated CLL were identified.[12-16] Koppler 2012 and Fischer 2011 reported the two largest trials of bendamustine in patients with relapsed or refractory CLL (Table 3).[12,13] Koppler et al enrolled patients with relapsed or refractory CLL with Binet stage C or A/B with active disease as defined by NCI-WG criteria.[12] Patients received a regimen including bendamustine and mitoxantrone (Table 3). Fischer et al enrolled patients with relapsed or refractory CLL requiring treatment as per NCI-WG guidelines.[13] Patients received a regimen including bendamustine and rituximab (Table 3). The primary outcome in both trials was the objective response rate.

Koppler et al reported that the aim of the study was to improve response rates for bendamustine and mitoxantrone from 30% to 50%.[12] With an alpha of 5% and power of 80%, 60 patients (with 27 overall responses) would be required to reject the null hypothesis. Response was assessed according to NCI-WG criteria. Overall survival was measured from the first day of treatment until death.

Fischer et al reported that the study was designed using a Simon two-stage optimal design, with alpha of 5% and power of 90% to detect an improvement in response rate from 50% to 70%.[13] The authors did not report the required sample size. The final analysis was intention-to-treat, defined

as all patients who received at least one dose of study drug. Objective response was assessed according to NCI-WG criteria.

The three remaining trials investigated bendamustine in patients with relapsed or refractory CLL in addition to other indications.[14-16] All three trials were small with sample sizes of the subgroup with relapsed or refractory CLL ranging from 4 patients to 15 patients (Table 3). Kath et al[16] and Bremer et al[14] both investigated the use of bendamustine monotherapy. Weide et al investigated the use of bendamustine in combination with mitoxantrone and rituximab.[15] None of the three studies reported the primary or secondary outcomes; however, response outcomes were reported in all three trials.

b) Populations

Randomized Controlled Trials

A total of 96 patients were randomized in the RCT reported by Medgenberg et al, with 92 eligible for the analysis (49 in the bendamustine arm and 43 in the fludarabine arm).[10] Table 12 provides details of the patient characteristics in the Medgenberg RCT. The two treatment arms appeared to be balanced on age, sex, Binet stage, B symptoms, and bulky disease. The median age was 68 years for the 49 patients analyzed in the bendamustine arm and 69 years for the 43 patients analyzed in the fludarabine arm. First-line treatment consisted of either chlorambucil or the Knopse regimen in 96% of all randomized patients.[10]

Table 15. Patient characteristics in Medgenberg RCT and five single-arm studies.[10,12-16]

	RCT		Single-arm studies				
	Medgenberg 2009 RCT[10]		Koppler 2012[12]	Fischer 2011[13]	Bremer 2002[14]	Weide 2002[15]	Kath 2001[16]
Interventions	**BEN**	**F**	**BEN+MTX**	**B+R**	**BEN**	**BEN+MTX+R**	**BEN**
N	49	43	59	78	15	4	10
Age, mdn	68 years	69 years	67 years	66.5 years	72 years	70 years	60 years
Sex							
Male	63%	63%	70%	65.4%	53.3%	-	50%
Female	37%	37%	30%	34.6%	46.7%	-	50%
Binet stage							Rai:
A	-	-	3%	18.7%	-	0	III: 20%
B	45%	51%	44%	32.1%	-	0	IV: 80%
C	55%	49%	53%	48.0%	-	100%	
B symptoms	41%	38%	-	35.1%	-	-	-
Bulky disease	11%	14%	-	-	-	-	-
PS			ECOG	WHO			
0			25%	42.3%	-	-	-
1			63%	51.3%	-	-	-
2			12%	2.6%	-	-	-
Number of prior regimens				Mdn: 2	Mdn: 5		
1	-	-	39%	46.2%	-	-	40%
2			42%	28.2%	-	-	30%
>2			19%	23.1%	-	-	30%
Prior regimens							
CLB	-	-	75%	-	-	75%	90%
F			42%	80.8%	-	25%	20%
BEN			20%	-	-	0	10%
CHOP/CVP-like			12%	-	-	50%	50%
Other			15%	-	-	50%	20%

Notes: BEN=bendamustine; CHOP=cyclophosphamide, doxorubicin, vincristine, prednisone; CLB=chlorambucil; CVP=cyclophosphamide, vincristine, prednisone; F=fludarabine; mdn=median; MTX=mitoxantrone; PS=performance status; R=rituximab.

Single-arm Trials

Table 15 contains several of the key patient characteristics for patients enrolled in the five single-arm trials investigating bendamustine in relapsed or refractory CLL. The median age ranged from 60 years to 72 years (Table 10), with the two larger trials reporting median age of 67 years in the bendamustine and mitoxantrone trial reported by Koppler et al[12] and a median age of 66.5 years in the bendamustine and rituximab trial reported by Fischer et al.[13] Koppler et al reported that 20% of 59 had previously received bendamustine, 75% had previously received chlorambucil, 42% had previously received fludarabine, and 12% had previously received cyclophosphamide-vincristine-prednisone or a CHOP-like regimen.[12]

c) Interventions

Randomized Controlled Trials

Medgenberg et al randomized 96 patients to receive bendamustine 100 mg/m^2/d i.v. on days 1 and 2, every 4 weeks or to receive fludarabine 25 mg/m^2/d i.v. on days 1 to 5, every 4 weeks.[10] Patients continued treatment until best response or a maximum of 8 cycles. The authors did not report the number of patients randomized to each arm; however, they did report the number who were randomized and eligible for the analysis: 49 patients in the bendamustine arm and 43 patients in the fludarabine arm.[10] Approximately half of the patients in each treatment arm received six or more cycles of therapy. No further details were reported.

Single-arm Trials

The details of the treatment interventions in the single-arm trials can be found in Table 12. Koppler et al administered bendamustine plus mitoxantrone to 59 patients with relapsed or refractory CLL.[12] Fischer et al administered bendamustine plus rituximab to 83 patients with relapsed or refractory CLL.[13] Bremer et al[14] and Kath et al[16] administered bendamustine monotherapy to 15 and 10 patients with relapsed or refractory CLL. Finally, Weide et al administered bendamustine plus mitoxantrone plus rituximab to patients with relapsed or refractory CLL.[15]

Koppler et al did not report further information on interventions.[12]

Fischer et al reported that a median number of six treatment courses were administered.[13] A total of 44 of 78 patients received the full six courses of therapy and 76.9% of patients received at least three courses. A total of 49 patients (62.8%) received prophylactic antibiotics. G-CSF was administered in 10 patients (12.8%). Dose reductions of either study drug by more than 10% of the planned dose were administered in 29 patients (37.2%). Eighteen patients (23.1%) had a reduction of bendamustine alone, five patients (6.4%) both bendamustine and rituximab, and 19 patients (24.4%) rituximab alone.

d) Patient Disposition

Randomized Controlled Trials

Medgenberg et al reported that 96 patients were randomized with 92 patients included in the reported analysis, with 49 in the bendamustine arm and 43 in the fludarabine arm.[10] No further information is reported regarding the disposition of patients in the RCT of bendamustine compared to fludarabine.

Single-arm Trials

Koppler et al enrolled 59 patients in the bendamustine plus mitoxantrone trial and included all patients in the reported analysis. No further data regarding patient disposition was reported.[12]

Fischer et al enrolled 83 patients in the bendamustine plus rituximab trial.[13] Five patients were excluded from the trial due to missing informed consent (n=3), or diagnosis other than CLL (n=2). The ITT analysis for efficacy and safety included 78 patients. Treatment was discontinued early in 34 patients (43.6%) as a result of withdrawal of consent (n=9), toxicity (n=15), progressive disease (n=8), or other reasons (n=2). In seven patients no response assessment was performed because of early death (n=4), withdrawal of consent after first course of therapy (n=2) or loss to follow-up (n=1).

e) Limitations/Sources of Bias

Randomized Controlled Trials

The Medgenberg et al study has only been published in abstract form and very little information with respect to the trial's quality is available.[10] Without this information, it is not possible to determine the quality of the study.

Single-arm Trials

Single-arm trials are not designed to allow for comparisons between different treatment regimens. Single-arm trials are instead designed to determine if an agent or regimen demonstrates an improvement in an efficacy outcome with respect to an expected estimate (based on best current therapy). That result is used to determine if the agent or regimen should be tested in the setting of a randomized controlled trial.

Single-arm trials can be useful in estimating the size of the treatment effect; however, in a general sense, smaller sample sizes will lead to greater uncertainty around the estimate of the effect. Therefore, trials with larger sample sizes generally provide a better estimate of the treatment effect than trials with very small sample sizes. Given the small sample sizes in the trials reported by Bremer et al[14], Weide et al[15], and Kath et al[16], any estimates of the treatment effect should be interpreted with caution.

6.3.2.2 B) Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Efficacy outcomes can be found in Table 4 for all trials of bendamustine in patients with relapsed or refractory CLL.

Randomized Controlled Trials

Overall Survival

Medgenberg et al reported that 24 patients in the bendamustine arm and 28 patients in the fludarabine arm have died after a median follow-up of 44 months an 41 months, respectively (HR 0.82, 90% CI 0.51 to 1.30; p=0.48).[10] No further data on overall survival were reported.

Progression-free Survival

After a median follow-up of approximately three years, 79 events were recorded, with no statistically significant difference observed for progression-free survival. The median progression-free survival was 20.0 months in the bendamustine arm and 15.6 months in the fludarabine arm (HR=0.87, 90% CI 0.59-1.28; p=0.27).[10]

Response

The objective response rate was 78% of 49 patients in the bendamustine arm compared to 65% of 43 patients in the fludarabine arm.[10] The authors did not report whether the difference was statistically significant nor did they report how response was evaluated. The complete response rates were 29% in the bendamustine arm and 10% in the fludarabine arm.

Single-arm Trials

Overall Survival

Koppler et al reported for 59 patients who received a combination of bendamustine and mitoxantrone, a median overall survival of 27 months after a median follow-up of 20 months.[12]

Fischer et al reported, for 78 patients who received combination therapy with bendamustine and rituximab, a median overall survival of 33.9 months (95% CI 25.5 to 42.1 months) after a median follow-up of 24.0 months.[13] Fischer et al also reported median overall survival for patients older than 70 years of age and for those 70 years or younger. For the 46 patients aged 70 years or younger, median overall survival was 33.9 months while for the 28 patients older than 70 years of age, median overall survival was not yet reached. The authors reported no statistically significant difference between the two subgroups with respect to overall survival (p=0.9).

Bremer et al reported median overall survival of 32 months for 15 patients who received bendamustine monotherapy.[14] Median follow-up was not reported.

The remaining trials did not report data on overall survival.[15,16]

Progression-free Survival

Koppler et al reported median progression-free survival of 22 months for 59 patients who received bendamusine and mitoxantrone (Table 11).[12]

Fischer et al reported median progression-free survival of 15.2 months (95% CI 12.5-17.9 months) in 78 patients who received bendamustine and rituximab.[13] The authors also reported that median progression-free survival was not statistically significantly different for patients aged older than 70 years (17.0 months) compared to patients 70 years or younger (14.7 months, p=0.9).

Bremer et al reported that median progression-free survival was not yet reached for 15 patients who received bendamustine monotherapy.[14] Data on patient follow-up were not reported.

The remaining trials did not report on progression-free survival.[15,16]

Response

Koppler et al reported an objective response rate of 51% of 59 patients who received bendamustine and mitoxantrone and a complete response of 8%.[12]

Fischer et al reported an objective response rate of 59.0% of 78 patients (95% CI 47.3%-70.0%) who received bendamustine and rituximab and a complete response rate of 9.0%.[13]

Bremer et al and Kath et al reported overall response rates of 93.4% of 15 patients and 60% of 10 patients who received bendamustine monotherapy.[14] Complete response rates were 6.7% and 30%, respectively.

Weide reported that one of four patients who received bendamustine, mitoxantrone, and rituximab had a complete response and all four patients had either a complete or partial response.[15]

Quality of Life

None of the trials investigating bendamustine in relapsed or refractory CLL reported quality of life data.

Harms Outcomes

Harms outcomes for all trials investigating bendamustine in relapsed or refractory CLL can be found in Table 5.

Randomized Controlled Trials

Medgenberg et al reported that grade 3 or 4 infections occurred in 13% of patients in the bendamustine arm and in 15% of patients in the fludarabine arm.[10] No further adverse event data are reported.

Single-arm Trials

Koppler et al reported that Grade 3 or 4 leukopenia occurred in 42% of 59 patients with grade 3 or 4 thrombocytopenia and infection occurring in 12%, each of patients.[12] Tumour lysis syndrome was reported to have occurred in one patient.

Fischer et al reported grade 3 or 4 neutropenia in 23.1% of 78 patients and grade 3 or 4 thrombocytopenia and anemia occurring in 28.2% and 16.6%, respectively.[13] Grade 3 or 4 infection occurred in 12.8% of patients receiving bendamustine and rituximab. No patient experienced tumour lysis syndrome. Fischer et al also reported that 46% of patients experienced at least one grade 3 or 4 adverse event. There were three patient deaths related to therapy: all were infections during the first two courses of treatment, septicemia (n=2) and pneumonia (n=1).

The remaining three single-arm trials reported limited adverse event data. Bremer et al did not report separate data for the 15 patients with CLL; however, grade 3 or 4 anemia, thrombocytopenia and leucopenia occurred in 7 of 102 patients (6.9%), 12 (11.8%), and 25 (24.5%) patients, respectively.[14] Weide et al reported that no patients experienced febrile neutropenia and that no patient experienced a grade 3 or 4 non-hematolgocial adverse event.[15] Kath et al reported that two of ten patients (20%) with relapsed or refractory CLL died due to leucopenia (treatment-related).[16]

6.4 Ongoing Trials

Four ongoing RCTs were identified investigating the use of bendamustine in patients with CLL through a search of clinical trial registries: NCT01056510, NCT00769522, NCT01657955, and NCT01109264. Details of the trials can be found in Tables 16 to 19.

Table16. Study NCT01056510: A randomized study to assess the effect on response rate of MabThera (rituximab) added to standard chemotherapy, bendamustine, or chlorambucil in patients with chronic lymphocytic leukemia (MaBLe).[61]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01056510 Open-label, active control, randomized phase III trial. Start date: March 2010 Expected completion date: June 2014 Estimated enrolment: 600 Sponsor: Hoffmann-La Roche	Patients with active Binet stage B or C CLL. If relapsed or refractory disease, prior treatmet must have been with rituximab or chlorambucil. Age ≥18 years. ECOG PS ≥2	**Two arms:** Rituximab 375 mg/m^2/d i.v. d1 of cycle 1, then 500 mg/m^2/d i.v. every 4 weeks for cycles 2-6 + Bendamustine 90 mg/m^2/d (first-line) or 70 mg/m^2/d (second-line) d1+2 every 4 weeks for 6 cycles. ***Or*** Rituximab 375 mg/m^2/d i.v. d1 of cycle 1, then 500 mg/m^2/d i.v. every 4 weeks for cycles 2-6 + chlorambucil 10 mg/m^2/d orally d1-7, every 4 weeks for up to 12 cycles.	<u>Primary outcomes:</u> Complete response rate <u>Secondary outcomes:</u> Overall response rate Progression-free survival Duration of Response Overall survival Molecular response Minimal residual disease Adverse events

Available from: http://clinicaltrials.gov/ct2/show/NCT01056510?term=nct01056510&rank=1

Table 17. Study NCT00769522: Phase III trial of combined immunochemotherapy with fludarabine, cyclophosphamide, and rituximab (FCR) versus bendamustine and rituximab (BR) in patients with previously untreated chronic lymphocytic leukemia (CLL10).[62]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT00769522 Open-label, active control, multicenter randomized phase III trial. Start date: September 2008 Expected completion date: July 2011 Estimated enrolment: 564	Confirmed diagnosis of B-cell CLL Binet stage C or A/B requiring treatment Binet B or A with one of more of: B-symptoms Progressive lymphocytosis Evidence of progressive marrow failure Massive progressive or painful splenomegaly or	**Two arms:** Bendamustine i.v. d1,2 + rituximab d0 cycle 1 then d1 of cycles 2-6, every 28 days for 6 cycles—no further details available. ***Or*** Fludarabine i.v. d1-3 + cyclophosphamide i.v. d1-3 + rituximab d0 of cycle 1 then d1 of	<u>Primary outcomes:</u> Progression-free survival <u>Secondary outcomes:</u> Minimal residual disease Duration of remission Event-free survival Overall survival Overall response rate Adverse events Quality of Life

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Sponsor: German CLL Study Group. Collaborators: Roche Pharma AG, Mundipharma	hypersplenism Massive lymph nodes No prior CLL-specific chemotherapy, radiotherapy, and/or immunotherapy WHO PS 0-2	cycles 2-6, every 28 days for 6 cycles—no further details available.	

Available from: http://clinicaltrials.gov/ct2/show/NCT00769522?term=nct00769522&rank=1

Table 18. Study NCT01657955: Study of bendamustine hydrochloride injection versus chlorambucil in previously untreated chronic lymphocytic leukemia patients.[63]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01657955 Open-label, active control, randomized phase III trial. Start date: January 2011 Expected completion date: October 2013 Estimated enrolment: 96 Sponsor: Shandong Lanjin Pharmaceuticals Co. Ltd.	Confirmed diagnosis of CLL Binet stage B or C, or symptomatic stage A Treatment required to control disease No prior or no standard treatment for CLL ECOG PS 0-2	**Two arms:** Bendamustine i.v. 100 mg/m^2/d on days 1 and 2, every 28 days, up to 6 cycles. ***Or*** Chlorambucil 0.4 mg/kg/d on days 1 and 2, every 28 days, up to 6 cycles.	Primary outcomes: Overall response Secondary outcomes: Progression-free survival Duration of response Overall survival

Available from: http://clinicaltrials.gov/ct2/show/NCT01657955?term=NCT01657955&rank=1.

Table 19. Study NCT01109264: Study of bendamustine hydrochloride injection versus chlorambucil in previously untreated chronic lymphocytic leukemia patients.[64]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study NCT01109264 Open-label, active control, randomized phase II trial. Start date: March, 2010 Expected completion date: December 2013	Confirmed diagnosis of CLL according to NCI working group criteria Binet stage B or C No prior treatment for CLL ECOG PS 0-2	**Two arms:** Bendamustine i.v. 100 mg/m^2/d on days 1 and 2, every 28 days, up to 6 cycles. ***Or*** Chlorambucil 0.4	Primary outcomes: Overall response Secondary outcomes: Progression-free survival Duration of response Overall survival Adverse events

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Estimated enrolment: 144 Sponsor: Jiangsu Simcere Pharmaceutical R&D Co. Ltd.		mg/kg/d on days 1 and 2, every 28 days, up to 6 cycles.	

Available from: http://clinicaltrials.gov/ct2/show/NCT01109264?term=NCT01109264&rank=1**.**

7 SUPPLEMENTAL QUESTIONS

No supplemental questions were addressed in this review.

8 ABOUT THIS DOCUMENT

This Clinical Guidance Report was prepared by the pCODR Leukemia 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 (Treanda) for CLL. 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 posted 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. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The Leukemia Clinical Guidance Panel is comprised of three clinical 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 leukemia, lymphocytic, Chronic, B-Cell/
6. CLL:.ti,ab,sh,hw,ot.
7. Chronic lymph: leuke?mia:.ti,ab,sh,hw,ot.
8. or/5-7
9. 4 and 8

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 *chronic lymphatic leukemia/
5. Chronic lymph: leuk?emia:.ti,ab.
6. CLL:.ti,ab.
7. Or/4-6
8. 3 and 7

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
29 results for: bendamustine* or treanda* or ribomustin* or sdx-105* or hsdb 7763* 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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