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A Canadian perspective on bendamustine for the treatment of chronic lymphocytic leukemia and non-Hodgkin lymphoma

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ABSTRACT

Despite the success of standard treatments in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), patients are often unable to tolerate aggressive regimens, and they require effective alternatives. Bendamustine is a bifunctional alkylator with unique properties that significantly distinguish it from other agents in its class. In untreated CLL, bendamustine has demonstrated rates of response and progression-free survival (PFS) that are superior to those with chlorambucil, with an acceptable toxicity profile. In the relapsed setting, combination treatment with bendamustine–rituximab (BR) has demonstrated promising activity in high-risk patients such as those refractory to fludarabine or alkylating agents. In untreated patients with indolent NHL and mantle cell lymphoma, BR has demonstrated a PFS significantly longer than that achieved with R-CHOP (rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone), with significantly reduced toxicity. In the relapsed setting, BR has demonstrated rates of response and PFS superior to those with fludarabine–rituximab, with comparable toxicity. In the United States and Europe, bendamustine has been approved for the treatment of CLL and indolent NHL; its approval in Canada is pending and eagerly awaited. Once available, bendamustine will benefit many Canadian patients with NHL and CLL.

KEY WORDS

Bendamustine, chronic lymphocytic leukemia, non-Hodgkin lymphoma, follicular lymphoma

1. BACKGROUND

Since the year 2000, considerable progress has been made in the treatment of chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma (NHL), and mantle cell lymphoma (MCL). However, because of reduced performance status or pre-existing comorbidities, many patients eventually relapse or do not qualify for standard therapies [1,2]. Additional treatment options that improve tolerability while maximizing efficacy are therefore needed in those settings.

Bendamustine hydrochloride is a bifunctional alkylating agent with clinical activity across a number of cancers, including breast cancer, small-cell lung cancer, multiple myeloma, CLL, indolent NHL, and MCL [2,3]. Ozegowski and colleagues first synthesized this agent in the early 1960s at the Institute for Microbiology and Experimental Therapy in the former German Democratic Republic. With the emerging importance of nitrogen mustards as anticancer agents, bendamustine was developed to improve tolerability without sacrificing clinical activity. Although bendamustine has been used extensively for more than 40 years, it was not systematically studied in lymphoproliferative disorders until the 1990s [4].

Bendamustine has three structural elements: a 2-chloroethylamine alkylating group, a benzimidazole ring, and a butyric acid side chain [3,5]. The 2-chloroethylamine alkylating group is similar to those in other alkylators such as cyclophosphamide, chlorambucil, and melphalan, and the butyric acid side chain resembles that in chlorambucil. To incorporate the antimetabolite properties of benzimidazole, a central ring system was added that is similar to that in purine analogues. As a whole, the bendamustine molecule is more stable than the molecules of other alkylators, and it causes more extensive and more durable damage to DNA. However, the extent to which the benzimidazole ring contributes to the antitumour activity of bendamustine is unclear.

Although its exact mechanism of action is unknown, bendamustine appears to be unique among chemotherapy agents [3–5]. Unlike other alkylating agents, bendamustine primarily targets base excision repair pathways rather than mismatch repair pathways, and it activates DNA-damage stress responses, apoptosis, inhibition of mitotic checkpoints, and induction of mitotic catastrophe. In addition, bendamustine is

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only partially cross-resistant with other alkylating agents, and it is active against primary NHL cells that are refractory to cyclophosphamide and doxorubicin [4].

For the treatment of CLL, follicular lymphoma, and aggressive B-cell NHL, bendamustine is administered as an intravenous infusion (over approximately 1 hour) on days 1 and 2 of a 21- to 28-day cycle. Bendamustine is administered at a dose ranging from 70 mg/m^2 to 120 mg/m^2, depending on whether it is given in the upfront or relapsed setting, or as monotherapy or combined with other agents. Although data are limited, sex, age, mild-to-moderate renal impairment, and mild-to-moderate hepatic impairment do not appear to influence the pharmacokinetic profile of bendamustine [5]. Bendamustine may be used with caution in patients with mild renal or hepatic impairment without dose alteration [6,7].

Bendamustine is currently approved for the treatment of various hematologic malignancies in the United States, the European Union, Singapore, Japan, and Hong Kong. In the United States and Europe, bendamustine is approved for the first-line treatment of CLL and relapsed indolent NHL. Currently, the use of bendamustine is recommended in both the European Society for Medical Oncology and the National Comprehensive Cancer Network consensus guidelines for the treatment of CLL and indolent NHL, and in the National Comprehensive Cancer Network guidelines for the treatment of MCL [4].

2. PURPOSE OF THIS DOCUMENT

Although bendamustine has been approved in a number of countries for the treatment of hematologic malignancies, it has not yet been approved in Canada. (It is currently under review at Health Canada.) Here, we review the role of bendamustine in CLL, indolent NHL, and MCL; however, the information presented does not reflect a true evidence-based guideline or systematic literature review. Furthermore, the application of bendamustine in other disorders, such as multiple myeloma and Hodgkin lymphoma, is beyond the scope of the present document.

3. CHRONIC LYMPHOCYTIC LEUKEMIA

3.1 Goals of Treatment

The goal of treatment in CLL is to maximize response while minimizing toxicities and improving quality of life. In Canada, the median age at diagnosis of CLL is approximately 72 years, with fewer than 2% of cases occurring in patients under 50 years of age [8]. Given that most patients with CLL are elderly, the efficacy of treatment needs to be balanced against patient tolerance. In making treatment decisions, age, comorbid conditions, organ function, performance status, and patient preference are important factors influencing the selection of therapy [9].

3.2 First-Line Treatment

Preferred standard first-line treatment options for CLL include fludarabine–cyclophosphamide–rituximab (FCR), and fludarabine–rituximab (FR). Although some patients can tolerate aggressive treatment, most patients with CLL are elderly and have pre-existing comorbidities. Based on Cumulative Illness Rating Scale criteria, Eastern Cooperative Oncology Group performance status, and renal function, only one third of an ongoing database of 100 patients seen at CancerCare Manitoba each year are eligible to receive FCR (Johnston J, CancerCareManitoba. Personal communication, 2011). Patients unable to tolerate aggressive therapy because of significant comorbidities or frailty are often treated with chlorambucil with or without rituximab—a regimen that offers more modest efficacy than either FCR and FR. There is a need for more effective agents with a favourable toxicity profile to be developed for CLL.

3.2.1 Bendamustine As Monotherapy

A European multicentre phase III study compared the efficacy and safety of bendamustine (100 mg/m^2 intravenously on days 1 and 2 every 4 weeks) with that of chlorambucil (0.8 mg/kg orally on days 1 and 15 every 4 weeks) in previously untreated patients with advanced CLL (Binet stage B or C) [10]. After a median observation time of 35 months, responses were observed in 110 of 162 bendamustine-treated patients (68%) and in 48 of 157 chlorambucil-treated patients (31%, $p < 0.0001$). In addition, more patients achieved a complete response (CR) with bendamustine than with chlorambucil (31% vs. 2%). Median progression-free survival (PFS) was 21.6 months with bendamustine and 8.3 months with chlorambucil ($p < 0.0001$). Compared with chlorambucil, bendamustine was also associated with an improvement in duration of remission (median: 21.6 months vs. 8.3 months) [11]. A study in the United States demonstrated that, although bendamustine led to higher costs relative to chlorambucil, bendamustine was associated with an additional year of PFS and had an acceptable incremental cost-effectiveness ratio of $50,763 per quality-adjusted life year [12].

Despite improved efficacy, grades 3 and 4 hematologic toxicities were more commonly seen in patients receiving bendamustine than in those receiving chlorambucil (40% vs. 19% of patients) [10]. Serious infections (grades 3 and 4) were also more common in the bendamustine treatment arm (8% vs. 3%). In addition, gastrointestinal events (nausea, vomiting, diarrhea) were reported more frequently in patients receiving bendamustine. Finally, 2 incidences of tumour lysis syndrome were reported, both occurring after the first cycle of bendamustine. A total of 23 patients—18 receiving bendamustine and 5 receiving chlorambucil—were withdrawn from the study because of unacceptable toxicity or because

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of an unfavourable risk–benefit assessment. Overall, although hematologic toxicity and infections were more common with its use, bendamustine had an acceptable safety profile, and the drug-related toxicities were manageable. Despite the increased toxicity of bendamustine compared with chlorambucil, no significant differences in quality of life were seen between the groups [13]. After the study, precautions were recommended for high-risk patients to prevent tumour lysis syndrome, including hydration and use of allopurinol [7].

3.2.2 Bendamustine Combination Regimens

Ongoing studies are examining a number of combination regimens with the aim of providing additional options that improve efficacy and tolerability. Bendamustine is being examined in combination with agents such as rituximab, ofatumumab, lenalidomide, and fludarabine.

The CLL2M study is a multicentre phase II trial by the German CLL Study Group (GCLLSG) assessing the efficacy and toxicity of bendamustine 90 mg/m^2 and rituximab (BR) in previously untreated CLL [14]. Interim results presented at the 2009 meeting of the American Society of Hematology (ASH) reported an overall response rate (ORR) of 91%, with 33% of patients achieving a CR. After 18 months of follow-up, 76% of patients were still in remission and median PFS had not been reached. Of 50 evaluable patients, 29 tested negative for minimal residual disease in peripheral blood, and of 25 patients evaluated, 7 achieved minimal residual disease negativity in bone marrow. In the high-risk group with *17p* deletions [del(17p)], 3 of 7 patients (43%) achieved a partial response and 56 of 63 patients (89%) with unmutated immunoglobulin heavy-chain variable-region status responded to BR.

The efficacy of BR is also being examined in untreated elderly patients with CLL. Preliminary data from a phase II study in 20 patients (9 with indolent nonfollicular NHL; 11 with CLL or small lymphocytic lymphoma) [15] showed that, of the 11 patients with CLL or small lymphocytic lymphoma, 10 (91%) achieved a CR. In all patients, the main adverse event was neutropenia, occurring in 39% of patients; severe neutropenia was recorded in 4 patients (20%). With a median follow-up of 16 months, overall survival (OS) and PFS were 94% and 100% respectively in the entire study population.

A number of phase III studies are examining bendamustine combination regimens in untreated CLL. The CLL10 study (NCT00769522) is an ongoing phase III trial by the GCLLSG that is comparing FCR with BR in patients with previously untreated CLL. The aim of the study is to examine efficacy, with PFS being the primary outcome; the incidence of major side effects such as myelosuppression and rate of infections are being tracked as secondary outcomes. The phase III MABLE study (NCT01056510) is comparing BR with chlorambucil plus rituximab in previously treated and untreated patients with CLL. Finally, the GALTON study (NCT01300247), a multicentre phase IB trial, is examining the safety and efficacy of obinutuzumab (GA101) plus bendamustine, or obinutuzumab plus fludarabine–cyclophosphamide in first-line CLL.

3.2.3 Treatment in the Relapsed Setting

Despite the improved outcomes seen with the use of FCR (or FR) as first-line therapy for CLL, almost all patients will eventually relapse and may become refractory to fludarabine-containing regimens. These refractory patients typically have a poor prognosis, with response rates of 22%–34% and a median OS of 10–19 months after salvage therapy [1]. In addition, many of these patients have high-risk features such as del(17p). Alternative treatment options that can prolong remission and overcome resistance to fludarabine-based regimens are therefore needed in the relapsed setting.

In the relapsed setting, bendamustine monotherapy has been compared with fludarabine with favourable results. A randomized phase II trial in fludarabine-naïve patients demonstrated comparable efficacy for bendamustine and fludarabine in relapsed CLL [16]. After a median follow-up of 2 years, the ORR was 78% in the bendamustine arm and 65% in the fludarabine arm, with a median PFS of 83 weeks compared with 64 weeks respectively (hazard ratio: 0.93; 90% confidence interval: 0.59 to 1.47).

Combination treatment with BR (bendamustine 70 mg/m^2) has been examined in high-risk patients with relapsed or refractory CLL in a phase II study from the GCLLSG [1]. Of 78 patients enrolled, 22 (28%) had fludarabine-refractory disease and 14 (18%) had del(17p). Patients had received a median of two prior therapies. In addition, 33 patients (42%) had a creatinine clearance of 70 mL/min or less, and 29 patients (37%) were 70 years of age or older. With a median follow-up of 24 months, the ORR was 59%, with 9% of patients achieving a CR. The ORR was 46% in fludarabine-refractory patients. Among cytogenetic subgroups, 93% of patients with del(11q), 100% with trisomy 12, 7% with del(17p), and 59% with unmutated immunoglobulin heavy-chain variable-region status responded to treatment. The median event-free survival (EFS) was 14.7 months. Overall, BR was well tolerated, with the most common toxicities being myelosuppression and infections. Grade 3 or 4 neutropenia, thrombocytopenia, and anemia were documented in 23%, 28%, and 17% of patients respectively, and severe infections occurred in 13% of patients.

Ongoing studies are also examining bendamustine combined with other agents in the relapsed setting, with preliminary ORRs ranging from 63.8% to 73% in heavily pretreated patients [17–19]. An ongoing phase II study (BENDALEM CLL 6 AGMT) is examining the efficacy and safety of bendamustine 70 mg/m^2

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plus alemtuzumab in relapsed high-risk patients, with promising preliminary results [18].

4. NON-HODGKIN LYMPHOMA

4.1 Goals of Treatment

With recent improvements in the treatment of NHL, patients are now surviving longer than they did at the end of the 1990s [20]. Despite a multitude of treatment options, indolent NHL and MCL remain incurable with standard therapies. The overall goal of treatment is to achieve effective and durable disease control using agents that minimize toxicity, with the aim of improving PFS, OS, and quality of life. Consideration should be given to sequencing therapies such that preceding treatments do not limit future options [21]. Prolonged remissions between treatments can improve quality of life by reducing time spent in hospitals and doctors' offices and dealing with therapy-associated side effects; they also slow the development of drug resistance. The subsection that follows focuses on the use of bendamustine in indolent NHL and MCL.

4.2 First-Line Treatment

The standard initial treatment for patients with indolent NHL varies across North America, with both rituximab–cyclophosphamide–doxorubicin–vincristine–prednisone (R-CHOP) and rituximab–cyclophosphamide–vincristine–prednisone (R-CVP) being widely accepted options [22,23]. Despite higher CR rates and possible improvements in PFS reported with R-CHOP compared with R-CVP, no difference in OS has been demonstrated to date [24–26]. In Canada, R-CVP remains widely used because of a more favourable toxicity profile. Young patients with MCL are often treated with induction therapy (such as R-CHOP) followed by autologous stem-cell transplantation [22,23]. Non-transplant-eligible patients with MCL are routinely treated with R-CHOP, R-CVP, or other chemotherapy combinations.

The first randomized phase III trial examining the use of bendamustine for the initial treatment of NHL compared bendamustine (60 mg/m^2)–vincristine–prednisone (BOP) with cyclophosphamide–vincristine–prednisone (COP) in untreated patients with indolent NHL or MCL [27]. The CR rates for BOP and COP were 22% and 20% respectively, and projected 5-year OS rates were 61% and 46% respectively (p = nonsignificant). Median time to progression was significantly longer for patients who responded to BOP (84+ months) than for those who responded to COP (28 months, p = 0.0369). That difference translates into a projected PFS after 5 years of 59% compared with 46%. Safety outcomes were also similar in both groups, although alopecia and leucopenia were more severe with COP ($p < 0.0001$).

More recently, a phase III study by the German Study Group for Indolent Lymphomas (StiL) compared 6 cycles of BR (bendamustine dose: 90 mg/m^2) with 6 cycles of R-CHOP in 549 treatment-naïve patients with indolent NHL and MCL [28]. At the time of initial analysis, the median observation time was 32 months. Although the ORRs were similar in the two groups, PFS, EFS, and time to next treatment were significantly longer after BR than after R-CHOP (PFS: 54.8 months vs. 34.8 months; p = 0.0002; EFS: 54 months vs. 31 months; p = 0.0002; time to next treatment: median not reached vs. 40.7 months; p = 0.0002). In addition, compared with R-CHOP, BR was associated with lower rates of hematologic toxicity, infectious complications, and peripheral neuropathy. Significant differences in hematologic toxicities were observed for neutropenia grades 3 and 4 (11% with BR vs. 47% with R-CHOP, $p <$ 0.0001) and for leucopenia grades 3 and 4 (12% with BR vs. 38% with R-CHOP; $p < 0.0001$). A lower number of infectious complications (95 with BR vs. 121 with R-CHOP, p = 0.0403) and peripheral neuropathy (18 with BR vs. 73 with R-CHOP, $p < 0.0001$) were observed in the BR group. Alopecia was also less common in the BR group (15% vs. 62% with R-CHOP); however, a greater number of erythematous skin reactions were reported in the BR group (p = 0.0122).

With the success of bendamustine combination regimens such as BOP and BR for the treatment of NHL, ongoing studies are examining novel bendamustine combinations with drugs including lenalidomide, bortezomib, mitoxantrone, obinutuzumab, or ofatumumab. Preliminary results of a phase II study of bendamustine plus ofatumumab presented at ASH 2011 demonstrated overall response and CR rates of 98% and 60% respectively [29]. Table I presents a description of ongoing studies.

4.2.1 Treatment in the Relapsed Setting

Despite being highly responsive to first-line therapies, indolent NHL remains largely incurable [32]. Approximately 60% of patients with follicular lymphoma receiving first-line treatment with R-CHOP will relapse after 3 years [26]. Patients who are refractory to initial therapy tend to be less responsive to subsequent treatments [32]. There is also a significant unmet treatment need in patients whose disease has progressed on or after previous rituximab-based therapies. There are a number of options for the treatment of relapsed NHL, but there is no consensus on the best agents to use in that setting, and the response duration tends to become shorter with each consecutive agent. Novel therapies that are effective and well-tolerated are greatly needed in this patient population.

4.2.2 Bendamustine As Monotherapy

A phase II study of bendamustine 120 mg/m^2 in patients with relapsed or refractory indolent NHL demonstrated a 73% response rate (11% CR) and a median time to progression of 16 months [33]. A more recent phase II study examined the efficacy of bendamustine 120 mg/m^2 in 76 patients with indolent NHL

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TABLE I Ongoing phase II and III studies examining first-line bendamustine combination regimens in non-Hodgkin lymphoma (NHL)

National Clinical Trials ID number (study name)	*Phase*	*Pts (n)*	*Condition*	*Treatment arms*
NCT00963534 [30] (LENA-BERIT)	I/II	60	Mantle cell lymphoma, ≥65 years	Bendamustine–lenalidomide–rituximab
NCT00992134 [31]	II	37	Mantle cell lymphoma	Bendamustine–cytarabine–rituximab
NCT01108341 [29]	II	50	Indolent NHL	Bendamustine–ofatumumab
NCT01286272	II	130	Follicular lymphoma	Bendamustine–ofatumumab vs. bendamustine–ofatumumab–bortezomib
NCT01029730	II	55		Bendamustine–bortezomib–rituximab
NCT00901927	II	37	High-risk follicular lymphoma	Bendamustine–mitoxantrone–rituximab
NCT00877006 (BRIGHT)	III	447	Indolent NHL, mantle cell lymphoma	Bendamustine–rituximab vs. rituximab–cyclophosphamide–vincristine–prednisone vs. rituximab–cyclophosphamide–vincristine–doxorubicin–prednisone
NCT01059630	III	360	Indolent NHL	Bendamustine–obinutuzumab vs. bendamustine
NCT01332968	III	1400	Indolent NHL	Obinutuzumab plus chemotherapy vs. rituximab plus chemotherapy, followed by maintenance obinutuzumab or rituximab (chemotherapy options can include bendamustine)

(80%) or transformed lymphoma (20%) refractory to rituximab [34]. Among 74 evaluable patients, the ORR was 77% (15% CR and 19% unconfirmed CR). In a subset of patients refractory to chemotherapy, the ORR was 61% (13% CR). Median PFS was 8.3 months among patients with an indolent histology. Finally, an ongoing Japanese phase II study is examining the efficacy and safety of bendamustine in relapsed indolent NHL and MCL [35]. Preliminary results of that study, presented at ASH 2010, with a median follow-up time of 20.6 months, demonstrated an ORR of 90% in follicular lymphoma and 100% in MCL. The median PFS was 20.0 months in indolent NHL and 21.7 months in MCL.

After the success of initial phase II studies, a pivotal study funded by the U.S. National Institutes of Health evaluated the efficacy and toxicity of bendamustine 120 mg/m^2 in 100 patients with rituximab-refractory indolent B-cell lymphoma [36]. Rituximab refractoriness was defined as nonresponse to a rituximab-containing regimen or progression within a 6-month period after completion of therapy. Given the lack of a standard treatment in this setting, no comparator was used in this study. Patients were heavily pretreated and had received up to 6 prior regimens (median: 2 regimens); 36% were refractory to their most recent chemotherapy regimen. The ORR was 75% (17% CR and unconfirmed CR) and was comparable regardless of clinical risk score or histologic subtype. Among patients who were refractory to chemotherapy, 64% responded to bendamustine. Median PFS in all patients was 9 months; it was 11.8 months for chemotherapy-sensitive patients and 7.5 months for chemotherapy-refractory patients. Although grade 3 or 4 neutropenia occurred in 61% of patients, that side effect was largely manageable. Infections of any grade occurred in 69% patients. Based on results of that study, bendamustine received accelerated approval by the U.S. Food and Drug Administration for refractory indolent NHL.

4.2.3 Bendamustine Combination Regimens

In patients with relapsed NHL, combination treatment with BR has been examined in two phase II studies.

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The German StiL group examined the efficacy and safety of BR (bendamustine dose: 90 mg/m^2) in rituximab-naïve patients with indolent NHL or MCL [37] (Table II). In the overall study population, the ORR was 90% (57 of 63 patients), with 96% of indolent follicular NHL and 75% of MCL patients responding. Median PFS was 24 months, and median OS has not yet been reached. Myelosuppression was the major toxicity, with grade 3 or 4 leukopenia occurring in 16% of cycles (35 of 216). A second phase II study examined the efficacy and safety of BR (bendamustine dose: 90 mg/m^2) in 67 relapsed patients with indolent B-cell lymphoma or MCL who were not refractory to rituximab [39]. The ORR was 92% in the overall study population, with no significant differences by histologic subtype. In patients previously treated with rituximab (n = 37), the ORR was 86%. Median PFS in the entire cohort was 23 months, and it was comparable across histologic subtypes.

Additional phase II studies of bendamustine in combination with other agents have recently been reported (Table III). Based on promising results in those studies, the German StiL group conducted a phase III study comparing the efficacy and safety of BR (bendamustine dose: 90 mg/m^2) with those of FR in relapsed patients with indolent NHL or MCL [42]. Results of their study were presented at the ASH 2010 annual meeting. Most patients had stage IV disease and had received one prior therapy. A median of 6 cycles were given, and the median observation time was 33 months in each treatment group. The ORR was significantly higher with BR than with FR (84% vs. 53%, $p < 0.0001$), and the PFS was significantly longer in the BR cohort (30 months) than in the FR cohort (11 months; hazard ratio: 0.51; $p < 0.0001$), although OS did not differ. There were no significant differences in the rates of overall adverse events, serious adverse events, and hematologic toxicities between the treatment groups.

Ongoing studies are examining the role of bendamustine in combination with other agents in relapsed NHL, including combinations with temsirolimus, bortezomib, cytarabine, obinutuzumab, and ofatumumab (Table III).

5. CONCLUSIONS

Bendamustine is a bifunctional alkylator with unique properties that distinguish it from other agents in its class, showing only partial cross-resistance to other alkylators such as cyclophosphamide [3–5]. In the United States and Europe, bendamustine has been approved for the treatment of CLL and indolent NHL; its approval in Canada is pending.

Despite the success of standard treatments in CLL, patients are often unable to tolerate aggressive regimens, and they require effective alternative options. Bendamustine has demonstrated significant activity and an acceptable toxicity profile in untreated CLL, with improved response rates and PFS rates compared with those achieved with chlorambucil [10]. In addition, combination regimens that include bendamustine continue to be examined in clinical trials and may provide more tolerable and effective alternatives.

TABLE II Phase II and III studies examining bendamustine in combination with other agents in relapsed or refractory non-Hodgkin lymphoma (NHL)

Reference	*Phase*	*Follow-up (months)*	*Agent*	*Pts (n)*	*Condition*	*ORR (%)*	*Median PFS (months)*
Rummel *et al.,* 2005 [37]	II	NR	Bendamustine–rituximab	63	Indolent NHL, mantle cell lymphoma	90	24
Weide *et al.,* 2007 [38]	II	27	Bendamustine–rituximab plus mitoxantrone	57	Indolent NHL, mantle cell lymphoma	89	19
Robinson *et al.,* 2008 [39]	II	20	Bendamustine–rituximab	66	Indolent NHL, mantle cell lymphoma	92	23
Fowler *et al.,* 2009 [40] (presented at ASH 2009)	II	NR	Bendamustine–rituximab plus bortezomib	63	Follicular lymphoma	84	NR
Friedberg *et al.,* 2009 [41] (presented at ASH 2009)	II	NR	Bendamustine–rituximab plus bortezomib	31	Indolent NHL, transformed	84	NR
Rummel *et al.,* 2010 [42] (presented at ASH 2010)	III	33	Bendamustine–rituximab vs. fludarabine–rituximab	219	Indolent NHL, mantle cell lymphoma	83.5 52.5 p<0.0001	30 11 p<0.0001

ORR = overall response rate; PFS = progression-free survival; NR = not reported; ASH = American Society of Hematology annual meeting.

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TABLE III Ongoing phase II/III studies examining bendamustine combination regimens in relapsed non-Hodgkin lymphoma (NHL)

National Clinical Trials ID number	*Phase*	*Pts (n)*	*Condition*	*Treatment arm*
NCT01170052	I/II	20	Mantle cell lymphoma	Bendamustine–temsirolimus
NCT01078142	I/II	72	Follicular lymphoma, mantle cell lymphoma	Bendamustine–temsirolimus–rituximab
NCT00992134	II	48	Mantle cell lymphoma	Bendamustine–cytarabine–rituximab
NCT01133158	II	60	Follicular lymphoma	Bendamustine–mitoxantrone–dexamethasone–rituximab
NCT01127841	II	60	Follicular lymphoma	Bendamustine–rituximab
NCT01294579	II	53	Indolent NHL	Bendamustine–ofatumumab
NCT01077518	III	388	Indolent NHL	Bendamustine–ofatumumab vs. bendamustine
NCT01059630	III	360	Indolent NHL	Bendamustine–obinutuzumab vs. bendamustine

In the relapsed setting, bendamustine has also demonstrated a high level of efficacy. Combination treatment with BR has demonstrated promising activity in high-risk CLL, including in patients who are refractory to fludarabine. Ongoing studies examining bendamustine combination regimens in both the upfront and relapsed settings should provide further insight into the optimal use of this agent, which has proved to be a valuable therapeutic option for the management of CLL.

Bendamustine has also been shown to be an effective agent in patients with indolent NHL and MCL. A randomized trial performed in previously untreated patients with indolent NHL and MCL demonstrated significantly longer PFS with BR than with R-CHOP, and lesser associated toxicity [28]. In light of those results, BR is routinely used in the first-line treatment of NHL in many countries across the world. In the relapsed setting, bendamustine has achieved promising response rates of approximately 75%, with significant activity in patients who are refractory to rituximab and prior chemotherapy [36]. Compared with FR treatment, combination treatment with BR has shown superior response rates and PFS, with comparable toxicity in patients with relapsed indolent NHL and MCL. Ongoing studies should further clarify the value of this highly effective agent in the treatment of NHL.

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