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Bendamustine for treatment of chronic lymphocytic leukemia

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Abstract

Introduction—Chronic lymphocytic leukemia (CLL) has an extended disease course in many patients. With a median age at diagnosis of 72 years, newer treatment options with less toxicity than standard nucleoside analogue-based regimens are needed. Historically, few therapy options are available once CLL has become refractory to nucleoside analogues. Bendamustine has emerged as a feasible therapy for older and less fit CLL patients, with clinical efficacy in previously untreated and refractory CLL.

Areas covered—This paper reviews several of the pivotal clinical trials establishing the clinical activity of bendamustine in previously untreated and relapsed/refractory CLL. The toxicity profile of bendamustine, primarily myelosuppression and infections, is reviewed and compared across different CLL populations. A review of the clinical data focuses on potential explanations for differences in response rates and duration of remission reported across studies and how this may impact the development of therapies for CLL.

Expert opinion—Bendamustine is a valuable new agent for the management of CLL. Ongoing clinical trials are comparing bendamustine to standard CLL regimens in untreated disease, and investigating bendamustine combinations with novel targeted therapies and monoclonal antibodies. These studies will help define the optimal role for bendamustine in CLL management.

Keywords

Bendamustine; chronic lymphocytic leukemia; small lymphocytic lymphoma; chemotherapy

1. Introduction

Bendamustine offers a therapeutic option for treatment of chronic lymphocytic leukemia (CLL) with clinical activity and a toxicity profile that will allow for treatment of a broad range of patients. Fludarabine-based regimens have been the mainstay of treatment for CLL for over a decade, but the toxicities of these regimens have been prohibitive in some subgroups and there have been limited options for patients with disease refractory to fludarabine.¹ Patients with CLL who have become refractory to fludarabine have very poor outcomes, with median survivals of 8–10 months reported.¹ Promising objective response rates have been observed with bendamustine even in the setting of heavily pretreated and fludarabine-refractory disease.^{2–5} This review will outline the data regarding activity of bendamustine in CLL, describe the evolution of combination regimens with bendamustine, and outline the probable role bendamustine will develop in management of CLL over the next 5–10 years.

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Declaration of interest

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2. Overview of the market

Approximately 16,060 new cases of CLL are estimated to be diagnosed in the United States in 2012, with an estimated 4580 deaths.⁶ Given the often variable and prolonged disease course of CLL, there are many opportunities for bendamustine to become incorporated into modern treatment approaches.

Bendamustine is currently approved in the United States by the Food and Drug Administration (FDA) for treatment of CLL and rituximab-refractory indolent non-Hodgkin lymphoma.⁷ Bendamustine is becoming increasingly recognized as a clinically active and feasible option for older patients with medical comorbidities and patients with disease relapse following nucleoside analogue-based therapy. In addition, there are accumulating data supporting the activity of bendamustine in previously untreated CLL.

3. Introduction to the compound

3.1 Chemistry

Bendamustine's origin arises from efforts to synthesize a nitrogen mustard compound with preserved efficacy and improved toxicity compared with other alkylating agents. Bendamustine was first synthesized in the early 1960's in the former East German Democratic republic as 1H-benzimidazole-2-butanolic acid, 5-[bis(2-chloroethyl)amino]-1-methyl-monohydrochloride (molecular formula $C_{16}H_{21}Cl_2N_3O_2 \cdot HCl$).⁸ Bendamustine is a mechlorethamine derivative with structural similarities to both alkylating agents and purine analogues, and is composed of 3 chemically active groups: a benzimidazole ring, a 2-chloroethyl group, and a butyric acid side chain.⁹ The 2-chloroethyl group has properties shared with chlorambucil and other nitrogen mustard agents, conferring anti-tumor properties common to alkylating agents.⁸⁻¹⁰ The benzimidazole ring is structurally similar to a purine ring, potentially contributing to the purine analog antagonism properties of bendamustine (Box 1).^{8, 11}

3.2 Pharmacokinetics and metabolism

In humans, bendamustine's primary route of metabolism is hydrolysis to the inactive metabolites monohydroxy- and dihydroxy-bendamustine.¹²⁻¹³ Two additional cytotoxic metabolites of bendamustine (gamma-OH-bendamustine and N-desmethyl-bendamustine) are formed by hepatic metabolism via the CYP1A2 oxidative pathway.^{8, 14-15} Fecal excretion is the primary route of elimination,⁷ although urinary excretion of the parent drug and major metabolites has been confirmed.^{14, 16} Although bendamustine has primarily been administered intravenously, oral bioavailability of 63% has been shown in non-fasting conditions, with improvement to nearly 100% in fasting states.¹⁵

There has generally been a paucity of bendamustine pharmacokinetic data.⁷ A recent report explored the exposure-response relationship to bendamustine among a subset of subjects with rituximab-refractory indolent NHL treated with bendamustine 120 mg/m² IV over 60 minutes on day 1 and 2.³ Up to 4 serum concentration levels were drawn per subject from 15 minutes to 10 hours post-infusion. The half-life of bendamustine was determined to be 40 minutes, with the observed decline in serum concentrations noted to occur in a triphasic manner, with rapid distribution followed by intermediate and slow terminal phases. Bendamustine's pharmacokinetics were not altered by age, sex, mild/moderate renal impairment, or mild liver impairment.¹³

Some small reports have documented clinical efficacy and acceptable toxicity with dosing of bendamustine in end-stage renal disease requiring dialysis. Preiss et al reported outcomes among 17 myeloma patients with renal failure (5 on hemodialysis) treated with

bendamustine, with only a moderate increase in hematologic toxicities observed and no requirements for dose reduction.¹⁷ Tolerability of bendamustine without dose modification was also reported in a small study of patients with advanced cholangiocarcinoma and hepatic dysfunction.¹⁸ Based on the available data, caution is still advised for administration of bendamustine to patients with renal failure (creatinine clearance <30–40 mL/min) or clinically significant hepatic dysfunction.⁷

3.3 Pharmacodynamics

Leoni et al compared the activity of bendamustine with other structurally similar compounds, including cyclophosphamide, chlorambucil and melphalan.¹⁰ These assays established a unique pattern of activity for bendamustine, including activation of p53-dependent apoptotic pathways and genes, inhibition of mitotic checkpoints, and activation of a base excision DNA repair pathway rather than an alkyltransferase DNA repair mechanism. Bendamustine promotes an independent mitotic catastrophic pathway of cell death, which may explain the observed activity of bendamustine in malignancies resistant to multiple previous chemotherapeutic agents.^{9–10}

In vitro synergy has been demonstrated between bendamustine and the purine analogues fludarabine¹⁹ and cladribine,²⁰ as well as rituximab.^{9, 21} Antagonism has been reported in vitro between bendamustine and anthracycline agents in leukemia and lymphoma cell lines,²⁰ although clinical studies have demonstrated activity of bendamustine, mitoxantrone, and rituximab combinations in CLL and NHL.^{22–23}

In vitro assays investigating the toxicity of bendamustine and fludarabine on hematopoietic progenitors from healthy donors noted lower toxicity to hematopoietic progenitors and stem cells from bendamustine compared with fludarabine. These preliminary data suggest that bendamustine-containing regimens will be more feasible than fludarabine prior to stem cell apheresis.²⁴

4. Clinical efficacy

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) represent different clinical manifestations of a common lymphoproliferative disorder. Generally, a peripheral blood lymphocyte count $>5000 \times 10^9$ lymphocytes/liter is defined as the threshold to separate CLL from SLL. Tsimberidou et al compared retrospective outcomes from 2126 patients with CLL and SLL, and found no difference in rates of response, survival, and failure-free survival between patients classified as CLL or SLL.²⁵ Based on these factors collectively, the discussion of efficacy data for bendamustine will focus on CLL and SLL as the same disease entity.

4.1 Phase I studies

Various dosing schedules of bendamustine have been explored in phase I studies in advanced solid tumors, with wide variation in recommended phase II dosing from 60–260 mg/m² and dosing schedules ranging from weekly schedules to consecutive dosing for 2–5 days repeated in 3–4 week cycles.⁸ Based on the experience gained in phase I studies in solid tumors, many of the phase I/II studies in lymphoproliferative disorders have included significantly less variation in bendamustine dosing schedules (Table 1).

An early phase I/II study by the German CLL Study Group (GCLLSG) evaluated the activity and toxicity of bendamustine in relapsed/refractory (R/R) CLL.²⁶ Sixteen patients were treated with bendamustine at a starting dose of 100 mg/m² IV on days 1–2 every 28 days. Dose de-escalation was required in 6 patients to a dose of 70 mg/m², and grade 3–4

infections were observed in 7 patients. Based on these outcomes, the recommended phase II dosing for R/R CLL patients was determined to be 70 mg/m² IV days 1–2 every 28 days.²⁶

Other phase I/II studies have investigated combination regimens of bendamustine with mitoxantrone, rituximab, and fludarabine.^{2, 5, 23, 27} A German trial evaluated the combination of bendamustine 80–90 mg/m² days 1–3 with mitoxantrone 10 mg/m² IV day 1 every 28 days and rituximab 375 mg/m² IV weeks 2–5.²³ Of 54 enrolled patients with indolent lymphoma, 21 had R/R CLL. An impressive 96% overall response rate (ORR) was observed, with an observed time to progression of 17 months.²³

4.2 Phase II studies

Bendamustine monotherapy demonstrated significant activity in R/R indolent NHL and CLL in two initial German phase II trials conducted in the 1990's. A study by Heider et al enrolled 58 patients with indolent NHL, with bendamustine administered at a dose of 120 mg/m² IV days 1–2 every 21 days.²⁸ Among this population with high rates of resistance to alkylating agents, an ORR of 73% was observed and median duration of response (DOR) of 16 months.²⁸ Bremer et al found lengthy response durations following treatment with a novel dosing schedule of bendamustine 60 mg/m²/day IV on days 1–5 of 4–6 weeks cycles.²⁹ Of the enrolled patients with indolent NHL and CLL, an ORR of 76.5% was observed, with an impressive median DOR of 39 months.²⁹ The less heavily pretreated nature of the enrolled population may be a factor in the long DOR reported. Of the 15 enrolled CLL patients, the most commonly reported prior regimen was chlorambucil (22 prior treatment courses) compared with relatively infrequent use of fludarabine (4 treatment courses), anthracycline agents (2 treatment courses), or cyclophosphamide (4 treatment course); none of the patients had received prior rituximab.²⁹

Friedberg et al⁴ reported their experience with bendamustine monotherapy for treating rituximab-refractory indolent NHL, using a dosing strategy of 120 mg/m² IV days 1–2 of each 21-day cycle. High rates of objective response exceeding 70% were reported, but the median DOR was only 6.7 months.⁴ In addition, dose modifications were frequently required due to neutropenia and thrombocytopenia.⁴

The activity of bendamustine combined with rituximab was reported by Robinson et al in population of patients with R/R indolent NHL and mantle cell NHL.⁵ Patients received bendamustine 90 mg/m² IV day 2–3 and rituximab 375 mg/m² IV on day 1 of each 28-day cycle. Of the 67 enrolled patients, 10 had SLL. An ORR of 92% was observed (41% complete responses), and a median progression-free survival (PFS) of 23 months was observed.⁵ Notably, this study did not permit rituximab-refractory patients. It is unclear whether the improvement in PFS relative to the Friedberg study is due to the inclusion of rituximab, the exclusion of rituximab-refractory patients, or both factors.

The GCLLSG CLL2M protocol investigated the activity of bendamustine and rituximab (BR) in 78 R/R CLL patients, including 22 (28.4%) with fludarabine-refractory disease.² An ORR of 59% was observed, with an observed event-free survival of 14.7 months. Myelosuppression was common, but only 12.8% of patients experienced grade 3–4 infections. This study also highlighted the very poor prognosis experienced by patients with the 17p deletion, in which median overall survival (OS) was statistically significantly lower at 16.3 months compared with the entire study population median OS of 33.9 months.² Based on these data, the GCLLSG has recommended the dose of bendamustine at 70 mg/m² on days 1–2 every 28 days for R/R CLL either as monotherapy or combined with rituximab.^{2, 26}

Another report by the GCLLSG found high rates of response in previously untreated CLL with BR chemoimmunotherapy, even among patients with high-risk cytogenetic profiles.³⁰ For example, among 110 patients evaluable for response, an ORR of 90.9% was reported, with 32.7% achieving a complete response (CR). Nineteen of 21 patients with presence of the adverse 11q deletion achieved an objective response (ORR 90.5%), including 9 CRs. Of patients with presence of the 17p deletion, 3 of 7 enrolled patients achieved a partial response (ORR 42.9%).³⁰

4.3 Phase III studies

Kahl et al reported outcomes with bendamustine in patients with rituximab-refractory indolent NHL histologies in a single-arm phase III multicenter trial.³ Although the majority of patients had follicular histology, 21 of 100 enrolled patients had R/R SLL. Patients received bendamustine 120 mg/m² IV days 1–2 every 21 days for a total of 6–8 cycles. Despite a high ORR of 75%, a modest median PFS of 9.3 months was observed.³ Dose modifications were required in 24 patients, most commonly due to neutropenia and thrombocytopenia. Grade 3 and 4 infections were observed in 21 patients.

Bendamustine received FDA approval for treatment of CLL based on the promising results of a large international phase III randomized clinical trial comparing bendamustine versus chlorambucil in previously untreated CLL.³¹ Significant improvements in ORR and median PFS were demonstrated favoring bendamustine. Dosing of bendamustine was 100 mg/m² IV days 1–2 every 28 days for up to 6 cycles. Within the bendamustine treated group, the ORR was 68% (31% CRs) compared with 31% in the chlorambucil treated group (2% CRs). Median PFS of 21.6 months was observed with bendamustine versus 8.3 months with chlorambucil ($p < .0001$).³¹ Bendamustine was well tolerated, with a 40% hematologic and 8% non-hematologic rate of grade 3–4 toxicities.³¹

Based on these collective data demonstrating activity of bendamustine in previously untreated CLL, the GCLLSG initiated a multicenter phase III protocol in 2008 (CLL10) comparing BR versus fludarabine, cyclophosphamide, and rituximab (FCR) in previously untreated CLL.³² The primary outcomes measure will be PFS at 24 months, with planned enrollment of 550 patients.

4.4 Post-marketing surveillance

Surveillance continues for secondary events of myelodysplasia (MDS) and acute leukemias. Reported events of secondary MDS and leukemia have occurred in heavily pretreated patients with exposures to multiple prior chemotherapy agents, radiotherapy, and radioimmunotherapy, and so the contribution of bendamustine to the risk profile is unclear. For example, Kahl et al reported 1 patient who developed MDS on day 470 of protocol therapy, but had previously received multiple agents including fludarabine, mitoxantrone, and I-131 tositumumab.³ Friedberg et al reported 3 events of secondary hematologic malignancies, including 2 events of MDS and 1 event of chronic myelomonocytic leukemia, again in the setting of multiple prior chemotherapy exposures.⁴

A number of serious skin reactions have been reported with bendamustine, including the bullous exanthema syndromes toxic epidermal necrolysis (TEN) and Stevens-Johnson Syndrome (SJS).⁷ One case of TEN was reported in a patient receiving BR,⁵ although TEN has also been reported with single-agent rituximab.³³ Bendamustine is frequently administered concurrently with allopurinol for tumor lysis syndrome (TLS) prophylaxis, yet severe skin toxicities including SJS have been reported from exposure to allopurinol alone.^{34–35} However, these risks may justify assessing risk for TLS³⁶ before administering allopurinol prophylaxis to all patients with CLL receiving bendamustine.

The rate of neurotoxicity with bendamustine is unclear, although individual case reports have described neurologic toxicities that appear to be related to bendamustine, with some severe toxicities documented.³⁷ Previous data have demonstrated an association with purine analogues and delayed neurotoxicity, which may be irreversible.³⁸ A case report described by Cheson et al reports an event of severe delayed neurotoxicity in a 63 year old man with follicular lymphoma treated with bendamustine for 7 cycles.³⁷ The patient had experienced mild sensory neuropathy after cycle 1 of bendamustine, but later experienced rapid progression over a 2-week interval of bilateral leg, buttock, and groin numbness as well as leg weakness, bowel and bladder incontinence, and altered mental status. MR imaging of the brain and spine were unremarkable, cerebrospinal fluid analysis revealed no clear etiology, and an infectious work-up was non-revealing. Given the lack of clear explanation for the rapidly developing constellation of neurologic complications, drug toxicity from bendamustine was considered likely. He had experienced minimal improvement with an initial course of steroids, although remarkably was able to regain his leg strength to allow for independent ambulation and resolution of bowel and bladder incontinence approximately 26 months from the onset of symptoms.³⁷ Although such events of severe neurotoxicity may be rare, it is important for clinicians to be aware of the potential risk. It remains unclear if mild peripheral neuropathy during the course of bendamustine therapy is predictive of risk for later severe events of neurotoxicity.³⁷

5.0 Safety and tolerability

Myelosuppression and infections are the most commonly observed toxicities with bendamustine (Table 2). Although high rates of neutropenia and thrombocytopenia have been reported, rates of neutropenic fever and infection are much lower and serious bleeding events are rare. For example, although Kahl et al reported that 61% of 100 enrolled patients experienced grade 3–4 neutropenia, only 7% of patients experienced neutropenic fever and 6% experienced grade 3–4 infections. Toxicity reports from the GCLLSG CLL2M protocol noted hematologic toxicities as the most frequent adverse drug events in this population with R/R CLL, but also with a more modest 12.8% rate of grade 3–4 infections.

Common non-hematologic toxicities with bendamustine have included primarily grade 1–2 events of nausea, vomiting, infection, fatigue, constipation, diarrhea, headache, and infusion-related or injection site reactions.⁷ Opportunistic infections have been reported with bendamustine therapy, most notably cytomegalovirus, with 5 cases reported in the largest bendamustine study to date.³

Other serious events such as TLS and hemolysis have been less commonly reported.⁷ Relative risk for bendamustine-induced hemolytic anemia (HA) is unknown, but remains a concern given the structural and functional similarities with purine analogues where the risk is clearly established.³⁹ A case report of probable bendamustine-associated HA in a woman receiving bendamustine and rituximab for relapsed follicular lymphoma provides evidence in favor of HA as a potential risk with bendamustine exposure.⁴⁰ The current Treanda™ (bendamustine) package insert does not include HA as a known risk,⁷ but caution is advised for use in the setting of possible drug-induced HA until further data become available. Use of bendamustine for patients with concurrent CLL and disease-associated HA is another area where data are limited. Fisher et al reported that 2 patients enrolled with active CLL-associated HA had stabilization of the HA with bendamustine for treatment of CLL.²

Alopecia is uncommon during bendamustine therapy. For example, in the German STiL trial comparing R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) and BR chemoimmunotherapy in previously untreated indolent and mantle cell NHL, only

15% of the 260 patients treated with BR experienced alopecia, with all limited to grade 1 events.⁴¹

6.0 Regulatory issues

Bendamustine was approved by the United States FDA in March 2008 for the treatment of CLL, based on a phase III study comparing bendamustine and chlorambucil as first-line therapy for CLL.³¹ No OS difference has been reported between the groups to date, but there was a statistically significant advantage for bendamustine in terms of overall and complete response rates and PFS.³¹ The FDA approved dosing schedule of bendamustine for CLL is 100 mg/m² IV over 30 minutes on days 1–2 of a 28-day cycle for up to 6 cycles.⁷ Bendamustine also received approval in the United States in October 2008 for treatment of indolent B-cell non-Hodgkin lymphoma that progresses during or within six months of treatment with rituximab or a rituximab-containing regimen.⁷

Bendamustine has been originally licensed in Germany under the brand name Ribomustin[®] for various indications, including treatment of CLL. In July 2010, the European Commission granted the approval of Levact[®] for the use of bendamustine as first-line treatment of CLL for patients for whom fludarabine-based combination chemotherapy is not appropriate.⁴²

7.0 Expert opinion

In the era before bendamustine, there was a considerable gap in effective therapies with acceptable toxicity once patients had relapsed or become refractory to fludarabine-based regimens. In addition, there are ongoing concerns about the toxicity and tolerability of fludarabine-based regimens in older and less fit patients. For example, although chlorambucil is an acceptable therapy for CLL, the rates of complete response are unacceptably low in many younger patients with CLL,^{31, 43} and may not be adequate therapy for older patients with progressive CLL. Alemtuzumab (Campath-1H) has been FDA approved for CLL that is refractory to fludarabine or as front-line treatment of CLL,^{44–46} but serious concerns remain about toxicities from myelosuppression and infectious complications. In addition, alemtuzumab has more limited efficacy in CLL associated with bulky lymphadenopathy.⁴⁴ Bendamustine is not without its own risks, but the toxicity profile is acceptable and rates of response have exceeded 70% in clinical trials of R/R CLL and indolent NHL.^{2–5}

Although there is little debate about the efficacy of bendamustine in the treatment of CLL in the R/R setting, the activity of BR compared with standard FCR chemoimmunotherapy for previously untreated CLL is currently unknown. An ongoing GCLLSG protocol that began enrollment in 2008 will try to answer this question.³² However, in the interim bendamustine appears to be an acceptable alternative for first-line therapy in CLL, particularly in patients with potential difficulty tolerating FCR chemoimmunotherapy.

Management of high-risk CLL with cytogenetic features that are associated with chemotherapy resistance and worse survival outcomes (i.e., 17p and 11q deletions) remains a major obstacle. For example, in the report by the GCLLSG of BR chemoimmunotherapy in 78 patients with CLL, 14 patients had presence of the 17p deletion, with only 1 objective response achieved in this subgroup.² The inherent chemotherapy resistance associated with these high-risk cytogenetic profiles raises questions as to whether the role of novel targeted agents may improve objective responses when combined with bendamustine. For example, the selective phosphatidylinositol 3-kinase- δ inhibitor CAL-101 (GS-1101) has been investigated in combination with BR in a phase I study, with objective responses observed in over 80% of patients with R/R CLL.⁴⁷ Another recent report investigated the activity of the oral small molecular bcl-2 inhibitor navitoclax (ABT-263) in combination with either FCR

or BR chemoimmunotherapy in R/R CLL. Among 5 patients with 17p deletions treated with BR + ABT-263, 3 partial responses were observed.⁴⁸ The activity of the novel Bruton's tyrosine kinase inhibitor PCI-32765 has been demonstrated in a phase I/II study in R/R CLL. Of the 12 enrolled patients with 17p deletions, 4 objective responses have been observed, and 7 additional patients are continuing on therapy with stable disease.⁴⁹ A phase I/II clinical study is evaluating PCI-32765 in combination with FCR or BR chemoimmunotherapy in CLL and SLL.⁵⁰

The short duration of remission observed after bendamustine therapy in rituximab-refractory disease represents another important obstacle highlighted by the bendamustine data.^{3–4} Several ongoing studies are investigating whether newer generation anti-CD20 monoclonal antibodies (i.e., ofatumumab,^{51–53} obinutuzumab^{54–55}) will improve outcomes compared with rituximab in relapsed or in rituximab-refractory disease.^{56–57} Lenalidomide, an oral immunomodulatory agent with activity in CLL,^{58–59} is being investigated as a maintenance strategy following BR induction chemoimmunotherapy to prolong remissions.⁶⁰ Recent reports of very high response rates with the combination of rituximab and lenalidomide in indolent NHL and CLL^{61–63} are the basis for a planned study of rituximab + lenalidomide maintenance therapy following BR induction chemoimmunotherapy.⁶⁴ An ongoing intergroup study will evaluate the contribution of lenalidomide as maintenance therapy in previously untreated CLL following a chemoimmunotherapy induction regimen of fludarabine and rituximab or FCR, with patients stratified in this 4-arm randomized study by cytogenetic risk profile.⁶⁵

Bendamustine-based combination regimens are expected to evolve over the next 5–10 years for treatment of R/R and newly diagnosed CLL. Ongoing clinical trials are investigating various bendamustine combinations with newer generation monoclonal antibodies and novel targeted agents (Table 3). The outcomes from these studies will be instrumental in further defining the optimal role for bendamustine in the management of CLL.

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ABBREVIATIONS

BR	Bendamustine + rituximab
CLL	Chronic lymphocytic leukemia
DOR	Duration of response
EMA	European Medicines Agency
FCR	Fludarabine, cyclophosphamide, rituximab
FDA	Food and Drug Administration
GCLLSG	German Chronic Lymphocytic Leukemia Study Group
HA	Hemolytic anemia
MDS	Myelodysplastic syndrome
NHL	Non-Hodgkin lymphoma
ORR	Overall response rate
OS	Overall survival

PFS	Progression-free survival
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone
R/R	Relapsed/refractory
SJS	Stevens-Johnson syndrome
SLL	Small lymphocytic lymphoma
TEN	Toxic epidermal necrolysis
TLS	Tumor lysis syndrome

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Box 1**Drug summary**

Drug name (generic)	Bendamustine
Phase (for indication under discussion)	Launched
Mechanism of action	DNA inhibitor Apoptosis stimulant
Route of administration	Intravenous
Chemical structure
Pivotal trials	[2,3,30]

Table 1

Clinical trials of bendamustine activity in CLL and indolent NHL

	Phase	Regimen	ORR	Median PFS/TTP (mos)	Median OS (mos)
Bergmann et al ²⁶ GCLLSG R/R CLL MPT=3	I/II N=16	B 70–100 mg/m ² IV D1-2 q28 days	56%	NR	45.6
Lissitchkov et al ⁶⁶ R/R CLL FD-naïve	I/II N=15	B 100 mg/m ² IV D1-2 q21 days	60% CR 27%	NR	NR
Weide et al ²³ R/R disease: CLL 39%	I/II N=54 CLL 39%	B 80–90 mg/m ² IV D1-2 M 10 mg/m ² IV D1 R 375 mg/m ² weekly (cycle 1) Cycles q28 days (max 6 cycles)	96% CR 41%	TTP 17 (CLL)	NR
Heider et al ²⁸ R/R indolent NHL MPT=2	II N=58 47% CLL	B 120 mg/m ² IV D1-2 cycles q21 days (until best response X 2 consecutive cycles)	73% CR 11%	PFS 1.6	36
van der Jagt et al ⁶⁷ Relapsed; not R-refractory (56% with prior R) MPT=1	II N=66 SLL 15%	B 90 mg/m ² D2-3 R 375 mg/m ² D1 Cycles q28 days (max 6 cycles)	94% CR/CRu 41%	NR	NR
Kahl et al ³ Relapsed, R-refractory MPT = 2	III N=100 SLL 21%	B 120 mg/m ² D1-2 Cycles q21 days (max 6–8 cycles)	75% CR/CRu 17%	PFS 9.3	NR
Friedberg et al ⁴ Relapsed, R- refractory, MPT= 2	II N=76 SLL 16%	B 120 mg/m ² D1-2 Cycles q21 days (max 6 cycles)	77% CR/CRu 34%	Median DOR 6.7	NR
Robinson et al ⁵ Relapsed; not R-refractory (56% with prior R) MPT=1	II N=67 SLL 15%	B 90 mg/m ² D2-3 R 375 mg/m ² D1 Cycles q28 days (max 6 cycles)	92% CR/CRu 55%	PFS 23	NR
Fischer et al ² R/R CLL 28% FD-refractory MPT=2	II N=78	B 70 mg/m ² D1-2 R 375 mg/m ² C1,D1 then R 500 mg/m ² D1 C2-6 (max 6 cycles)	59% CR 9%	PFS 15.2	33.9
Knauf et al ³¹ B vs chlorambucil	III N=162	B 100 mg/m ² D1-2 Cycles q28 days (max 6 cycles)	68% CR 31%	PFS 21.6	NR

	Phase	Regimen	ORR	Median PFS/TTP (mos)	Median OS (mos)
Previously untreated CLL					
Friedberg et al ⁶⁸ R/R indolent NHL 33% R-refractory MPT=4	II N=31 SLL 9.7%	B 90 mg/m ² D1 & 4 R 375 mg/m ² D1 Bortezomib 1.3 mg/m ² D1,4,8,11 Cycles q28 days (max 6 cycles)	84% CR/CRu 52%	NR	NR

Abbreviations: B=bendamustine, CR=complete response, CRu=unconfirmed complete response, D=day(s), DOR=duration of response, FD=fludarabine, GCLL.SG=German CLL Study Group, IV=intravenous, M=mitoxantrone, mos=months, MPT=median number of prior therapies, NHL=non-Hodgkin lymphoma, NR=not reported or not yet reached, PR=partial response, PFS=progression-free survival, R=rituximab, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma, TTP=time to progression.

Table 2

Toxicity profile of bendamustine in CLL and indolent NHL [†]

	Infection		Neutropenia		Platelets		Other
	Gr3 %	Gr4 %	Gr3 %	Gr4 %	Gr3 %	Gr4 %	
GCLLSG CLL2M protocol Fisher et al ² R/R CLL BR	12.8	0	9	14.1	14.1	14.1	Gr 3 hemolysis 2.6% No TLS
Kahl et al ³ Indolent NHL, R-refractory Benda alone	15	6	38	23	19	6	Gr 3 nausea 4% Gr 3 vomiting 2% Gr 3 anorexia 3% Gr 3-4 TLS 2%
Robinson et al ⁵ Indolent NHL, Not R-refractory BR	8	2	23	14	8	2	Gr 3 diarrhea 3% Gr 3 fatigue 5%
Friedberg et al ⁴ Indolent and transformed NHL, R-refractory Benda alone	4	0	30	24	16	9	Gr 3 nausea 4% Gr 3 vomiting 2% Gr 3 fatigue 7%
Knauf et al ³¹ Untreated CLL Benda alone	1.9		23		11.8		Gr 3-4 rash 2.5% Gr 3 nausea 0.6% Gr 3-4 vomiting 1.2% Gr 4 fatigue 1.2%

[†] Expressed as % of enrolled patients.

Benda=bendamustine, BR=bendamustine + rituximab, CLL=chronic lymphocytic leukemia, GCLLSG=German CLL Study Group, NHL=non-Hodgkin lymphoma, R=rituximab, TLS=tumor lysis syndrome.

Table 3

Ongoing bendamustine-based chemotherapy trials in CLL

Study	Investigational agent	Phase	NCT identifier
BR versus FCR Untreated CLL	No novel agents; standard FCR, BR chemoimmunotherapy	III	NCT00769522
PCI-32765 + BR vs PCI-32765 + FCR R/R CLL	PCI-32765 (oral BTK inhibitor)	I/II	NCT01292135
ABT-263 + BR vs ABT-263 + FCR R/R CLL	ABT-263 (oral bcl-2 inhibitor)	I	NCT00868413
GS-1101 + rituximab vs GS-1101 + BR vs GS-1101 + bendamustine vs GS-1101 + ofatumumab vs GS-1101 + fludarabine R/R CLL or indolent NHL	GS-1101 (CAL-101) (oral PI3 kinase δ isoform inhibitor)	I	NCT01088048
Bendamustine + ofatumumab R/R CLL	Ofatumumab	II	NCT01010568
Bendamustine + ofatumumab, pentostatin R/R CLL	Ofatumumab	I	NCT01352312
BR + lenalidomide R/R CLL or B-cell NHL	Lenalidomide	I	NCT00864942
BR induction chemotherapy followed by lenalidomide maintenance R/R CLL	Lenalidomide maintenance	II	NCT00974233
Bendamustine + GA-101 vs FC + GA-101 Untreated CLL	GA-101 (RO5072759)	I	NCT01300247

BTK=Bruton's tyrosine kinase inhibitor, BR=bendamustine + rituximab, CLL=chronic lymphocytic leukemia, FC=fludarabine, cyclophosphamide, FCR=fludarabine, cyclophosphamide, rituximab, GCLLSG=German CLL Study Group, NCT=National Clinical Trials (identifier accessible at www.clinicaltrials.gov), NHL=non-Hodgkin lymphoma /R=relapsed/refractory, SLL=small lymphocytic lymphoma