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REVIEW

Optimal use of bendamustine in hematologic disorders: Treatment recommendations from an international consensus panel – an update

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ABSTRACT

Bendamustine has achieved widespread international regulatory approval and is a standard agent for the treatment for chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphoma and multiple myeloma. Since approval, the number of indications for bendamustine has expanded to include aggressive non-Hodgkin lymphoma and Hodgkin lymphoma and novel targeted therapies, based on new bendamustine regimens/combinations, are being developed against CLL and lymphomas. In 2010, an international panel of bendamustine experts met and published a set of recommendations on the safe and effective use of bendamustine in patients suffering from hematologic disorders. In 2014, this panel met again to update these recommendations since the clarification of issues including optimal dosing and management of bendamustine-related toxicities. The aim of this report is to communicate the latest consensus on the use of bendamustine, permitting the expansion of its safe and effective administration, particularly in new combination therapies.

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Introduction

More than 50 years ago, bendamustine was developed in the former German Democratic Republic [1]. Since the pivotal trial in chronic lymphocytic leukemia (CLL) in Germany [2] and studies in follicular-low grade non-Hodgkin lymphoma (NHL) in the US [3,4], the drug has achieved widespread international regulatory approval. Not only is bendamustine the sole chemotherapy drug still currently under study in lymphomas and CLL, but it now serves as the backbone for the development of novel regimens including new targeted therapies.

In 2010, an international group of experts in the use of bendamustine published a consensus on its use in CLL, NHL and multiple myeloma (MM) [5]. Since that time, a number of issues regarding the use of bendamustine have been further clarified, including optimal dosing and drug-related toxicities and their management. As a result, another consensus meeting was held in London, England in 2014 to update recommendations on the use of bendamustine in hematologic disorders. The following is the result of those deliberations.

Molecular characteristics and metabolism

Bendamustine, γ-[1-methyl-5-bis(β-chloroethyl)-amino-benzimidazolyl-2]-butyric acid hydrochloride, is a nitrogen mustard derivative which consists of a meclorethamine group, butyric acid and a benzimidazole ring. The meclorethamine and butyric acid groups are responsible for the alkylating properties of the drug, with structural features similar to other alkylating agents, although bendamustine exhibits only partial cross-resistance to other alkylating agents [6,7]. The anti-metabolic activity of the drug is provided by the benzimidazole ring, similar to purine analogs. A number of mechanisms of action have been hypothesized, including stimulating apoptosis, inducing mitotic catastrophe, inhibiting mitotic checkpoints, and inducing extensive and durable DNA damage [6,8,9].

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Following intravenous administration, bendamustine is metabolized in the liver into monohydroxy- and dihydroxy-bendamustine [7]. The generation of two less active metabolites, gamma hydroxyl-bendamustine and N-desmethyl-bendamustine, is mediated by cytochrome P450 1A2 [10]. More than 90% of bendamustine is excreted in the feces, with less than 10% via the kidneys [11]. Thus, bendamustine can be administered safely to patients with mild-to-moderate renal insufficiency and even to myeloma patients on dialysis [12]. It can also be used in patients with moderate hepatic insufficiency, with anecdotal case reports responding to the drug in the setting of obstructive jaundice, with no adverse effects [13].

Chronic lymphocytic leukemia

Bendamustine in the front-line setting

Bendamustine has become a cornerstone of current treatment regimens in CLL, for front-line and relapsed patients. Bendamustine was approved by the FDA in 2008 in the front-line setting at a dose of 100 mg/m^2 on days 1 and 2 every 4 weeks for six cycles [2]. This regimen was superior to chlorambucil monotherapy, both with respect to overall response rate (ORR) (67% vs. 30%) and progression-free survival (PFS) (21.5 months vs. 8.3 months). However, in current clinical practice bendamustine is mostly used in combination with rituximab (BR), based on data from a phase II trial [14]. Here, bendamustine dosing was 90 mg/m^2 on days 1 and 2 per cycle, every 28 days up to six cycles and the rituximab dose was 375 mg/m^2 for the first course and 500 mg/m^2 for all subsequent courses. The ORR was 88%, with a complete response (CR) rate of 23.1% and a median event-free survival of 33.9 months. Meanwhile, data from a randomized phase III trial comparing BR vs fludarabine + cyclophosphamide + rituximab (FCR) in fit CLL patients demonstrated that, while BR was inferior to FCR in terms of CR (39.7% for FCR vs 30.8% for BR; $p = 0.034$) and median PFS (55.2 months for FCR vs 41.7 months for BR $p < 0.001$), after a median observation time of 37.1 months; the ORR (95.4% for FCR and 95.7% for BR) and OS at 36 months (FCR, 90.6%; BR, 92.2%; $p = 0.897$) were similar between the two treatments [14]. Importantly, PFS in patients older than 65 years was not significantly different between the two treatment options. Toxicity, especially with respect to severe infections, significantly favored BR, particularly in patients >65 years.

Bendamustine in the relapsed/refractory setting

Early studies demonstrated single-agent activity for bendamustine in patients with relapsed or refractory CLL [8,15,16]. Subsequently, Fischer et al. [17], from the German CLL Study Group, treated 78 patients with BR and demonstrated an ORR of 45.5% in fludarabine-refractory patients and 60.5% in fludarabine-sensitive patients, with a median event-free survival of 14.7 months. Thus, BR should be considered as an effective treatment for patients, except those with 17p or who are refractory to FCR, in the relapsed/refractory setting, especially if bendamustine has not been used before or if a durable remission to previous bendamustine was achieved (see re-treatment below).

Bendamustine combinations with targeted agents

Current clinical investigations are exploring combinations of bendamustine with second generation anti-CD20 monoclonal antibodies (mAbs), such as ofatumumab (studies OMB115991 [18] and GIMEMA CLL0809 [NCT01244451] [19] and obinutuzumab (GA101) (the GALTON study [NCT01300247] [20]), in the first-line setting. In addition, BR serves as the chemotherapy-backbone for combinations with the BTK inhibitor, ibrutinib (PCYC1108 trial [21,22]); the PI3K-delta inhibitor, idelalisib (relapsed patients NCT01569295; untreated patients NCT01980888); the BH3 mimetic, venetoclax and others.

Consensus panel recommendations – Chronic lymphocytic leukemia

- Front-line setting:
  - For fit patients ≥ 65 years, BR is preferred over FCR;
  - For elderly and co-morbid patients, a reduced dose of bendamustine (70 mg/m^2) is recommended for up to six cycles;
  - For younger patients with the mutated IGHV-gene, unable to receive FCR:
    - With del 17p, BR may be useful for initial "debulking", but not for definite treatment; ibrutinib preferred,
    - Some young patients with mutated CLL may be "cured" with FCR, but the risk of secondary fludarabine-related cancers must be considered thus, BR is a suitable alternative, and
    - FCR is preferred in unmutated patients;
  - For unfit patients with significant comorbidities, BR is an alternative to idelalisib/rituximab:
    - Renal or hepatic insufficiency,
    - Cumulative Illness Rating Scale >6 or impaired creatinine clearance and

  - Autoimmune hemolytic anemia or immune thrombocytopenia;

- In patients with del 17p or p53 mutation, novel agents should be considered;

- In the relapsed/refractory setting:
  - A reduced dose of bendamustine (70 mg/m^2) on days 1 and 2, with no more than four cycles of BR;
  - Quality of response and tolerability to prior treatment needs to be considered;
  - Re-treatment with BR is reasonable if prior remission lasted $\geq$ 12 months;
  - Bendamustine is not indicated for del 17p and/or p53 mutation, where novel agents are preferred;
  - For patients who relapse after FCR (however, if relapse occurs after $\geq$ 3 years; FCR re-treatment can be considered); and
  - Combinations with new targeted agents should not be used until safety and efficacy have been determined in clinical trials.

Indolent NHL (iNHL)

BR in the frontline setting

Two randomized clinical trials have compared BR against standard frontline regimens in iNHL. A phase 3 non-inferiority study from the Study Group indolent Lymphomas (StiL) compared BR to rituximab/cyclophosphamide/doxorubicin/vincristine/prednisone (R-CHOP) [23]. Bendamustine was given at a dose of 90 mg/m^2 on days 1 and 2 per cycle, every 28 days up to six cycles. Eligible patients had iNHL (follicular grade 1–2, marginal zone, lymphoplasmacytic) or mantle cell lymphoma (MCL). With a median follow-up of 45 months, the median PFS was significantly longer in the BR group vs the R-CHOP group (69.5 vs 31.2 months, $p < 0.0001$) and the benefit of BR was seen across each histologic subtype. BR was better tolerated than R-CHOP in terms of alopecia, peripheral neuropathy and infections [Table I] [14,17,20,24–33]. Skin reactions/rashes were more common in patients receiving BR. Updated results with a median follow-up of 78 months demonstrated a significant PFS and time-to-next-treatment benefit of BR over R-CHOP with a trend towards an overall survival (OS) benefit in patients with iNHL (Hazard ratio = 0.7189, $p = 0.0958$) [34].

In the "BRIGHT" trial, which included follicular grade 1–2 and MCL [34], CR rate with BR was non-inferior to other standard therapies (BR: 31% vs R-CHOP/R-CVP: 25%, $p = 0.0225$). ORR were statistically superior for the BR treatment group (97% vs 91%, $p = 0.0102$). Unfortunately, the BRIGHT trial was not designed to rigorously capture PFS and OS. Toxicity profiles of the two arms were distinct; patients receiving BR experienced more skin rashes and nausea/vomiting, while the R-CHOP/R-CVP patients experienced more neutropenia, alopecia, peripheral neuropathy and constipation (all $p < 0.05$). The incidence of infections was similar between treatment arms. Based on the available data, a recent consensus statement from the Lymphoma Canada Scientific Advisory Board recommended that BR be the standard regimen for follicular lymphoma [35].

Re-treatment of CLL or iNHL with bendamustine-containing regimens

There are limited data on re-treatment with bendamustine-containing regimens. In a retrospective review of iNHL and CLL patients previously treated with bendamustine, 88 were re-treated with bendamustine, bendamustine plus mitoxantrone (BM), BR or bendamustine plus mitoxantrone plus rituximab (BMR) [33]. In all regimens, the bendamustine dose was 90 mg/m^2 on days 1 and 2, repeated every 28 days. The ORR was 76%, with 7% CR and 69% partial response (PR). ORR according to regimen was B: 57%, BM: 70%, BR: 55%, and BMR: 84%. Grade 3–4 hemotoxicity (leukocytopenia, granulocytopenia, thrombocytopenia and anemia) occurred after 35% of therapies.

No other Grade 3–4 toxicities were observed.

Consensus panel recommendations – Indolent NHL

- Front-line setting:
  - BR (at the dose and schedule utilized in StiL and BRIGHT) in patients with iNHL (grade 1–3a) requiring treatment;

- Re-treatment with bendamustine is feasible and can be considered, especially in cases with previous long-term remissions (> 1 year):
  - Due to potential cumulative myelotoxicity, it is recommended to apply only four cycles (70–90 mg/m^2);

- For unfit patients, including compromized patients and those with renal or hepatic insufficiency;
- For patient previously treated with R-CHOP; and
- For patients with relapsed follicular lymphoma whether they are eligible or ineligible for auto-PBSCT, as stem cell harvest is feasible after BR treatment.

Table I. Grade 3/4 toxicities associated with bendamustine by disease area.

Disease area	Toxicity category	Reference	Toxicity	% patients with toxicities	*p* value
CLL	Non-hematological	Fischer et al. [17]	Severe infections	7.7	—
		Eichhorst et al. [14]	Severe infections	BR: 26.8/FCR: 39.1	<0.001
			Severe infections (>65 years)	BR: 20.6/FCR: 47.7	<0.001
		Fischer et al. [24]	Severe infections	12.8	—
iNHL	Hematological	Flinn et al. [25]	Lymphocytopenia	BR: 61/R-CHOP;R-CVP: 33;28	<0.05
		Weide et al. [33]	Leukocytopenia	24	—
			Thrombocytopenia	13	
	Non-hematological	Rummel et al. [23]	Alopecia	BR: 0/R-CHOP: 100	<0.0001
			Peripheral neuropathy	BR: 7/R-CHOP: 29	<0.0001
			Infections	BR: 37/R-CHOP: 50	0.0025
			Skin reactions/rashes	BR: 16/R-CHOP: 9	0.024
		Brown et al. [22]	Severe infections	BO: 5/FCO: 19	—
		Flinn et al. [25]	Alopecia	BR: 4/R-CHOP;R-CVP: 51;21	All <0.05
			Peripheral neuropathy	BR: 9/R-CHOP;R-CVP: 44;47	
			Infections	BR: 55/R-CHOP;R-CVP: 57;50	
			Skin rashes	BR: 20/R-CHOP;R-CVP: 12;16	
			Nausea	BR: 63/R-CHOP;R-CVP: 58;39	
			Vomiting	BR: 29/R-CHOP;R-CVP: 13;13	
			Constipation	BR: 32/R-CHOP;R-CVP: 40;44	
Other indolent lymphomas	Hematological	Salar et al. [26]	Neutropenia	5.35% of cycles	—
	Non-hematological	Salar et al. [26]	Infections	1.9% of cycles	—
Aggressive NHL	Hematological	Weidmann et al. [27]	Neutropenia	23% of cycles	—
		Weidmann et al. [28]	Neutropenia	6.7	—
			Thrombocytopenia	8.3	
		Ohmachi et al. [29]	Lymphocytopenia	78.0	—
			Neutropenia	76.3	
			Leukopenia	72.9	
			CD4 lymphocytopenia	66.1	
			Thrombocytopenia	22.0	
		Vacirca et al. [30]	Neutropenia	36	—
			Leukopenia	29	
			Thrombocytopenia	22	
			Anemia	12	
	Non-hematological	Weidmann et al. [27]	Infections	10% of cycles	—
			Nausea	6% of cycles	
			Renal impairment	4% of cycles	
			Fatigue	6% of cycles	
			Diarrhea	4% of cycles	
		Weidmann et al. [28]	Alopecia	6.7	—
			Infections	3.3	
			Nausea	1.7	
			Fever	1.7	
		Ohmachi et al. [29]	Increased ALT	8.5	—
			Increased -GTP	6.8	
			Anorexia	6.8	
			Maculopapular rash	5.1	
			Increased AST	3.4	
			Constipation	3.4	
T-cell lymphoma	Hematological	Damaj et al. [31]	Neutropenia	30	—
			Thrombocytopenia	24	
		Zaja et al. [32]	Neutropenia	44	—
			Thrombocytopenia	25	
	Non-hematological	Damaj et al. [31]	Infections	20	—
MCL [see Table II]					

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BO, bendamustine plus obinutuzumab; FCO, fludarabine plus cyclophosphamide plus obinutuzumab; -GTP, gamma-glutamyl transferase.

Other indolent lymphomas

Upfront treatment in marginal zone lymphoma (MZL), Waldenstrom's macroglobulinemia (WM) and mucosa-associated lymphoid tissue (MALT)-lymphoma

In the StiL NHL-1 2003 trial, BR was non-inferior to R-CHOP in MZL ($n = 67$) and superior in WM ($n = 41$) in terms of PFS [23]. The overall CR rates were higher with BR (40%) compared with R-CHOP (30%). In a survival update of this trial the beneficial results in favor of BR are maintained at a median follow-up of 87 months. The median OS in patients with WM and MZL were not yet reached and were not significantly different [34].

In the BRIGHT trial, BR was as effective as R-CHOP or R-CVP in patients with MZL ($n = 46$) in terms of CR rates,

Table II. Bendamustine-rituximab combinations in Mantle cell lymphoma.

Reference	Regimen	Study type	Line of therapy	Patient no.	ORR (%)	CR (%)	Leukocytopenia grade 3/4	Thrombocytopenia grade 3/4
Rummel *et al.* [23]	6 × BR, no maintenance	Phase III	First line	46	93	40	37%*	5%*
Flinn *et al.* [25]	6 × BR	Phase III	First line	36	94	50	33%*	10%*
Rummel *et al.* [37]	4 × BR	Phase II	Relapse	16	75	25	35%*	7%*
Robinson *et al.* [43]	6 × BR	Phase II	Relapse	12	92	42	30%*	3%*
Weide *et al.* [44]	4 × BMR	Phase II	Relapse	18	78	33	78%	10%
Visco *et al.* [45]	6 × R-BAC	Phase II	First line	20	100	95	32%	70%
Relapse	20	80	70	67%	83%			
Friedberg *et al.* [46]	6 × BR + Bortezomib	Phase II	Relapse	7	71	N/A	17%*	17%*
Jerkeman *et al.* [47]	6 × BR + Lenalidomide	Phase II	First line	51	97	79	32%	6%
Zaja *et al.* [48]	6 × BR + Lenalidomide	Phase II	Relapse	42	90	71	69%	14%
Hess *et al.* [49]	4 × BR + Temsirolimus	Phase II	Relapse	11	91	45	40%*	13%*

*Includes also follicular lymphoma.
N/A, not available.

with a possibly better therapeutic index [25,36]. The CR rate/ORR was 20%/92% with BR and 24%/71% with R-CHOP/R-CVP, respectively.

A non-randomized phase II study was recently performed in 58 evaluable patients with untreated CD20 + MALT lymphoma (median age = 62 years; Stage III/IV = 34%) [36]. After three cycles, the ORR was 100%, with 76% CR/CRu. Of the patients in PR after three cycles, 93% converted to CR after six cycles; 77% of patients required only four cycles to achieve CR.

Bendamustine in relapsed/refractory patients

The efficacy of bendamustine was also investigated in rituximab-pre-treated or rituximab-refractory patients with non-follicular, indolent B-cell lymphoma [4,37]. In the multi-center American trial, several MZL patients were treated with single-agent bendamustine. The ORR varied from 71–86%, with a CR/CRu rate of 43% in patients with MZL. Several other trials in rituximab-refractory patients also included patients with iNHL other than FL and have shown promising results, although the numbers of patients in these trials were quite small [38]. The only randomized phase III trial in pre-treated patients is the NHL-2 2003 trial [39], in which BR was compared to fludarabine plus rituximab (FR: fludarabine 25 mg/m^2 days 1–3) and was superior with a PFS of 18 months in the BR-treated patients. The OS update revealed a significant difference in favor of BR (110 months) over FR (49 months; $p = 0.0125$) [40].

Recently, BR has also been shown to be active in pre-treated patients ($n = 14$) with non-gastric MALT lymphoma in a retrospective analysis [41]. The CR rate was 71%, the PR rate 21% and treatment was generally well tolerated. At a median follow-up of 23 months, only one patient relapsed.

Consensus panel recommendations – Other indolent lymphomas

- BR may be considered as front-line treatment in WM and MZL;
- Four cycles of BR should be considered for rituximab-pretreated patients; and
- Single-agent bendamustine can be considered for rituximab-refractory patients.

Aggressive non-Hodgkin lymphoma

To date, there are limited data regarding the use of bendamustine or BR in aggressive lymphoma. Weidmann et al. [28] delivered bendamustine at 120 mg/m^2 on days 1 and 2, every 3 weeks up to six cycles [28] in 18 patients evaluable for response and toxicity, 10 of whom were refractory to previous chemotherapy. ORR in the evaluable 18 patients was 44% (16% CR). Based on those data, Weidmann et al. combined a dose of 120 mg/m^2 given on days 2 and 3 with rituximab (375 mg/m^2) every 3 weeks in 14 patients > 80 years (median age = 85 years) not eligible for CHOP-like regimens [27]. Response was achieved in 69% (54% CR) of patients. The median OS was 7.7 months, although 43% of patients were alive without disease at 2 years. Treatment was delayed in eight patients and in 33% of treatment cycles.

In a phase I study of BR in patients with relapsed/refractory aggressive B-cell NHL [42], bendamustine (120 mg/m^2/day) combined with rituximab (375 mg/m^2) was well-tolerated and active ($n = 6$; five complete and one partial response). Two phase II studies of BR in relapsed/refractory aggressive B-NHL also have been reported [29,30]. In a Japanese/Korean study, patients ($n = 59$; median age = 67 years) with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) treated with 1–3 prior chemotherapy regimens received rituximab

375 mg/m^2 on day 1 and bendamustine 120 mg/m^2 on days 2 and 3 of each 21-day cycle up to six cycles [29]. The ORR was 62.7% (CR 37.3%), with a median PFS of 6.7 months. Treatment delay and dose reduction was necessary in 35.3–50% and 17–32% in each cycle, respectively. In the US study, patients with relapsed/refractory DLBCL ($n = 48$; median age = 74) received bendamustine mostly at 120 mg/m^2 ($n = 57$) on days 1 and 2 and rituximab (375 mg/m^2) on day 1 every 28 days up to six cycles [30]. In total, 89% had stage III or IV disease and 63% had high International Prognostic Index scores; the median number of prior therapies was one. The ORR was 45.8% (CR = 15.3%) with a median PFS of 3.6 months.

Consensus panel recommendations – Aggressive non-Hodgkin lymphoma

- Front-line setting:
  - For patients who do not qualify for CHOP-like regimens (especially elderly patients with severe co-morbidities, particularly cardiac disease), BR can be considered;
  - A dose reduction from 120 to 90 mg/m^2 is recommended in cases of unacceptable toxicity;
- For patients with relapsed/refractory DLBCL:
  - Recommended dose of 90–120 mg/m^2 given on 2 consecutive days combined with rituximab every 3 weeks for 4–6 cycles; and
  - A dose de-escalation (120-90-70 mg/m^2 on days 1 and 2) is recommended in cases of toxicity.

Mantle-cell lymphoma (MCL)

The activity of BR has been demonstrated in two prospective trials. In the first, this regimen achieved an ORR of 75% (25% CR) in relapsed MCL; however, none of these patients were rituximab pre-treated [37]. These data were confirmed by Robinson et al. [43] in relapsed MCL, including 56% of patients pre-treated with rituximab. The ORR was 92%, with 42% CR. Results were further supported by two randomized first line studies. In the StiL trial, BR achieved high ORR (93%, 40% CR) comparable to R-CHOP (90%, 30% CR) and a longer PFS [23]. Similarly, in the BRIGHT trial, an ORR of 94% (50% CR) was similar to R-CHOP (87%, 30% CR), but significantly better than with R-CVP (50%, 14% CR) [25]. Most importantly, BR was well tolerated with a favorable toxicity profile [Table II] [23,25,37,43–49].

Bendamustine chemotherapy combinations + Rituximab

Various other chemotherapy combinations have been explored including fludarabine, mitoxantrone, cytarabine and other drugs [44,45]. While these combinations have been active, the increased hematological toxicity makes them unattractive options. As an example, the combination with mitoxantrone (10 mg/m^2 day 1) achieved high response rates in relapsed MCL (78%, 33% CR), but was hampered by Grade 4 leukocytopenias [44]. In both the Visco et al. [45] and Weide et al. [44] studies the results were considered superior to BR alone.

BR plus targeted approaches

At least four different combinations with targeted agents have been reported in relapsed MCL: bortezomib, ibrutinib, lenalidomide and temsirolimus [50–53]. Based on the favorable toxicity profile of BR and the hypothesis that these molecular approaches have a different mechanism of action on the malignant cell, numerous phase II/III studies have been recently reported or are currently ongoing.

At least three phase II studies have explored the combination of BR and lenalidomide [47,48,54]. In one Phase I study, patients received bendamustine (90 mg/m^2 days 1 and 2 every 28 days) and lenalidomide (escalating from 5 mg 21/28 days) for six cycles followed by 6 months of lenalidomide [54]. At the highest dose, rituximab 375 mg/m^2 was added on day 1 of each cycle for patients with B-NHL. Of 20 patients, seven responded (35%), including four durable complete remissions. A Scandinavian trial administered bendamustine and lenalidomide at a dose of 90 mg/m^2 on days 1 and 2 and 15 mg on days 1–21, respectively, in first-line treatment, but none of the patients could tolerate this scheme due to cutaneous toxicity and myelosuppression [47]. After starting lenalidomide at a reduced dose (10 mg) beginning at cycle 2, all 18 patients responded to this regimen. The Italian trial investigated BR at a reduced dose (70 mg/m^2 days 1 + 2) combined with lenalidomide (10 mg on days 1–14) in relapsed MCL [48]. So far, no unexpected toxicity has been observed. Thus, the combination of BR and lenalidomide seems to be highly effective, but dose reductions should be considered.

Finally, BR (90 mg/m^2 days 1 + 2) plus temsirolimus in relapsed MCL and FL has been tested [49]. All evaluable patients of the phase I part of the study responded, with no unexpected hematotoxicity.

Table III. Main characteristics of the published studies on Bendamustine in R/R PTCL.

Reference	Study	Patient no.	Histology	% refractory patients	Median age (years)	B. dosage (mg/m^2)	ORR (%)	CR (%)	PFS (months)
Damaj *et al.* [31]	Phase II	60	AILT PTCL-nos sALCL	45	66	120 day 1–2/3 w	50	28	3.63
Zaja *et al.* [32]	Retrospective	20	AILT PTCL-nos sALCL, T-PLL, T-LGL, MF, SS	68	73	60-100 day 1–2/4 w	55	10	6 PFS 44%
Herbaux *et al.* [58]	Retrospective	15	T-PLL	33	62	70–120 day 1–2/3 w	53	20	5

AILT, angioimmunoblastic T-cell lymphoma; PTCL-nos, peripheral T-cell lymphoma-not otherwise specified; sALCL, systemic anaplastic large cell lymphoma; T-PLL, T-cell prolymphocytic leukemia; T-LGL, T-large granular lymphocytosis; MF, mycosis fungoides; SS, Sezary Syndrome.

Consensus panel recommendations – Mantle-cell lymphoma

- Front-line setting:
  - For elderly and compromized patients who are not candidates for autologous stem cell transplantation (ASCT);
  - Also an option for younger patients with low proliferation/lactate dehydrogenase (LDH);
  - Other bendamustine chemotherapy combinations + rituximab are hampered by significant myelotoxicity; and

- BR is recommended in relapsed patients as an alternative to ibrutinib.

T-cell lymphoma

T-cell lymphomas are a heterogeneous group of diseases with a very poor outcome with CHOP or related regimens [55–57].

There are currently no data using bendamustine as first-line treatment of peripheral T-cell lymphoma (PTCL). Limited data, however, exist in relapsed/refractory PTCL [Table III] [31,32,58]. Prospective data from a French study included 60 patients with predominantly angioimmunoblastic lymphadenopathy and PTCL not otherwise specified [31]. Twenty-seven patients (45%) were refractory to their last prior chemotherapy. Bendamustine was dosed at 120 mg/m^2 on days 1 and 2 every 3 weeks up to six cycles. The ORR was 50%, including CR in 28% of patients. The maximal response rate was obtained after four cycles and transformation from PR to CR has been obtained after four cycles. The median values for duration of response (DoR), PFS and OS were 3.5, 3.6 and 6.2 months, respectively. Seven per cent of patients had a prolonged response of >1 year.

A second retrospective study involved 20 patients with leukemic, nodal and cutaneous T-cell lymphoma [32]. Bendamustine was dosed at 90 (60–100) mg/m^2 on days 1 and 2 every 4 weeks up to eight cycles. In this group of very high risk patients, ORR was 55% (CR 10%).

In a small series of relapsed/refractory T-prolymphocytic leukemia ($n = 9$) or in first-line ($n = 6$), bendamustine was given at 70–120 mg/m^2, days 1 and 2, every 3 weeks for an intended total of six cycles. ORR was obtained in 53% (CR 20%). Median PFS and OS were 5 months and 8.7 months, respectively [58].

Consensus panel recommendations – T-cell lymphoma

- In relapsed/refractory PTCL, bendamustine at a dose of 90–120 mg/m^2 on days 1 and 2 every 3 weeks for four cycles:
  - G-CSF is recommended for primary prevention of febrile neutropenia; and

- No combination therapy can be recommended until additional information becomes available.

Hodgkin lymphoma (HL)

A number of case reports suggest activity for bendamustine monotherapy in heavily pre-treated patients, even after previous autologous or ASCT [Table IV] [59–62]. Corazzelli et al. [60] reported a retrospective analysis of 41 relapsed/refractory patients who had received single-agent bendamustine through an Italian named-patient program (NPP). Patients received bendamustine with different doses and schedules: 90-100-120 mg/m^2 on 2 consecutive days every 3 or 4 weeks, according to physicians' choice. Patients had received a median of four prior chemotherapy lines, including ASCT in 85% of cases. The ORR after 2–4 cycles was 78% (29% CR); after the completion of 6–8 courses it was 58% (31% CR). Median PFS and median DoR were 11 months and 9 months, respectively. Another study included patients from a French compassionate use program for patients with relapsed/refractory HL after

Table IV. Clinical activity in Hodgkin lymphoma.

Reference	Patient no.	Dose/schedule	ORR %	CR %	Median PFS (months)
Moskowitz *et al.* [62]	36	120 mg/m^2 on days 1 and 2 every 28 days	53	33	5.2
Corazzelli *et al.* [60]	41	90–120 mg/m^2 on days 1 and 2 every 28 days	58	31	11
Ghesquieres *et al.* [61]	28	90–120 mg/m^2 on days 1 and 2 every 28 days	50	29	5.7
Anastasia *et al.* [60]	67	90–120 mg/m^2 on days 1 and 2 every 28 days	57	25	10

ASCT or those refractory to three lines of chemotherapy [61]. The initial dose of bendamustine varied between 90–120 mg/m^2 on days 1 and 2 every 28 days. The median number of therapies before bendamustine was five (range = 3–8) and 89% (25/28) of the patients had prior ASCT. The median PFS was 5.7 months and 10.2 months in patients with CR; the median DoR was 4.6 months. Toxicity was mild, with infrequent Grade 3/4 AEs in the aforementioned studies. In a Phase II study in 36 patients with relapsed/refractory HL and a median of four prior treatments, bendamustine was associated with an ORR of 53%, including 12 complete responses (33%) and seven partial responses (19%) [62]. The median response duration was 5 months and five patients (20% of those eligible) proceeded to alloSCT.

These studies confirm the activity of bendamustine monotherapy in a sub-set of heavily pre-treated patients. The response appears to be quite rapid.

It is important to note that none of these studies included patients previously pre-treated with brentuximab vedotin [63]. Recently two patients relapsed/refractory to brentuximab vedotin were reported to be chemosensitive to subsequent bendamustine therapy [64]. In addition, Zinzani et al. [65] reported retrospective data on the effectiveness of bendamustine in patients after failure of brentuximab vedotin. Twenty-seven patients were available for the response after six cycles of bendamustine treatment, 10 (37%) patients obtaining a CR with an ORR of 55% [65].

Recently, LaCasce et al. [66] reported preliminary data on a phase I/II single arm study of brentuximab vedotin in combination with bendamustine for patients with relapsed/refractory HL (bendamustine at 90 mg/m^2 [potential de-escalation dose of bendamustine to 70 or 50 mg/m^2] and brentuximab vedotin at 1.8 mg/kg). Forty-eight of 54 patients were available for the response after four cycles of bendamustine plus brentuximab vedotin, with 40 (83%) patients obtaining a CR and an ORR of 96%. This combination did not interfere with stem cell collection.

Consensus panel recommendations – Hodgkin lymphoma

- Bendamustine represents an appropriate salvage approach in elderly patients; and
- Bendamustine can also be used as a bridge to ASCT, especially in combination with Brentuximab.

Multiple myeloma

The standard treatment approach is combination therapy incorporating bortezomib, lenalidomide or thalidomide, usually followed by ASCT in patients < 75 years. In relapsed/refractory disease, treatment options include lenalidomide and bortezomib or carfilzomib. However, options are very limited for those who become resistant to these agents. Consequently, the lack of effective treatment for the resistant relapsed setting is a significant unmet need.

Bendamustine has been used for more than a decade for the treatment of myeloma. However, only recently a number of studies reporting on its efficacy and safety in different settings and combinations have emerged [67].

A phase III trial showed that a combination of bendamustine (150 mg/m^2 on days 1 and 2 of a 28-day cycle) and prednisone (BP) was superior to melphalan and prednisolone (MP) in 131 newly diagnosed patients with myeloma [68]. BP led to significant increases in CR (32% vs 13%, $p = 0.007$), duration of remission (18 vs 12 months, $p < 0.02$) and time to treatment failure (14 vs 10 months, $p < 0.02$) compared with MP. More recently, a combination of bendamustine (60 mg/m^2, days 1 and 2), prednisone and bortezomib achieved an ORR of 82% among 49 patients with newly-diagnosed myeloma [69].

Retrospective studies and early phase clinical trials have demonstrated activity of bendamustine in combination with other agents (including thalidomide, lenalidomide and bortezomib) in patients with relapsed/refractory disease, many of whom were heavily pre-treated [Table V] [70–78]. While data from comparative trials are not yet available, PFS and OS data from bendamustine-containing combinations [70–78] compare favorably with those from a retrospective analysis of patients refractory to current treatments (PFS 5 months and OS 9 months) [79].

Bendamustine has a favorable toxicity profile without peripheral neuropathy and generally moderate hematological and gastrointestinal events. Although the efficacy achieved with combinations of bendamustine and other

Table V. Bendamustine in relapsed/refractory multiple myeloma.

Author	Regimen	Study type	Median no. (range) of lines of prior therapy	Patient no.	Overall response/remission rate (%)	Median PFS (months)	Median OS (months)
Bendamustine ± steroids							
Michael *et al*. [76]	B (80–150 mg/m^2; days 1, 2 of 28-day cycle): 39% monotherapy; 61% + steroids	Retrospective analysis	2 (1–5)	39	36 (PR and vgPR)	7 (EFS)	17
Damaj *et al*. [71]	B (120 –150 mg/m^2; days 1, 2 of 28-day cycle) + prednisolone	Compassionate use program	4 (1–9)	110	30 (≥ PR)	9.3	12.4
Bendamustine + steroids + thalidomide/lenalidomide							
Pönisch *et al*. [77]	B (60 mg/m^2; days 1, 8, 15) + escalating doses of thalidomide + prednisolone	Phase I	2 (1–6)	28	86 (≥ PR)	11	19
Grey-Davies *et al*. [72]	B (60 mg/m^2; days 1, 8 [15*] of 28-day cycle) + thalidomide + dexamethasone	Compassionate use program	5 (3–7)	23	61 (≥ SD)	3	13
Lau *et al*. [73]	B (cumulative dose up to 200 mg/m^{2§}; 28-day cycles) + thalidomide + dexamethasone	Retrospective analysis	4 (3–6)	30	87 (≥ SD)	4	7.2
Lentzsch *et al*. [74]	B (MTD 75 mg/m^2; days 1, 2 of 28-day cycle) + lenalidomide + dexamethasone	Phase I/II	3 (1–6)	29	76 (incl. minimal responses)	6.1	Not reached
Bendamustine + bortezomib ± steroids							
Ludwig *et al*. [74]	B (70 mg/m^2; days 1, 4 of 28-day cycle) + bortezomib + dexamethasone	Phase II	2 (1–6)	79	60.8 (75.9% incl. minor responses)	9.7	25.6
Berenson *et al*. [70]	B (MTD 90 mg/m^2; days 1, 4 of 28-day cycle) + bortezomib	Phase I/II	75% received ≥ 4 prior therapies	31 (at MTD)	52 (incl. minimal responses)	8.4**	13.3**
Pönisch *et al*. [78]	B (60 [–120] mg/m^2; days 1, 2 of 21-day cycle) + bortezomib + prednisone	Restrospective	2 (1–9)	78	69 (≥PR) (76%†; 61%‡)	11† 3‡	50† 5‡

*Day 15 administration discontinued for the final 13 patients due to hematologic toxicity.
**Among all 40 patients enrolled.
†Among patients without severe hematologic toxicity due to previous treatments.
‡Among patients with severe hematologic toxicity due to previous treatments.
§Starting dose either 60 mg/m^2 on days 1, 8 and 15 or 100 mg/m^2 on days 1 and 8. Dose scaled up to 200 mg/m^2/cycle based on neutrophil counts.
EFS, event-free survival; MTD, maximum tolerated dose; N/A, not available; OS, overall survival; PFS, progression-free survival; PR, partial response/remission; SD, stable disease; vgPR, very good partial response/remission.

agents is promising, the overlapping myelosuppressive effects of these agents [80] may be problematic.

In general, the doses of bendamustine used in combination with steroids are higher than those used in combination with biological agents (60–150 mg/m^2 vs 60–90 mg/m^2, respectively).

Renal impairment

Bendamustine is a suitable treatment option for patients with renal impairment, including those with MM undergoing dialysis [81]. In the frontline setting, bendamustine (60 mg/m^2 on days 1 and 2) combined with bortezomib and prednisone led to an 83% response rate among 18 patients with myeloma and renal insufficiency (glomerular filtration rate $<$ 35 ml/min) [82]. Renal function improved in 72% of patients. Among 36 patients with relapsed/refractory myeloma and renal failure, a combination of bendamustine (60 mg/m^2 on days 1 and 2), bortezomib and prednisone was associated with a 67% response rate, with 11 patients demonstrating a complete response [83].

ASCT conditioning

Data are also emerging on the use of bendamustine to intensify ASCT conditioning regimens. In a recent phase I study in 25 patients, bendamustine, up to a dose of 225 mg/m^2, added to melphalan 200 mg/m^2, did not increase either the toxicity of melphalan or the transplant risk [84]. The efficacy of this approach is now being investigated in a phase II study.

Consensus panel recommendations – Multiple myeloma

- In the front-line setting, a dose of 100 mg/m^2 every 4 weeks is recommended, rather than 120–150 mg/m^2, as suggested by the label;
- In front-line combination therapy, a 4-weekly bendamustine dose of 60 mg/m^2, escalated to 100 mg/m^2, is recommended; and
- For relapsed/refractory patients, a 4-weekly bendamustine dose of 60–90 mg/m^2 is recommended.

Hairy cell leukemia

One study has reported significant activity for BR in the treatment of patients with multiple relapsed/refractory ($\geq$2 prior therapies) hairy cell leukemia, using two different dose levels of bendamustine [85]. At 70 mg/m^2 ($n = 6$) and 90 mg/m^2 ($n = 6$) doses of bendamustine, the ORR was 100%, with seven (58%) achieving complete remission. Minimal residual disease was absent in 67% and 100% of complete remissions, respectively. All six without minimal residual disease remained in complete remission at 30–35 (median = 31) months of follow-up. Further studies into the long-term efficacy and safety of BR in hairy cell leukemia are underway, utilizing the higher dose (90 mg/m^2) [85].

Practical recommendations for bendamustine

Routine schedule

The FDA-approved dose of 120 mg/m^2 IV for 2 consecutive days every 3 weeks is rarely used, except in patients with aggressive lymphoma, because of its poor tolerability, resulting in frequent dose reductions and delays [3,4,29]. The more commonly used doses and schedules of bendamustine vary depending on the line of therapy, whether it is being delivered as a single agent or in combination with other drugs, and a number of patient and disease characteristics [Table VI]. Increasing the dose of bendamustine in patients not responding to a lower dose has not been shown to be associated with benefit and is discouraged.

However, in most indications, bendamustine is combined, primarily, with rituximab [23,37,43] as well as other agents [46,86]. In the front-line setting, therapy is generally administered every 4 weeks for six cycles, unless prohibitive toxicity is encountered. The same doses can be considered in the relapsed setting; however, four cycles of therapy generally suffices because of the risk of prolonged myelotoxicity.

It should be noted that, where a dose of 90 mg/m^2 at an interval of 28 days for the treatment of CLL and low-grade NHL and where the use of bendamustine in a renal impairment setting have been recommended in this Consensus panel review, these reflect the personal opinions of the authors based on currently available clinical evidence and differ from the bendamustine prescribing information.

Data with rituximab maintenance after induction therapy with bendamustine alone or BR have only recently been reported [34] and, therefore, experience with this strategy is limited.

Administration of bendamustine

Bendamustine can be administered over 30 min; however, acute infusion-related events are less common if it is delivered over 60 min. Bendamustine can also induce a chemical-related phlebitis, the risk of which can be minimized by diluting the drug in 500 ml of normal saline. Since bendamustine is moderately emetogenic, 5-HT3 antagonists should be used, with

Table VI. Consensus panel dose recommendations and dose reductions with bendamustine therapy.

Dose recommendation	Dose (days 1 and 2)	Cycles	Notes
CLL			
Front line, single agent	100 mg/m^2 every 4 weeks	6	Rarely used in this situation
Front line + rituximab	90 mg/m^2 every 4 weeks	6	
R/R ± rituximab	70 mg/m^2 every 4 weeks	4	
iNHL			
Front line + rituximab	90 mg/m^2 every 4 weeks	6	No rituximab maintenance
R/R ± rituximab	70–90 mg/m^2 every 4 weeks	4	
Follicular		6	
Waldenstroem		4–6	
Marginal zone		4–6	
Aggressive non-Hodgkin lymphoma			
Front line + rituximab	120 mg/m^2 every 3 weeks	6	Reduced as needed
R/R ± rituximab	90–120 mg/m^2 every 3–4 weeks	6	Clinical experience suggests that 120 mg/m^2 is not well tolerated by a significant sub-population of patients
Peripheral T-cell lymphoma (includes angioimmunoblastic and NOS)			
R/R	90–120 mg/m^2 every 3 weeks	4–6	Start with 120 mg/m^2; can be reduced to 90 mg/m^2 if needed
Mantle-cell lymphoma			
Front line + rituximab	90 mg/m^2 every 4 weeks	6	Patients not considered for high-dose therapy
R/R ± rituximab	90 mg/m^2 every 4 weeks	4–6	Can be reduced to 70 mg/m^2 if needed.
Hodgkin lymphoma			
R/R	90 mg/m^2 every 3 weeks	4–6	No difference has been observed at doses 100–120 mg/m^2 Number of cycles based on tolerance
Multiple myeloma			
Front line single agent	100 mg/m^2 every 4 weeks	6	Label suggests 120–150 mg/m^2, but this is not recommended by the panel
Front line combination therapy	60–90 mg/m^2 every 4 weeks	6	Start at 60 mg/m^2 and escalate to 90 mg/m^2 with tolerability
R/R	60–90 mg/m^2 every 4 weeks	6	
Dose reduction			
CLL			
Front line + rituximab	90 to 70 mg/m^2		
R/R + rituximab	70 mg/m^2 to dose delay*		
iNHL			
Front line or retreatment	60-min infusion of 500 mL		To reduce skin reactions The reconstituted concentrate (50 mL) should be diluted immediately with 0.9% sodium chloride solution, otherwise there is an increased risk of rash Once reconstituted and diluted it is stable for 3–4 h at room temperature or for 48 h in the fridge
Dose reduction	90 to 70 mg/m^2		Discontinue if still problems at 70 mg/m^2
Aggressive non-Hodgkin lymphoma			
Front line	120 to 90 mg/m^2		
R/R	1st reduction: 120 to 90 or 90 to 70 mg/m^2 2nd reduction: 90 to 70 mg/m^2		In a Japanese/Korean phase II study, the 2nd dose reduction was from 90 mg/m^2 to 60 mg/m^2
Hodgkin lymphoma			
R/R	90 to 70 mg/m^2		
Multiple myeloma			
Monotherapy	100 to 70 mg/m^2		
Combination therapy	90 to 60 mg/m^2		

iNHL: in the front-line setting, bendamustine should not be used as a single agent. Consider pre-medicating with dexamethasone (8 mg, IV, in combination with 5-HT3 antagonist) or hydrocortisone (50–100 mg). Normally recommend dose delay before dose reduction. Use dose reduction as a first step in those patients with transient non-hematological toxicity.

Aggressive non-Hodgkin lymphoma: BR can be used in those patients who cannot use R-CHOP or a CHOP-like regimen. Definition includes follicular lymphoma, grade 3b. No recommendations for Burkitt's lymphoma or lymphoblastic lymphoma.

T-cell lymphoma: bendamustine has no known role in the front-line setting.

Mantle-cell lymphoma: further dose reductions of bendamustine are needed when in combination with potentially myelosuppressive agents (e.g. ibrutinib, bortezomib, lenalidomide).

Multiple myeloma: bendamustine should be dosed on two days (Days 1 + 2, Days 1 + 8 or Days 1 + 4) within a 28 day cycle. Bendamustine would be considered first-line therapy in non-transplant-eligible patients.

*Doses < 60 mg/m^2 are considered sub-therapeutic and dose delays are preferred.

8 mg of concomitant IV dexamethasone in those patients who experience severe nausea or vomiting.

Prophylactic antimicrobials are not recommended for routine use, but may be considered especially in CLL patients with a history of recurrent infections or with a CD4 count under 200/mm^3. These can be discontinued when the count returns to > 200/mm^3. Due to a high incidence of CD4 lymphocytopenia (44% of Grade 4) and the occasional observance of herpes viral infections [29] in aggressive NHL patients, use of prophylactic antiviral agents such as acyclovir may be considered for patients deemed to be at an increased risk.

Prophylactic administration of G-CSF should be given according to consensus guidelines and may be considered especially in patients receiving a higher dose of bendamustine (120 mg/m^2) [87]. Patients with HBV infection and HBV carriers should be given antiviral prophylaxis if BR is used. Patients should also be instructed to avoid live vaccines. If an influenza vaccine is to be given, it should be administered at least 6 months after completion of therapy.

Bendamustine-related hypersensitivity reactions were previously considered uncommon as they often occurred after the patient had returned home and, thus, often went unreported. It is now more widely recognized that infusion reactions are common following bendamustine therapy and may be acute and/or delayed. Several hours after administration, patients often experience fevers as high as 102°F (38.9°C), accompanied by chills. This syndrome tends to be responsive to acetaminophen.

Because patients with CLL or NHL with a large tumor burden or renal insufficiency are at risk of tumor lysis syndrome, allopurinol is often prescribed prophylactically in conjunction with bendamustine therapy. However, this practice is strongly discouraged as co-administration increases the likelihood of a mild-to-severe skin rash that may require treatment with corticosteroids and delay subsequent cycles of therapy. If considered necessary, such as in patients with hyperuricemia prior to treatment, allopurinol can be prescribed, but it should be stopped at least 24 h prior to the first dose of bendamustine.

Dose modifications

Bendamustine is myelosuppressive, especially in patients who have received prior chemotherapy. Dose reductions should be considered in the setting of neutropenic fever, if G-CSF is unsuccessful, or with prolonged myelosuppression. Prophylactic growth factors should not be used unless there has been an episode of neutropenic fever or prolonged neutropenia. Dose reductions [Table VI] should be also considered in those patients with reversible non-hematologic toxicity.

Toxicities

Despite the lengthy history of use of bendamustine, few new adverse effects have been identified. The major toxicities of bendamustine include myelosuppression, nausea, vomiting and fatigue [Table I]. Rash can be problematic, with no generally accepted strategy for management of severe cases except for topical and/or systemic steroids and supportive measures. However, empirical combinations of bendamustine with other myelosuppressive agents are discouraged outside of clinical trials. An anecdotal case of neurologic toxicity has been reported [88].

Co-morbidities

There is no difference in drug metabolism based on age [89]; therefore, dose modifications are not required for fit patients. However, the dose of bendamustine alone or in combination with rituximab may be reduced one dose level according to patient performance status and co-morbidities.

Autoimmune complications are not considered contraindications to the use of bendamustine. Treatment with bendamustine, alone or with rituximab, may be initiated in CLL patients with an associated autoimmune hemolytic anemia (AIHA) or immune thrombocytopenia (ITP) unresponsive to steroids. AIHA or ITP following bendamustine with or without rituximab is uncommon [2,14,90].

Liver impairment

As a result of the short intermediate half-life of bendamustine, the standard dosing schedule of 2 consecutive days in 21- or 28-day cycles, and the extensive metabolism of bendamustine via multiple pathways, accumulation is unlikely in patients with hepatic insufficiency [91]. In particular, bendamustine is primarily metabolized by hydrolysis via extrahepatic pathways, with more limited hepatic metabolism. One study, however, has shown a longer intermediate half-life and slower clearance of bendamustine in patients with moderate-to-severe hepatic impairment [92]. However, bendamustine has been given safely and effectively in patients with a serum bilirubin $>$ 20 mg% [13,93].

Second malignancies

Based on the results of randomized trials, there is no signal for an increase in second malignancies with bendamustine compared with other available therapies [2,23].

Current status and future directions

Since bendamustine became available worldwide, the indications for its use have expanded considerably. It is now a standard agent for the treatment of CLL, indolent and aggressive B-NHL and T-NHL and HL, as well as MM. With additional experience has come a better

understanding of how to deliver the drug in a safer manner. However, we are entering a revolutionary period in the treatment of CLL and lymphomas. Superiority over rituximab has been suggested for newer anti-CD20 mAb such as obinutuzumab, at least for CLL patients in combination with chlorambucil [94]. Considerable interest is focused on novel agents that target the pathways within the B cells, including Syk (spleen tyrosine kinase), BTK (Bruton tyrosine kinase) and PI3K (phosphotidylinositol 3-kinase). Impressive activity has been reported with the BTK inhibitor ibrutinib in relapsed/refractory patients with CLL, notably in the unfavorable sub-group of patients with 17p-deletion CLL [95,96]. The PI3K-delta inhibitor, idelalisib, has also been recently approved for small lymphocytic lymphoma, follicular NHL and, in combination with rituximab, for relapsed CLL [97]. Additional active oral agents include the Bcl-2 inhibitor venetoclax, plus other drugs like immunomodulatory agents, proteasome and mTOR inhibitors, as well as small molecules targeting SYK, BTK and PI3K. Currently, however, these new pathway inhibitors achieve partial responses as single agents and require indefinite administration. Bendamustine is currently being used as the backbone of choice on which to build novel combinations incorporating these new targeted agents.

With the markedly increased use of bendamustine since the prior Consensus panel, additional information has been gained regarding its use. Hopefully the current recommendations will help expand the safe and effective administration of this agent, particularly in combination with novel agents leading to an improved patient outcome.

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