



## Brentuximab vedotin: clinical updates and practical guidance

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### Abstract

Brentuximab vedotin (BV), a potent antibody-drug conjugate, targets the CD30 antigen. Owing to the remarkable efficacy shown in CD30-positive lymphomas, such as Hodgkin's lymphoma and systemic anaplastic large-cell lymphoma, BV was granted accelerated approval in 2011 by the US Food and Drug Administration. Thereafter, many large-scale trials in various situations have been performed, which led to extensions of the original indication. The aim of this review was to describe the latest updates on clinical trials of BV and the in-practice guidance for the use of BV.

**Key Words** Brentuximab vedotin, CD30, Antibody-drug conjugate, Hodgkin's lymphoma, Anaplastic large cell lymphoma.

## INTRODUCTION

Since the first treatment of B-cell lymphoma in 1982 [1], extraordinary progress ensued in the development of monoclonal antibodies (mAbs) for lymphoma treatment. After the approval of the anti-CD20 antibody (rituximab) by the US Food and Drug Administration (FDA) in 1997, the development of other anti-CD20 mAbs with enhanced or novel mechanisms followed, such as ofatumumab or obinutuzumab. Alemtuzumab, an anti-CD52 mAb, has demonstrated promising activity against several T-cell neoplasms.

CD30 is preferentially expressed by several lymphoid neoplasms, such as classical Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL) [2]. Under physiological conditions, CD30 expression is confined to activated lymphocytes and eosinophils, usually on lymphoid tissues, but not on peripheral blood cells, which makes this antigen an attractive therapeutic target. However, early efforts to target CD30 with naked mAbs failed [3, 4], as CD30 is rapidly endocytosed after antibody binding, and subsequent effector cell activation does not occur.

Brentuximab vedotin (BV, SGN-35, ADCETRIS, Seattle Genetics Inc.) is an antibody-drug conjugate (ADC) comprising an anti-CD30 mAb conjugated to a highly potent anti-mi-

crotubule agent, monomethyl auristatin E (MMAE) [5]. Early trials were predominantly conducted in heavily treated patients with HL or ALCL. Unprecedented success led to the evaluation of the efficacy and safety of BV in a range of situations and patients. The aims of the current review were to summarize the most recent clinical outcomes of BV trials and to provide evidence-based guidance for the use of BV in practice. To find the most recent BV trials, we searched various databases including PubMed, EMBASE, and the Cochrane Central Register of Controlled Trials, and the clinical trial registers at ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP).

## CD30 IN LYMPHOMA

CD30 was first recognized in 1982, by using a monoclonal antibody (Ki-1), as a transmembrane glycoprotein highly expressed on Reed-Sternberg (RS) cells [6]. Subsequently, it was found in unique lymphoid neoplasms that consisted of bizarrely shaped large cells, which were later categorized as ALCLs [7]. Several other lymphoid neoplasms express CD30.

### Classical Hodgkin's lymphoma (HL)

Constitutive NF- $\kappa$ B activation, important for the proliferation, survival, and immune escape of RS cells, is a major pathogenic mechanism in HL [8, 9]. Complex receptor-cytokine networks, including CD30, BAFF, APRIL, RANKL, various interleukins, and LMP1 encoded by EBV, are established contributory factors [10]. CD30 is invariably expressed on RS cells and this receptor was thought to be activated by CD30L on eosinophils [11] and mast cells [12]. Conflicting reports also suggest that CD30-mediated NF- $\kappa$ B activation may be induced through ligand-independent pathways [13, 14].

### Anaplastic large cell lymphoma (ALCL)

ALCL is an aggressive T-cell lymphoma that accounts for 3% of all non-Hodgkin's lymphomas in adults [15]. Systemic ALCL (sALCL) is composed of ALK-positive and ALK-negative ALCL; the prognosis of sALCL is worse than that of indolent ALCL, including breast implant-associated ALCL and primary cutaneous ALCL (pcALCL) [16, 17]. The overall 5-year survival is 70%–80% for ALK-positive ALCL, but only 50% for ALK-negative ALCL [16, 18]; this may occur as patients with ALK-negative disease are often older at presentation.

By definition, as it was once called 'Ki-1 lymphoma', all types of sALCL express CD30 on the cell membrane and in the Golgi region [7]. In contrast with HL, the role of CD30 in pathogenesis of ALCL is poorly defined. In ALK-positive ALCL, in which various translocations involving an *ALK* gene and other partner genes occur [19–22], fusion proteins such as NPM-ALK regulate CD30 expression via JunB activation [23, 24]. Contradictory data exist on the role of CD30 activation in ALCL. In early studies, CD30 activation failed to induce NF- $\kappa$ B activation, instead inducing cellular apoptosis [25]; in contrast, CD30 activation was shown to induce NF- $\kappa$ B activation, which then upregulated cellular inhibitors of apoptosis [26]. It is now thought that short, physiological stimulation triggers apoptosis, whereas constitutive stimulation induces NF- $\kappa$ B activation [27]. In ALK-negative ALCL, the role of CD30 remains poorly understood.

### Other CD30 positive lymphomas

CD30 is expressed in approximately 20% of diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS) [28–30]; this is associated with favorable clinical outcomes, particularly in the germinal center B-cell-like (GCB) subtype, but not in the presence of EBV infection [29]. In primary mediastinal large B-cell lymphoma, CD30 is present in more than 70% of cases, although the expression is weak and heterogeneous compared with HL [31, 32]. EBV-positive DLBCL, NOS, formerly called EBV-positive DLBCL of the elderly, is frequently associated with CD30 expression [33, 34]. Rare lymphomas such as primary effusion lymphoma [35] and lymphomatoid granulomatosis [36] may express CD30.

CD30 is expressed in approximately 30% of peripheral

T-cell lymphoma, not otherwise specified (PTCL, NOS); this is associated with an adverse prognosis [16, 37]. Several extranodal T-cell lymphomas, such as enteropathy-associated T-cell lymphoma (13%–87%) [38, 39], and extranodal NK/T cell lymphoma (13%–75%) [40, 41], also express CD30. Primary cutaneous CD30-positive T-cell lymphoproliferative disorders (LPDs), which account for 30% of cutaneous T-cell lymphomas (CTCLs), always express CD30, except for a rare subtype named type B lymphomatoid papulosis (LyP) [42]. In mycosis fungoides (MF), CD30 expression was more frequently observed in the advanced stages [43, 44], with up to 100% expression when large cell transformation occurred [45, 46].

## MECHANISM OF ACTION OF BV

As CD30 is highly expressed on lymphoma cells and the cross-reactivity with normal tissue is minimal, this molecule is an ideal drug target. However, after only modest outcomes with naked antibodies were achieved [3, 4], a potent inhibitor of tubulin polymerization, MMAE, was conjugated at the ratio of four MMAEs per one SGN-30 via a protease-cleavable linker, which was named SGN-35. When bound to CD30, it was endocytosed and delivered to lysosomes, where MMAE was released to the cytosol to induce G2/M phase growth arrest and apoptosis [5, 47]. In addition, MMAE release into the adjacent malignant cells also contributed to the anti-tumor effect of BV [48].

## PRECLINICAL DATA

Several studies investigated the preclinical efficacy of BV. Early reports demonstrated the following key findings [49, 50]: 1) conjugation of MMAE to CD30 mAb did not affect the affinity for CD30 compared with the naked mAb; 2) compared with naked mAbs, conjugated mAbs demonstrated markedly enhanced cytotoxicity in CD30-positive cell lines only; and 3) *in vivo* studies using the mouse-xenograft model demonstrated that treatment with conjugated mAbs induced dose-dependent tumor regression and prolonged survival compared with untreated or control-treated mice.

## CLINICAL DATA

### Phase I studies

A phase I trial was conducted in patients with relapsed or refractory CD30-positive lymphoma [51]. BV (0.1–3.6 mg/kg) was administered every 3 weeks. Three of 12 patients who received 2.7 mg/kg BV experienced dose-limiting toxicities, such as febrile neutropenia or acute renal failure; consequently, the maximum tolerated dose (MTD) was determined as 1.8 mg/kg. The most common adverse events were fatigue (36%), pyrexia (15 patients, 33%), and diarrhea, nausea, and neutropenia (22% each) and were predominantly

limited to grades 1/2. Cumulative, dose-related peripheral neuropathy occurred in 16 patients and led to treatment discontinuation in 3 patients. The median time to onset was 9 weeks (range, 3–24 wk); at the final safety assessment, the resolution of symptoms was noted in 10 patients. Overall, 11 complete responses (CRs) and 6 partial responses (PRs) were noted. In the MTD (1.8 mg/kg) cohort, 4 CRs (33%) and 2 PRs (17%) were noted, yielding an overall response rate (ORR) of 50%.

Another phase I trial evaluated the MTD and the safety of weekly administration [52]. BV (0.4–1.4 mg/kg) was administered on days 1, 8, and 15, of each 28-day cycle to 44 patients with relapsed or refractory CD30-positive lymphoma. In the MTD cohort (1.2 mg/kg, N=12), three patients achieved CR. The most common adverse events were peripheral neuropathy (66%), fatigue (52%), nausea (50%), and diarrhea (32%). Thirteen patients (30%) experienced adverse events that led to treatment discontinuation; 8 of these were peripheral neuropathy. The weekly administration of BV was associated with a higher incidence of adverse events, with the potential for more frequent treatment interruptions.

### Efficacy in Hodgkin's lymphoma

Inspired by the outstanding outcomes, a pivotal phase II trial was initiated in which 102 patients who did not respond to autologous stem cell transplantation (ASCT) were treated with 1.8 mg/kg BV every 3 weeks for up to 16 cycles [53]. The patients had received a median of 3.5 (range, 1–13) prior chemotherapy regimens, with a CR rate of 34% and an ORR of 75%. The median duration of response was 6.7 months (95% confidence interval [CI]: 3.6–14.8); among complete responders, it was 20.5 months (95% CI: 10.8–not estimable (NE)). A subsequent report demonstrated that durable remission was maintained with a 3-year cutoff [54]. The median progression-free survival (PFS) was 9.3 months (95% CI: 7.1–12.2); among complete responders, 47% remained progression free. The median overall survival (OS) was 40.5 months (95% CI: 28.7–NE), but it was not reached

in complete responders. The 5-year results confirmed the robust long-term efficacy of BV [55]. The estimated 5-year OS rate was 64%, with 52% PFS in patients who achieved CR; among these, 13 patients (38%) remained in remission, which may imply there is a cure for the disease.

The promising outcomes shown in refractory or relapsed HL patients led to trials with larger numbers of patients with less advanced disease. In the phase III AETHERA trial, 329 patients with relapsed or refractory HL were allocated to either consolidation therapy of up to 16 cycles of BV or placebo after ASCT [56]. PFS by independent review (the primary end-point of the study) was significantly longer in patients in the BV group. The median PFS was 42.9 months (95% CI: 30.4–42.9) for the BV arm and 24.1 months (95% CI: 11.5–NE) for the placebo arm ( $P=0.0013$ ). When patients were grouped by the number of risk factors, a higher number led to more notable benefits in the consolidation arm. BV was well tolerated; a median of 15 cycles was administered.

These results in HL led to the approval of BV by the US FDA [57] and the European Medicines Agency (EMA) [58] for (1) treatment after the failure of ASCT or after the failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and (2) consolidation treatment after ASCT in patients at risk of relapse or progression.

The current indications of BV do not cover patients who are suitable for ASCT, but did not achieve suitable response with conventional chemotherapy to progress to ASCT. A phase II study evaluated the role of BV as a “bridge” to SCT [59]. In 37 patients with HL that was relapsed or refractory to the first-line therapy (usually ABVD; doxorubicin, bleomycin, vincristine, dacarbazine), BV was administered for 4 cycles, after which patients with OR proceeded to ASCT. The ORR was 68% and 32 patients (86%) proceeded to ASCT. The role of BV in the first-line therapy for non-transplant candidates was evaluated in a phase II trial [60]: when BV was administered to 27 patients with HL that were  $\geq 60$  years old and ineligible for conventional combination chemotherapy, 19 and 5 patients achieved CR

**Table 1.** Real-world data of BV monotherapy in patients with relapsed or refractory Hodgkin's lymphoma compared with the pivotal study.

Study	N	N of previous cancer regimens (median, range)	Patients with previous SCT (%)	CR rate (%)	ORR (%)	PFS (median, mo)
Rothe <i>et al.</i> [61]	45	4 (2–12)	87	22	60	8.0
Zinzani <i>et al.</i> [62]	65	4 (2–13)	92	22	71	6.8
Perrot <i>et al.</i> [63]	240	3 (1–13)	59	29	60	6.8
Salihoglu <i>et al.</i> [64]	58	4 (2–7)	84	22	53	7.0
Yang <i>et al.</i> [65]	22	1–2 (N=2), 3 or more (N=20)	77	18	73	5.7
Carlo-Stella <i>et al.</i> [66]	16	8 (4–15)	100	31	69	7.0
Garciaz <i>et al.</i> [67]	24	2 (2–4)	58	46	67	Not estimable
Monjanel <i>et al.</i> [68]	32	4 (2–8)	88	34	56	6.6
Gandolfi <i>et al.</i> [69]	43	3 (2–7)	60.5	46.5	69.8	10.2
Pivotal phase II [53]	102	3.5 (1–13)	100	34	75	5.6

Abbreviations: CR, complete response; ORR, overall response rate; PFS, progression-free survival; SCT, stem cell transplantation (either autologous and/or allogeneic).

and PR, respectively, with a median duration of response of 9.1 months (range, 2.8–20.9).

Several studies have reported the outcomes of compassionate use of BV and retrospective data [61–70] (Table 1). In general, real-world data provided similar clinical outcomes to the pivotal phase II trial, with a CR rate of 18%–46% and PFS between 5.7 months and 10.2 months.

Given the outstanding results of monotherapy and the synergism demonstrated by preclinical data [71], several combinations were evaluated in newly diagnosed patients with HL. In a phase I study, BV doses of 0.6, 0.9, and 1.2 mg/kg every 2 weeks were combined with either ABVD or bleomycin-omitted AVD (doxorubicin, vincristine, dacarbazine) for up to 6 cycles [72]. The MTD was determined as 1.2 mg/kg and both combinations yielded a CRR of over 95%. However, in the ABVD arm, 44% of patients experienced pulmonary toxicity, but this was not observed in the AVD arm. PFS at 1 year was 85% for the ABVD arm and 95% for the AVD arm. In a multicenter pilot study, 30 patients with treatment-naïve, unfavorable-risk, early-stage HL received 4 cycles of BV (1.2 mg/kg every 2 wk) plus AVD [73]. BV plus AVD resulted in 90% and 93% of positron emission tomography (PET) negativity, after 2 and 4 cycles, respectively, without the development of significant pulmonary toxicity and yielded a 1-year PFS rate of 93.3%. A randomized phase III trial to compare first-line BV in combination with AVD and ABVD for the treatment of advanced stage HL is in progress (The ECHELON-1 trial, NCT01712490). In another phase II trial, BV was administered in combination with two variants of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) for 6 cycles in 104 newly diagnosed patients with HL [74]. After the omission of vincristine and bleomycin, patients were randomly allo-

cated to either BrECAPP (BV, etoposide, cyclophosphamide, doxorubicin, procarbazine, and prednisone) or BrECADD (BV, etoposide, cyclophosphamide, doxorubicin, dacarbazine, and dexamethasone). Both combinations produced a similar CR rate (86% for BrECAPP and 88% for BrECADD) and 1-year PFS rate (98% for BrECAPP and 94% for BrECADD) to BEACOPP. These variants also reduced the rate of grade 4 hematologic toxicities. A randomized phase III trial of first-line BrECADD compared with BEACOPP in advanced stage HL is currently underway (the HD21 trial, NCT02661503). In an interim analysis of a phase II trial in which BV was combined with either dacarbazine or bendamustine in untreated patients with HL who were a minimum of 60 years old [75], the CR rate was 67% in the dacarbazine arm and 81% in the bendamustine arm.

For relapsed or refractory patients with HL, the combination of BV plus bendamustine or other drugs has been evaluated [76–78]. BV combined with nivolumab also demonstrated remarkable activity [79, 80] (Table 2).

### Efficacy in sALCL

In the pivotal phase II trial, patients with relapsed or refractory sALCL were administered BV 1.8 mg/kg every 3 weeks for up to 16 cycles [81]. The patients were heavily treated, with a median of 2 prior treatment regimens (range, 1–6) and 15 (26%) patients that failed to respond to ASCT. The study comprised 16 (28%) ALK-positive patients and 42 (72%) ALK-negative patients; in these 58 patients, the ORR was 86% and 33 patients achieved CR. The median duration of objective response was 12.6 months (95% CI: 5.7–NE). The estimated 4-year survival rate was 64% (95% CI: 51–76) and PFS was 20.0 months (95% CI: 9.4–NE) [82]. The 5-year survival data were recently announced [83], with estimated 5-year OS and PFS rates of 60% and 39%,

**Table 2.** Results of BV-based combinations in patients with relapsed or refractory Hodgkin's lymphoma.

Study	Combined agents	N	CR rate (%)	ORR (%)	Stem cell collection (median)	Main toxicities
LaCasce <i>et al.</i> [76]	Bendamustine 90 mg/m <sup>2</sup> (D1–2)	55	74	93	Success in 93% 4.1 × 10 <sup>6</sup> /kg	IRR (56%), pyrexia (26%), chills (20%), dyspnea/nausea (15% each), flushing (13%), hypotension (11%).
Cassaday <i>et al.</i> [77]	Ifosfamide 5 g/m <sup>2</sup> (D2) Carboplatin AUC 5 (D2) Etoposide 100 mg/m <sup>2</sup> (D1–3)	16	88 (INV) 69 (CIR)	94	Not described	Grade 3–4 neutropenia, lymphopenia, anemia (12% each), neuropathy (31%)
Garcia-Sanz <i>et al.</i> [78]	Etoposide 40 mg/m <sup>2</sup> (D1–4) Solu-Medrol 250 mg (D1–4) Cytarabine 2 g/m <sup>2</sup> (D5) Cisplatin 25 mg/m <sup>2</sup> (D1–4)	66	70	96	Success in 95% 5.75 × 10 <sup>6</sup> /kg	Fever (20%), grade 3–4 neutropenia (27%), thrombocytopenia (18%), anemia (8%), death (3%)
Herrera <i>et al.</i> [79]	Nivolumab 3 mg/kg (D1)	25	50 (3/6)	100 (6/6)	Success in 100% (6/6) 12.9 × 10 <sup>6</sup> /kg	No grade 4 adverse events Fatigue (35%), nausea (26%), rash (22%), dyspnea, myalgia, pruritus (17%)
Diefenbach <i>et al.</i> [80]	Nivolumab 3 mg/kg (D1)	10	62.5 (5/8)	100 (8/8)	Not described	No grade 4 adverse events pneumonitis (N=1), rash (N=4), pruritus (N=1), transaminitis (N=9), peripheral sensory neuropathy (N=6)

Abbreviations: CIR, central independent review; CR, complete response; INV, investigator; ORR, overall response rate.



**Table 3.** Real-world data for BV monotherapy in patients with relapsed or refractory systemic anaplastic large cell lymphoma compared with the pivotal study.

Study	N	N of previous cancer regimens (median, range)	Patients with previous SCT (%)	CR rate (%)	ORR (%)	PFS (median, mo)
Monjanel <i>et al.</i> [68]	13	2 (1–6)	7	77	77	10.2
Gandolfi <i>et al.</i> [69]	10	3 (2–10)	40	80	100	3-yr PFS: 61.7%
Lamarque <i>et al.</i> [84]	24	Not described	Not described	63	63	10.5
Pivotal phase II [81]	58	2 (1–6)	26	57	86	13.3

Abbreviations: CR, complete response; ORR, overall response rate; PFS, progression-free survival; SCT, stem cell transplantation (either autologous and/or allogeneic).

respectively. For the patients who achieved CR (N=38), the median OS and PFS were not reached. At the closure of the study, 16 patients remained in CR; of these patients, eight did not receive any further treatment after the completion of BV, which suggested a potential cure.

At present, BV is approved by the US FDA and EMA for the treatment of refractory or relapsed sALCL. Owing to the sparse number of studies, only a small amount of retrospective data is available for patients with ALCL who were treated with BV [68, 69, 84]. Despite the lack of data, the real-world efficacy of BV appears to be comparable (Table 3).

BV-based combinations have also been evaluated. In a phase I trial, 39 treatment-naïve patients with a diagnosis of CD30-positive PTCL were administered either sequential treatment or combination treatment [85]. Among the 32 patients with sALCL, 13 patients received sequential treatment, yielding a 62% CR rate and an 85% ORR. The remaining 19 patients received the combination treatment, which led to CR in 16 patients and PR in three patients. For the patients in the combination arm, the estimated 4-year PFS and OS rates were reported as 52% and 80%, respectively [86]. Based on these results, a randomized phase III trial was commenced to compare BV-CHP (Brentuximab vedotin-cyclophosphamide, hydroxydaunorubicin, prednisolone) versus CHOP (cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone) in CD30-positive PTCL (The ECHELON-2 trial, NCT01777152).

### Efficacy in other CD30-positive lymphomas

The efficacy of BV in B-cell lymphoma was evaluated in a phase II trial [87]. The study comprised 65 patients with CD30-positive relapsed or refractory B-cell lymphoma that were administered 1.8 mg/kg BV. Among the 48 evaluable patients with DLBCL, 8 patients achieved CR and 13 patients achieved PR. The median PFS was 4 months. In the 19 evaluable patients with other B-cell lymphomas, 3 CRs and 2 PRs were noted. Subsequently, a further 13 patients with DLBCL were recruited and administered BV (1.8 mg/kg) in combination with rituximab (375 mg/m<sup>2</sup>), yielding an ORR of 46%. First-line treatment with 1.2 mg/kg BV (N=22) or 1.8 mg/kg BV (N=29) plus rituximab-CHOP for patients with DLBCL is currently under evaluation in a phase II

study [88]. Interim analysis revealed a higher CR (76% vs. 63%) and PFS rate at 12 months (82% vs. 56%) in CD30-positive patients (N=25) than in CD30-negative patients (N=19). The second phase of the study was initiated in patients with CD30-positive high-intermediate/high-risk DLBCL by the administration of 1.8 mg/kg BV combined with rituximab-CHP [89]. Currently, 11 patients have completed the treatment, with 9 CRs and 1 PR observed (ORR: 91%).

As a considerable portion of CTCLs express CD30, BV was tested against CTCL in two studies. In a phase II study, 48 patients with CD30-positive CTCL were treated with BV [90], which resulted in an ORR of 73% (MF, 54%; pcALCL/LyP, 100%). Although patients with pcALCL/LyP demonstrated a more rapid response than patients with MF (3 wk vs. 12 wk), the duration of response was shorter (26 wk vs. 32 wk). In another phase II study, 32 patients with MF were treated with BV, irrespective of CD30 expression [91]. An objective global response was observed in 70% of patients, with most patients experiencing a reduction in skin disease burden. The phase III ALCANZA trial, which compared BV with the physician's choice of methotrexate or bexarotene in 131 patients with CD30-positive CTCL, awaits data maturation, but the interim analysis showed that the BV arm was associated with a significantly higher ORR that lasted for at least 4 months (56% vs. 13%,  $P < 0.0001$ ) in addition to longer PFS (16.7 mo vs. 3.5 mo) [92].

### Safety

BV can be administered intravenously over 30 min in 0.9% sodium chloride injection, 5% dextrose injection, or lactated Ringer's injection. Premedication may include acetaminophen, an antihistamine, and a corticosteroid to prevent an infusion-related reaction (IRR). In a phase I trial [51], one case of anaphylaxis was reported at a dose of 1.8 mg/kg. In two pivotal phase II trials conducted in HL [53] and sALCL [81], no grade 3/4 IRRs were reported in 160 patients, whereas grade 1/2 IRRs, which were easily manageable, were reported in 19 patients (12%). No IRRs were reported in the AETHERA trial [56].

The most significant adverse event of BV that prompted treatment interruption was peripheral neuropathy, of which the sensory type is the most frequent. BV-induced peripheral neuropathy is dose dependent and cumulative. In a phase

I trial, 16 of 45 patients (36%) experienced peripheral neuropathy and limb pain. The median time to onset was 9 weeks (range, 3–24) and six patients remained symptomatic at the last safety assessment. In a pivotal phase II trial in HL, 43 patients (42%) experienced sensory neuropathy, which was at grade 3 in 8 patients (8%). Eleven patients (11%) experienced motor neuropathy, which was at grade 3 in 1 patient (1%). In this trial, among the 20 patients who refused further BV administration owing to adverse events, 9 patients attributed this to peripheral neuropathy. The median time to the onset of any peripheral neuropathy event was 12.4 weeks and 80% of patients experienced either resolution or improvement of peripheral neuropathy after dose reduction or discontinuation after a median time of 13.2 weeks. In the pivotal phase II trial in sALCL, 31 patients (53%) experienced peripheral neuropathy of any grade, including sensory neuropathy (41%), paresthesia (7%), neuralgia (5%), motor neuropathy (5%), burning sensation (2%), and polyneuropathy (2%). In this trial, 14 patients discontinued further treatment; 6 of these patients attributed this to peripheral sensory neuropathy. The median time to onset of any peripheral neuropathy event was 13.3 weeks, but 25 of 31 patients (81%) experienced a resolution or improvement after a median time of 9.9 weeks (range, 0.3–32.9). A higher incidence of peripheral neuropathy was found in the AETHERA trial. Among the 167 patients in the BV arm, 94 cases (56%) of peripheral sensory neuropathy occurred, of which 17 cases (10%) were grade 3. Overall, 112 patients (67%) experienced peripheral neuropathy, with a median time to onset of 13.7 weeks (range, 0.1–47.4); this led to treatment discontinuation in 38 patients (23%). After a median time of 23.4 weeks (range, 0.1–138), the neuropathy was resolved or improved in 95 patients (85%).

Combination treatment increased the incidence of peripheral neuropathy. In a phase I trial in which BV was combined with either ABVD or AVD in patients with HL [72], more than 70% of patients experienced sensory neuropathy. Although most neuropathies were grade 1/2, peripheral neuropathy led to treatment discontinuation in 12% and 8% of the ABVD and the AVD arms, respectively, usually at the fifth or sixth cycle. In a phase I trial in which BV was sequentially administered with CHOP or concurrently administered with CHP in patients with PTCL [85], 77% and 69% of patients experienced sensory neuropathy, respectively, with 15% and 8% at grade 3/4.

Neutropenia was the most frequent hematologic toxicity; 19%–35% of patients experienced neutropenia of any grade and 12%–20% of patients experienced grade 3/4 neutropenia. However, this toxicity was easily managed with an appropriate dose delay and rarely led to febrile neutropenia. Other hematologic toxicities, including anemia and thrombocytopenia, occurred in approximately 10% of patients. Other commonly observed non-hematologic toxicities were nausea, fatigue, diarrhea, pyrexia, rash, or upper respiratory infection. As pulmonary toxicities can occur in conjunction with concurrent or prior bleomycin use [72, 93], the concomitant use of BV with bleomycin is contraindicated. Several reports

indicated that BV treatment may induce the reactivation of polyomavirus JC, which can cause fatal progressive multifocal leukoencephalopathy [94–96].

## PRACTICAL GUIDANCE ON BV

### Optimal doses and cycles of BV

The recommended dose of BV is 1.8 mg/kg, up to 180 mg, every 3 weeks. Both the liver and the kidney are involved in MMAE clearance. The pharmacokinetics of a 1.2 mg/kg dose were studied in patients with hepatic or renal dysfunction [97]. For patients with hepatic impairment, decreased ADC exposure and increased MMAE exposure were observed, most likely owing to hypoalbuminemia. All patients with moderate-to-severe hepatic impairment experienced grade 3/4 adverse events. Although mild-to-moderate renal impairment caused no apparent change in pharmacokinetic parameters, decreased ADC exposure and increased MMAE exposure was noted in patients with severe renal impairment, who all experienced grade 3/4 adverse events. Dose modification is not recommended in mild-to-moderate renal impairment and a dose of 1.2 mg/kg is recommended in cases of mild hepatic impairment. BV should be avoided in patients with moderate-to-severe hepatic impairment or severe renal impairment.

The treatment duration varied among trials. In a phase I trial [51], BV was administered until disease progression. The maximum number of cycles administered was 14 in the 1.2 mg/kg cohort and 12 in the 1.8 mg/kg cohort. In the pivotal phase II trials in HL [53] and sALCL [81], which designated a maximum of 16 cycles, the median number of administered cycles was 9 (range, 1–16) and 7 (range, 1–16), respectively. The 5-year follow-up data for the HL trial was interesting [55]: among the 34 patients that achieved CR, 5 patients (15%) achieved the response after 10 cycles and 1 patient achieved CR after 16 cycles. Similar findings were found in the sALCL trial, where CR was achieved after 16 cycles. As some patients achieved CR in the latter courses of treatment, if sustained clinical benefits are observed, administration for more than 16 cycles in relapsed or refractory patients could be considered in patients who are not candidates for SCT. The current FDA guidelines do not indicate a maximum number of treatment cycles, whereas the EMA indicates a maximum of 16.

### Re-treatment with BV

A small phase II study investigated the safety and efficacy of BV re-treatment in patients who previously achieved either CR or PR with BV [98]. Among 28 patients with HL or sALCL, 11 CRs and 8 PRs were obtained with an estimated median PFS of 9.9 months for HL and 12.9 months for sALCL, which were similar to the two pivotal trials. Therefore, in patients who obtained OR in a previous treatment and who can tolerate additional treatment, BV may be used for re-treatment.

## Management of adverse events

**Peripheral neuropathy:** Inform patients that peripheral neuropathy may occur during or after BV treatment; symptoms including hypoesthesia, hyperesthesia, paresthesia, discomfort, burning sensation, neuropathic pain, or weakness should be monitored. If grade 2/3 neuropathy occurs, the treatment should be withheld until the toxicity is less than grade 1 or at baseline and restarted at a reduced dose of 1.2 mg/kg every 3 weeks. If grade 4 neuropathy occurs, discontinue treatment.

**Neutropenia:** If grade 1/2 neutropenia occurs (i.e., absolute neutrophil count  $\geq 1,000/\mu\text{L}$ ), treatment modification is not necessary. If grade 3/4 neutropenia occurs, BV should be delayed until resolution of the toxicity to baseline or grade 2 or lower. Granulocyte-colony stimulating factor (G-CSF) prophylaxis should be considered in patients who experienced grade 3/4 neutropenia in the previous cycle. In patients that experience recurrent grade 4 neutropenia despite prophylaxis, discontinuation or dose reduction to 1.2 mg/kg BV should be considered.

## Drug-drug interactions

The liver is the primary organ for MMAE metabolism and excretion. In vitro data indicate that MMAE is a substrate of CYP3A4 and the efflux transporter P-glycoprotein (P-gp) [99]. BV was administered to 56 patients with CD30-positive hematologic malignancies and the interactions with a CYP3A4 substrate (midazolam), an effective inducer (rifampin), or a strong inhibitor (ketoconazole) were evaluated [100]. MMAE exposure was reduced by 46% with rifampin and increased by 34% with ketoconazole. Thus, patients who are concomitantly administered strong CYP3A4 inhibitors and BV should be closely monitored for adverse events.

## CONCLUSION

We have provided a comprehensive review of the up-to-date clinical outcomes in BV trials and suggested clinical guidance. The efficiency and safety of BV has been demonstrated in patients with HL and sALCL in the latter stages of the disease; the use of BV has also expanded to first-line treatment, bridge therapy, and treatment of other CD30-expressing lymphomas. BV has also been assessed in combination with conventional anti-lymphoma regimens and novel agents. Although several potential adverse events were observed, most were predictable and easily managed.

BV heralded a new era of targeted therapies for lymphoma for two reasons. First, it established CD30 as a new druggable target in patients with certain types of lymphoma; after the therapeutic role of BV was established, efforts were made to detect CD30 in other lymphomas and use it therapeutically. Second, an increasing number of ADCs have been assessed in the field of hematology. The first approved ADC,

gemtuzumab ozogamicin for acute myeloid leukemia, was quickly withdrawn from the market owing to inadequate efficacy and safety. BV, the second approved ADC, demonstrated outstanding efficacy and acceptable toxicity. The robustness of BV was followed by development of ADCs targeted to various antigens with novel drug conjugates.

In HL, in addition to better clinical outcomes, the reduction of late treatment-related complications, such as secondary malignancy, cardiovascular disease, and pulmonary dysfunction, is a key treatment end-points. Consequently, the status of BV in the treatment of HL has been elevated to first-line therapy, similar to the treatment of CD30-positive T-cell lymphoma. Although the evidence is not sufficient, the use of BV outside of the current indications, for example, as a “bridge” therapy, should also be considered depending on the circumstances.

Several questions remain unanswered; for example, it is uncertain which patients will benefit the most from BV treatment. The methods of quantitation and cut-off values for CD30 positivity are different between studies. Although immunohistochemistry is widely used, several studies have debated its worth [87, 91]. Another unsolved problem is the mechanism of BV resistance and how to overcome it. A recent in vitro study suggested that CD30 downregulation, MMAE resistance, and MDR1 overexpression are the potential resistance mechanisms [101]. Current trials of BV-based combinations may provide a solution to overcome BV resistance.

## Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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