BLOOD RESEARCH
VOLUME 52 · NUMBER 4
December 2017
REVIEW ARTICLE

Brentuximab vedotin: clinical updates and practical guidance

Jun Ho Yi[1], Seok Jin Kim[2], Won Seog Kim[2]

[1]*Division of Hematology-Oncology, Department of Medicine, Chung-Ang University Hospital,* [2]*Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea*

p-ISSN 2287-979X / e-ISSN 2288-0011
https://doi.org/10.5045/br.2017.52.4.243
Blood Res 2017;52:243-53.

Received on May 10, 2017
Revised on November 30, 2017
Accepted on December 1, 2017

Correspondence to
Won Seog Kim, M.D., Ph.D.
Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 06351, Korea
E-mail: wskimsmc@skku.edu

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-microtubule 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-κB 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-κB 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-κB activation, instead inducing cellular apoptosis [25]; in contrast, CD30 activation was shown to induce NF-κB activation, which then upregulated cellular inhibitors of apoptosis [26]. It is now thought that short, physiological stimulation triggers apoptosis, whereas constitutive stimulation induces NF-κB 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 DLBLC 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 ≥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 *et al.* [61]	45	4 (2–12)	87	22	60	8.0
Zinzani *et al.* [62]	65	4 (2–13)	92	22	71	6.8
Perrot *et al.* [63]	240	3 (1–13)	59	29	60	6.8
Salihoglu *et al.* [64]	58	4 (2–7)	84	22	53	7.0
Yang *et al.* [65]	22	1–2 (N=2), 3 or more (N=20)	77	18	73	5.7
Carlo-Stella *et al.* [66]	16	8 (4–15)	100	31	69	7.0
Garciaz *et al.* [67]	24	2 (2–4)	58	46	67	Not estimable
Monjanel *et al.* [68]	32	4 (2–8)	88	34	56	6.6
Gandolfi *et al.* [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 allocated 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 *et al.* [76]	Bendamustine 90 mg/m^2 (D1–2)	55	74	93	Success in 93% 4.1×10^6/kg	IRR (56%), pyrexia (26%), chills (20%), dyspnea/nausea (15% each), flushing (13%), hypotension (11%).
Cassaday *et al.* [77]	Ifosfamide 5 g/m^2 (D2) Carboplatin AUC 5 (D2) Etoposide 100 mg/m^2 (D1–3)	16	88 (INV) 69 (CIR)	94	Not described	Grade 3–4 neutropenia, lymphopenia, anemia (12% each), neuropathy (31%)
Garcia-Sanz *et al.* [78]	Etoposide 40 mg/m^2 (D1–4) Solu-Medrol 250 mg (D1–4) Cytarabine 2 g/m^2 (D5) Cisplatin 25 mg/m^2 (D1–4)	66	70	96	Success in 95% 5.75×10^6/kg	Fever (20%), grade 3–4 neutropenia (27%), thrombocytopenia (18%), anemia (8%), death (3%)
Herrera *et al.* [79]	Nivolumab 3 mg/kg (D1)	25	50 (3/6)	100 (6/6)	Success in 100% (6/6) 12.9×10^6/kg	No grade 4 adverse events Fatigue (35%), nausea (26%), rash (22%), dyspnea, myalgia, pruritus (17%)
Diefenbach *et al.* [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 *et al.* [68]	13	2 (1–6)	7	77	77	10.2
Gandolfi *et al.* [69]	10	3 (2–10)	40	80	100	3-yr PFS: 61.7%
Lamarque *et al.* [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 (cyclophosphamiade, 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^2), 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/μL), 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.

REFERENCES

1. Miller RA, Maloney DG, Warnke R, Levy R. Treatment of B-cell lymphoma with monoclonal anti-idiotype antibody. N Engl J Med 1982;306:517-22.
2. Chiarle R, Podda A, Prolla G, Gong J, Thorbecke GJ, Inghirami G. CD30 in normal and neoplastic cells. Clin Immunol 1999;90:157-64.
3. Bartlett NL, Younes A, Carabasi MH, et al. A phase 1 multidose study of SGN-30 immunotherapy in patients with refractory or recurrent CD30+ hematologic malignancies. Blood 2008;111:1848-54.
4. Ansell SM, Horwitz SM, Engert A, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. J Clin Oncol 2007;25:2764-9.
5. Senter PD, Sievers EL. The discovery and development of brentuximab vedotin for use in relapsed Hodgkin lymphoma and systemic anaplastic large cell lymphoma. Nat Biotechnol 2012;30:631-7.
6. Schwab U, Stein H, Gerdes J, et al. Production of a monoclonal

antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. Nature 1982;299:65-7.
7. Stein H, Mason DY, Gerdes J, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood 1985;66:848-58.
8. Bargou RC, Emmerich F, Krappmann D, et al. Constitutive nuclear factor-kappaB-RelA activation is required for proliferation and survival of Hodgkin's disease tumor cells. J Clin Invest 1997;100:2961-9.
9. Hinz M, Löser P, Mathas S, Krappmann D, Dörken B, Scheidereit C. Constitutive NF-kappaB maintains high expression of a characteristic gene network, including CD40, CD86, and a set of antiapoptotic genes in Hodgkin/Reed-Sternberg cells. Blood 2001;97:2798-807.
10. Aldinucci D, Celegato M, Casagrande N. Microenvironmental interactions in classical Hodgkin lymphoma and their role in promoting tumor growth, immune escape and drug resistance. Cancer Lett 2016;380:243-52.
11. Pinto A, Aldinucci D, Gloghini A, et al. The role of eosinophils in the pathobiology of Hodgkin's disease. Ann Oncol 1997;8(Suppl 2):89-96.
12. Molin D, Fischer M, Xiang Z, et al. Mast cells express functional CD30 ligand and are the predominant CD30L-positive cells in Hodgkin's disease. Br J Haematol 2001;114:616-23.
13. Horie R, Watanabe T, Ito K, et al. Cytoplasmic aggregation of TRAF2 and TRAF5 proteins in the Hodgkin-Reed-Sternberg cells. Am J Pathol 2002;160:1647-54.
14. Hirsch B, Hummel M, Bentink S, et al. CD30-induced signaling is absent in Hodgkin's cells but present in anaplastic large cell lymphoma cells. Am J Pathol 2008;172:510-20.
15. Hapgood G, Savage KJ. The biology and management of systemic anaplastic large cell lymphoma. Blood 2015;126:17-25.
16. Savage KJ, Harris NL, Vose JM, et al. ALK- anaplastic large-cell lymphoma is clinically and immunophenotypically different from both ALK+ ALCL and peripheral T-cell lymphoma, not otherwise specified: report from the International Peripheral T-Cell Lymphoma Project. Blood 2008;111:5496-504.
17. Falini B, Pileri S, Zinzani PL, et al. ALK+ lymphoma: clinico-pathological findings and outcome. Blood 1999;93:2697-706.
18. Gascoyne RD, Aoun P, Wu D, et al. Prognostic significance of anaplastic lymphoma kinase (ALK) protein expression in adults with anaplastic large cell lymphoma. Blood 1999;93:3913-21.
19. Pulford K, Lamant L, Morris SW, et al. Detection of anaplastic lymphoma kinase (ALK) and nucleolar protein nucleophosmin (NPM)-ALK proteins in normal and neoplastic cells with the monoclonal antibody ALK1. Blood 1997;89:1394-404.
20. Lamant L, Dastugue N, Pulford K, Delsol G, Mariamé B. A new fusion gene TPM3-ALK in anaplastic large cell lymphoma created by a (1;2)(q25;p23) translocation. Blood 1999;93:3088-95.
21. Trinei M, Lanfrancone L, Campo E, et al. A new variant anaplastic lymphoma kinase (ALK)-fusion protein (ATIC-ALK) in a case of ALK-positive anaplastic large cell lymphoma. Cancer Res 2000;60:793-8.
22. Feldman AL, Vasmatzis G, Asmann YW, et al. Novel TRAF1-ALK fusion identified by deep RNA sequencing of anaplastic large cell lymphoma. Genes Chromosomes Cancer 2013;52:1097-102.
23. Hsu FY, Johnston PB, Burke KA, Zhao Y. The expression of CD30 in anaplastic large cell lymphoma is regulated by nucleophosmin-anaplastic lymphoma kinase-mediated JunB level in a cell type-specific manner. Cancer Res 2006;66:9002-8.
24. Watanabe M, Sasaki M, Itoh K, et al. JunB induced by constitutive CD30-extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling activates the CD30 promoter in anaplastic large cell lymphoma and reed-sternberg cells of Hodgkin lymphoma. Cancer Res 2005;65:7628-34.
25. Mir SS, Richter BW, Duckett CS. Differential effects of CD30 activation in anaplastic large cell lymphoma and Hodgkin disease cells. Blood 2000;96:4307-12.
26. Hübinger G, Schneider C, Stöhr D, et al. CD30-induced up-regulation of the inhibitor of apoptosis genes cIAP1 and cIAP2 in anaplastic large cell lymphoma cells. Exp Hematol 2004;32:382-9.
27. Wright CW, Rumble JM, Duckett CS. CD30 activates both the canonical and alternative NF-kappaB pathways in anaplastic large cell lymphoma cells. J Biol Chem 2007;282:10252-62.
28. Slack GW, Steidl C, Sehn LH, Gascoyne RD. CD30 expression in de novo diffuse large B-cell lymphoma: a population-based study from British Columbia. Br J Haematol 2014;167:608-17.
29. Hu S, Xu-Monette ZY, Balasubramanyam A, et al. CD30 expression defines a novel subgroup of diffuse large B-cell lymphoma with favorable prognosis and distinct gene expression signature: a report from the International DLBCL Rituximab-CHOP Consortium Program Study. Blood 2013;121:2715-24.
30. Campuzano-Zuluaga G, Cioffi-Lavina M, Lossos IS, Chapman-Fredricks JR. Frequency and extent of CD30 expression in diffuse large B-cell lymphoma and its relation to clinical and biologic factors: a retrospective study of 167 cases. Leuk Lymphoma 2013;54:2405-11.
31. Higgins JP, Warnke RA. CD30 expression is common in mediastinal large B-cell lymphoma. Am J Clin Pathol 1999;112:241-7.
32. Pileri SA, Gaidano G, Zinzani PL, et al. Primary mediastinal B-cell lymphoma: high frequency of BCL-6 mutations and consistent expression of the transcription factors OCT-2, BOB.1, and PU.1 in the absence of immunoglobulins. Am J Pathol 2003;162:243-53.
33. Ok CY, Li L, Xu-Monette ZY, et al. Prevalence and clinical implications of epstein-barr virus infection in de novo diffuse large B-cell lymphoma in Western countries. Clin Cancer Res 2014;20:2338-49.
34. Hong JY, Ko YH, Kim SJ, Kim WS. Epstein-Barr virus-positive diffuse large B-cell lymphoma of the elderly: a concise review and update. Curr Opin Oncol 2015;27:392-8.
35. Bhatt S, Ashlock BM, Natkunam Y, et al. CD30 targeting with brentuximab vedotin: a novel therapeutic approach to primary effusion lymphoma. Blood 2013;122:1233-42.
36. Song JY, Pittaluga S, Dunleavy K, et al. Lymphomatoid

granulomatosis-a single institute experience: pathologic findings and clinical correlations. Am J Surg Pathol 2015;39:141-56.
37. Weisenburger DD, Savage KJ, Harris NL, et al. Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project. Blood 2011;117:3402-8.
38. Delabie J, Holte H, Vose JM, et al. Enteropathy-associated T-cell lymphoma: clinical and histological findings from the international peripheral T-cell lymphoma project. Blood 2011;118:148-55.
39. Murray A, Cuevas EC, Jones DB, Wright DH. Study of the immunohistochemistry and T cell clonality of enteropathy-associated T cell lymphoma. Am J Pathol 1995;146:509-19.
40. Schwartz EJ, Molina-Kirsch H, Zhao S, Marinelli RJ, Warnke RA, Natkunam Y. Immunohistochemical characterization of nasal-type extranodal NK/T-cell lymphoma using a tissue microarray: an analysis of 84 cases. Am J Clin Pathol 2008; 130:343-51.
41. Pongpruttipan T, Kummalue T, Bedavanija A, et al. Aberrant antigenic expression in extranodal NK/T-cell lymphoma: a multi-parameter study from Thailand. Diagn Pathol 2011;6:79.
42. Swerdlow SH, Campo E, Harris NL, et al, eds. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon, France: IARC Press, 2008.
43. Talpur R, Jones DM, Alencar AJ, et al. CD25 expression is correlated with histological grade and response to denileukin diftitox in cutaneous T-cell lymphoma. J Invest Dermatol 2006;126:575-83.
44. Benner MF, Jansen PM, Vermeer MH, Willemze R. Prognostic factors in transformed mycosis fungoides: a retrospective analysis of 100 cases. Blood 2012;119:1643-9.
45. Edinger JT, Clark BZ, Pucevich BE, Geskin LJ, Swerdlow SH. CD30 expression and proliferative fraction in nontransformed mycosis fungoides. Am J Surg Pathol 2009;33:1860-8.
46. Cerroni L, Rieger E, Hödl S, Kerl H. Clinicopathologic and immunologic features associated with transformation of mycosis fungoides to large-cell lymphoma. Am J Surg Pathol 1992; 16:543-52.
47. Alley SC, Okeley NM, Senter PD. Antibody-drug conjugates: targeted drug delivery for cancer. Curr Opin Chem Biol 2010;14:529-37.
48. Okeley NM, Miyamoto JB, Zhang X, et al. Intracellular activation of SGN-35, a potent anti-CD30 antibody-drug conjugate. Clin Cancer Res 2010;16:888-97.
49. Francisco JA, Cerveny CG, Meyer DL, et al. cAC10-vcMMAE, an anti-CD30-monomethyl auristatin E conjugate with potent and selective antitumor activity. Blood 2003;102:1458-65.
50. Doronina SO, Toki BE, Torgov MY, et al. Development of potent monoclonal antibody auristatin conjugates for cancer therapy. Nat Biotechnol 2003;21:778-84.
51. Younes A, Bartlett NL, Leonard JP, et al. Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. N Engl J Med 2010;363:1812-21.
52. Fanale MA, Forero-Torres A, Rosenblatt JD, et al. A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. Clin Cancer Res 2012;18:248-55.
53. Younes A, Gopal AK, Smith SE, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012;30:2183-9.
54. Gopal AK, Chen R, Smith SE, et al. Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Blood 2015;125:1236-43.
55. Chen R, Gopal AK, Smith SE, et al. Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood 2016;128: 1562-6.
56. Moskowitz CH, Nademanee A, Masszi T, et al. Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;385:1853-62.
57. US Food and Drug Administration. Brentuximab Vedotin information. Silver Spring, MD: US Food and Drug Administration, 2015. (Accessed April 8, 2017, at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125388s080lbl.pdf).
58. European Medicines Agency. Brentuximab Vedotin information. London, UK: European Medicines Agency, 2016. (Accessed April 8, 2017, at http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002455/WC500135055.pdf).
59. Chen R, Palmer JM, Martin P, et al. Results of a multicenter phase II trial of brentuximab vedotin as second-line therapy before autologous transplantation in relapsed/refractory hodgkin lymphoma. Biol Blood Marrow Transplant 2015;21:2136-40.
60. Forero-Torres A, Holkova B, Goldschmidt J, et al. Phase 2 study of frontline brentuximab vedotin monotherapy in Hodgkin lymphoma patients aged 60 years and older. Blood 2015;126: 2798-804.
61. Rothe A, Sasse S, Goergen H, et al. Brentuximab vedotin for relapsed or refractory CD30+ hematologic malignancies: the German Hodgkin Study Group experience. Blood 2012;120: 1470-2.
62. Zinzani PL, Viviani S, Anastasia A, et al. Brentuximab vedotin in relapsed/refractory Hodgkin's lymphoma: the Italian experience and results of its use in daily clinical practice outside clinical trials. Haematologica 2013;98:1232-6.
63. Perrot A, Monjanel H, Bouabdallah R, et al. Impact of post-brentuximab vedotin consolidation on relapsed/refractory CD30+ Hodgkin lymphomas: a large retrospective study on 240 patients enrolled in the French Named-Patient Program. Haematologica 2016;101:466-73.
64. Salihoglu A, Elverdi T, Karadogan I, et al. Brentuximab vedotin for relapsed or refractory Hodgkin lymphoma: experience in Turkey. Ann Hematol 2015;94:415-20.
65. Yang QM, Hong JY, Ko YH, et al. Brentuximab vedotin for relapsed or refractory CD30+ Hodgkin lymphoma: a multicenter analysis from Asia. Onco Targets Ther 2014;7:1717-22.
66. Carlo-Stella C, Ricci F, Dalto S, et al. Brentuximab vedotin in patients with Hodgkin lymphoma and a failed allogeneic stem cell transplantation: results from a named patient program at four Italian centers. Oncologist 2015;20:323-8.
67. Garciaz S, Coso D, Peyrade F, et al. Brentuximab vedotin

followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematol Oncol 2014;32:187-91.
68. Monjanel H, Deville L, Ram-Wolff C, et al. Brentuximab vedotin in heavily treated Hodgkin and anaplastic large-cell lymphoma, a single centre study on 45 patients. Br J Haematol 2014; 166:306-8.
69. Gandolfi L, Pellegrini C, Casadei B, et al. Long-term responders after brentuximab vedotin: single-center experience on relapsed and refractory hodgkin lymphoma and anaplastic large cell lymphoma patients. Oncologist 2016;21:1436-41.
70. Gibb A, Jones C, Bloor A, et al. Brentuximab vedotin in refractory CD30+ lymphomas: a bridge to allogeneic transplantation in approximately one quarter of patients treated on a Named Patient Programme at a single UK center. Haematologica 2013;98:611-4.
71. Oflazoglu E, Kissler KM, Sievers EL, Grewal IS, Gerber HP. Combination of the anti-CD30-auristatin-E antibody-drug conjugate (SGN-35) with chemotherapy improves antitumour activity in Hodgkin lymphoma. Br J Haematol 2008;142:69-73.
72. Younes A, Connors JM, Park SI, et al. Brentuximab vedotin combined with ABVD or AVD for patients with newly diagnosed Hodgkin's lymphoma: a phase 1, open-label, dose-escalation study. Lancet Oncol 2013;14:1348-56.
73. Kumar A, Casulo C, Yahalom J, et al. Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma. Blood 2016;128:1458-64.
74. Borchmann P, Eichenauer DA, Pluetschow A, et al. Targeted BEACOPP variants in patients with newly diagnosed advanced stage classical Hodgkin lymphoma: Final analysis of a randomized phase II study. Blood (ASH Annual Meeting Abstracts) 2015;126(Suppl):580.
75. Brentuximab vedotin in combination with dacarbazine or bendamustine for frontline treatment of hodgkin lymphoma in patients aged 60 years and above: interim results of a multi-cohort phase 2 study. Clin Adv Hematol Oncol 2016; 14(2 Suppl 1):13-5.
76. LaCasce AS, Bociek G, Sawas A, et al. Brentuximab vedotin plus bendamustine: A highly active salvage treatment regimen for patients with relapsed or refractory Hodgkin lymphoma. Blood (ASH Annual Meeting Abstracts) 2015;126(Suppl):3982.
77. Cassaday RD, Fromm J, Cowan AJ, et al. Safety and activity of brentuximab vedotin (BV) plus ifosfamide, carboplatin, and etoposide (ICE) for relapsed/refractory (Rel/Ref) classical Hodgkin lymphoma (cHL): Initial results of a phase I/II trial. Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):1834.
78. Garcia-Sanz R, Sureda A, Gonzalez AP, et al. Brentuximab vedotin plus ESHAP (BRESHAP) is a highly effective combination for inducing remission in refractory and relapsed Hodgkin lymphoma patients prior to autologous stem cell transplant: A trial of the Spanish Group of Lymphoma and Bone Marrow Transplantation (GELTAMO) Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):1109.
79. Herrera AF, Bartlett NL, Ramchandren R, et al. Preliminary results from a phase 1/2 study of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):1105.
80. Diefenbach CS, Hong F, David KA, et al. A Phase I study with an expansion cohort of the combination of ipilimumab and nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma: A trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E). Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):1106.
81. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012;30:2190-6.
82. Pro B, Advani R, Brice P, et al. Four-year survival data from an ongoing pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood (ASH Annual Meeting Abstracts) 2014; 124(Suppl):3095.
83. Pro B, Advani RH, Brice P, et al. Five-year survival data from a pivotal phase 2 study of brentuximab vedotin in patients with relapsed or refractory systemic anaplastic large cell lymphoma. Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):4144.
84. Lamarque M, Bossard C, Contejean A, et al. Brentuximab vedotin in refractory or relapsed peripheral T-cell lymphomas: the French named patient program experience in 56 patients. Haematologica 2016;101:e103-6.
85. Fanale MA, Horwitz SM, Forero-Torres A, et al. Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. J Clin Oncol 2014;32:3137-43.
86. Fanale MA, Horwitz SM, Forero-Torres A, et al. Four-year survival and durability results of brentuximab vedotin in combination with CHP in the frontline treatment of patients with CD30-expressing peripheral T-cell lymphomas. Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):2993.
87. Jacobsen ED, Sharman JP, Oki Y, et al. Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression. Blood 2015;125:1394-402.
88. Yasenchak CA, Halwani A, Advani R, et al. Brentuximab vedotin with RCHOP as frontline therapy in patients with high-intermediate/high-risk diffuse large B cell lymphoma (DLBCL): Results from an ongoing phase 2 study. Blood (ASH Annual Meeting Abstracts) 2015;126(Suppl):814.
89. Budde LE, Halwani A, Yasenchak CA, et al. Results of an ongoing phase 2 study of brentuximab vedotin with rchp as frontline therapy in patients with high-intermediate/high-risk diffuse large B cell lymphoma (DLBCL). Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):104.
90. Duvic M, Tetzlaff MT, Gangar P, Clos AL, Sui D, Talpur R. Results of a phase II trial of brentuximab vedotin for CD30+ cutaneous T-cell lymphoma and lymphomatoid papulosis. J Clin Oncol 2015;33:3759-65.
91. Kim YH, Tavallaee M, Sundram U, et al. Phase II investigator-initiated study of brentuximab vedotin in mycosis fungoides and Sézary syndrome with variable CD30 expression level: A Multi-Institution Collaborative Project. J Clin Oncol 2015;33:3750-8.
92. Kim YH, Whittaker S, Horwitz SM, et al. Brentuximab vedotin demonstrates significantly superior clinical outcomes in patients

with CD30-expressing cutaneous T cell lymphoma versus physician's choice (methotrexate or bexarotene): The phase 3 ALCANZA Study. Blood (ASH Annual Meeting Abstracts) 2016;128(Suppl):182.
93. Sabet Y, Ramirez S, Rosell Cespedes E, et al. Severe acute pulmonary toxicity associated with brentuximab in a patient with refractory Hodgkin's lymphoma. Case Rep Pulmonol 2016;2016:2359437.
94. Wagner-Johnston ND, Bartlett NL, Cashen A, Berger JR. Progressive multifocal leukoencephalopathy in a patient with Hodgkin lymphoma treated with brentuximab vedotin. Leuk Lymphoma 2012;53:2283-6.
95. von Geldern G, Pardo CA, Calabresi PA, Newsome SD. PML-IRIS in a patient treated with brentuximab. Neurology 2012;79:2075-7.
96. Carson KR, Newsome SD, Kim EJ, et al. Progressive multifocal leukoencephalopathy associated with brentuximab vedotin therapy: a report of 5 cases from the Southern Network on Adverse Reactions (SONAR) project. Cancer 2014;120:2464-71.
97. Zhao B, Chen R, O'Connor OA, et al. Brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive haematologic malignancies and hepatic or renal impairment. Br J Clin Pharmacol 2016;82:696-705.
98. Bartlett NL, Chen R, Fanale MA, et al. Retreatment with brentuximab vedotin in patients with CD30-positive hematologic malignancies. J Hematol Oncol 2014;7:24.
99. Seattle Genetics Inc. ADCETRIS® (brentuximab vedotin) package insert. Bothell, WA: Seattle Genetics Inc, 2012. (Accessed April 8, 2017, at http://www.seattlegenetics.com/application/files/2515/1059/6728/ADCETRIS_USPI_USP-BVP-2015-01625pdf.pdf).
100. Han TH, Gopal AK, Ramchandren R, et al. CYP3A-mediated drug-drug interaction potential and excretion of brentuximab vedotin, an antibody-drug conjugate, in patients with CD30-positive hematologic malignancies. J Clin Pharmacol 2013; 53:866-77.
101. Chen R, Hou J, Newman E, et al. CD30 downregulation, MMAE resistance, and MDR1 upregulation are all associated with resistance to brentuximab vedotin. Mol Cancer Ther 2015; 14:1376-84.