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REVIEW

Safety and Efficacy of Brentuximab Vedotin in the Treatment of Classic Hodgkin Lymphoma

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Abstract: Classical Hodgkin lymphoma (cHL) is a B-cell-derived lymphoid malignancy with the most favorable prognosis among various adult malignancies. However, once it becomes refractory disease to chemotherapy or relapses after high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT), it is difficult to manage with conventional cytotoxic chemotherapy. The introduction of brentuximab vedotin (BV) has changed the treatment landscape of cHL in the past decade. Several studies demonstrated high efficacy of BV monotherapy in heavily treated patients with cHL relapsed or refractory after HDC/ASCT. Recent studies also reported high efficacy of concurrent or sequential combination of BV and chemotherapy in patients with transplant-eligible relapsed/refractory cHL at the second-line setting. In addition, a randomized phase III trial ECHELON-1 reported a positive result of BV in combination with AVD (doxorubicin, vinblastine, and dacarbazine) in patients with newly diagnosed advanced-stage cHL. In this review, we summarize available data of BV for cHL and discuss the current and future role of BV in the management of cHL.

Keywords: brentuximab vedotin, classic Hodgkin lymphoma, CD30, antibody-drug conjugate, MMAE

Introduction

Classic Hodgkin lymphoma (cHL) is a B-cell-derived lymphoid malignancy with the most favorable prognosis among various adult malignancies. Approximately 80%-90% of patients with newly diagnosed cHL can be cured when treated with the appropriate first-line therapy.[1,2] However, once cHL becomes a refractory disease to chemotherapy or relapses after high-dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT), it is difficult to manage with conventional cytotoxic chemotherapy.[3,4] Until recently, advances in the treatment of cHL was primarily based on the modification of conventional cytotoxic chemotherapy and radiotherapy. However, the introduction of brentuximab vedotin (BV), an antibody-drug conjugate targeting CD30, has markedly changed the treatment landscape of cHL in the past decade. In this review, we summarize available data of BV for cHL and discuss the current and future role of BV in the management of cHL.

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Targeting CD30 in Lymphoma

CD30 (initially known as Ki-1) was firstly identified as a specific antigen for Hodgkin and Reed-Sternberg cells in the HL cell line L428.[5,6] The CD30 molecule is a 120-kD transmembrane glycoprotein receptor that belongs to the tumor necrosis factor

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receptor superfamily. Subsequent studies revealed that its overexpression in cHL is associated with constitutive activation of extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling.[7] CD30 is also expressed on a small subset of activated B-cells or T-cells[8] and various lymphoid neoplasms other than cHL. These include anaplastic large cell lymphoma (ALCL) and a subset of peripheral T-cell lymphomas (58%–64% in peripheral T-cell lymphoma, not otherwise specified; 43%–63% in angioimmunoblastic T-cell lymphoma),[9–12] adult T-cell leukemia-lymphoma (55%),[12,13] extranodal NK/T-cell lymphoma (60%–70%),[14,15] and diffuse large B-cell lymphoma (14%–25%).[16–19] Because CD30 is not expressed on non-hematologic benign tissues or on resting lymphocytes and monocytes,[20] it is supposed to be an optimal therapeutic target in the treatment of CD30-positive lymphomas.

Nevertheless, naked monoclonal antibodies targeting CD30 demonstrated limited efficacy in patients with CD30-positive lymphomas (Table 1). Ansell et al conducted a phase I/II study of MDX-060, a fully human anti-CD30 immunoglobulin G1kappa monoclonal antibody, in patients with cHL and ALCL.[21] MDX-060 was well tolerated, and the maximum-tolerated dose (MTD) has not been reached. However, the objective response was observed only in 6 of 72 evaluable patients (8%). Similarly, SGN-30 (also known as cAC10), another chimeric mouse-human anti-CD30 monoclonal antibody developed by Seattle Genetics, was tested in a Phase II study in patients with relapsed/refractory cHL and ALCL.[22] In total, 79 patients (38 with cHL and 41 with ALCL) were enrolled, but no patients with cHL achieved objective responses. The objective response rate (ORR) in patients with ALCL was only 17%. Another approach for CD30-targeted therapy is antibody-immunotoxin conjugates. Most of the anti-CD30 immunotoxins utilize ribosome-inactivating proteins (RIP) such as saporin,[23] Pseudomonas exotoxin A,[24] and ricin A chain.[25] These agents demonstrated efficacy in preclinical studies but not in human trials partly because of the high rates of the development of anti-therapeutic antibodies, downregulation of CD30, and non-specific binding of immunotoxin.

Table 1 Naked Anti-CD30 Monoclonal Antibody Therapy for cHL and ALCL

Dose and Schedule		MDX-060	SGN-30
		0.1, 1, 5, 10, 15 mg/kg, Weekly for 4 Weeks	6 or 12 mg/kg, Weekly for 6 Weeks, 8-Week Cycle
cHL	Number of pts	63	38
	ORR	6% (4 of 63)	0
	%CR	3% (2 of 63)	0
ALCL	Number of pts	7	41
	ORR	29% (2 of 7)	17% (7 of 41)
	%CR	29% (2 of 7)	5% (2 of 41)

Abbreviations: ALCL, anaplastic large cell lymphoma; cHL, classic Hodgkin lymphoma; CR, complete remission; ORR, objective response rate; pts, patients.

Brentuximab Vedotin

To augment the efficacy of anti-CD30 antibody therapy, a novel antibody-drug conjugate brentuximab vedotin (BV; SGN-35) has been developed.[26,27] BV consists of a chimeric anti-CD30 monoclonal antibody (cAC10) and monomethyl auristatin E (MMAE, a microtubule-disrupting agent). It is conjugated by a linker protein that is a highly stable peptide selectively cleaved by lysosomal enzymes (Figure 1A).[28] BV binds to CD30 expressed on the surface of lymphoma cells and is internalized via endocytosis. The cytoplasmic lysosomal enzymes decompose the linker protein that conjugates the CD30 antibody and MMAE. The MMAE released to the cytoplasm inhibits the synthesis of microtubules and leads to apoptosis of lymphoma cells (Figure 1B).[29]

Based on the promising results obtained from preclinical studies, a phase I study of BV in patients with relapsed/refractory CD30 positive lymphomas was conducted.[29] BV was administered intravenously at doses of 0.1–3.6 mg/kg in a 21-day cycle. In total, 45 patients (42 with cHL, 2 with systemic ALCL, and 1 with angioimmunoblastic T-cell lymphoma) received BV. Although BV was well tolerated in each dose level, one patient who received a maximum dose level (3.6 mg/kg) experienced febrile neutropenia and sepsis, resulting in death 14 days after the first dose of BV. Subsequently, the 1.8-mg/kg and the 2.7-mg/kg cohorts were both expanded to include 12 patients each. In the 2.7-mg/kg cohort, 3 of 12 patients experienced 4 dose-limiting toxicities (DLT): grade 3 acute renal failure, hyperglycemia, prostatitis, and grade 3 febrile neutropenia. Meanwhile, the 1.8-mg/kg cohort experienced a single DLT in 1 of 12 patients: grade 4 thrombocytopenia. Based on these results, 1.8 mg/kg was judged as the MTD. The most common adverse events (AE) were fatigue (16 patients, 36%), pyrexia (15 patients,

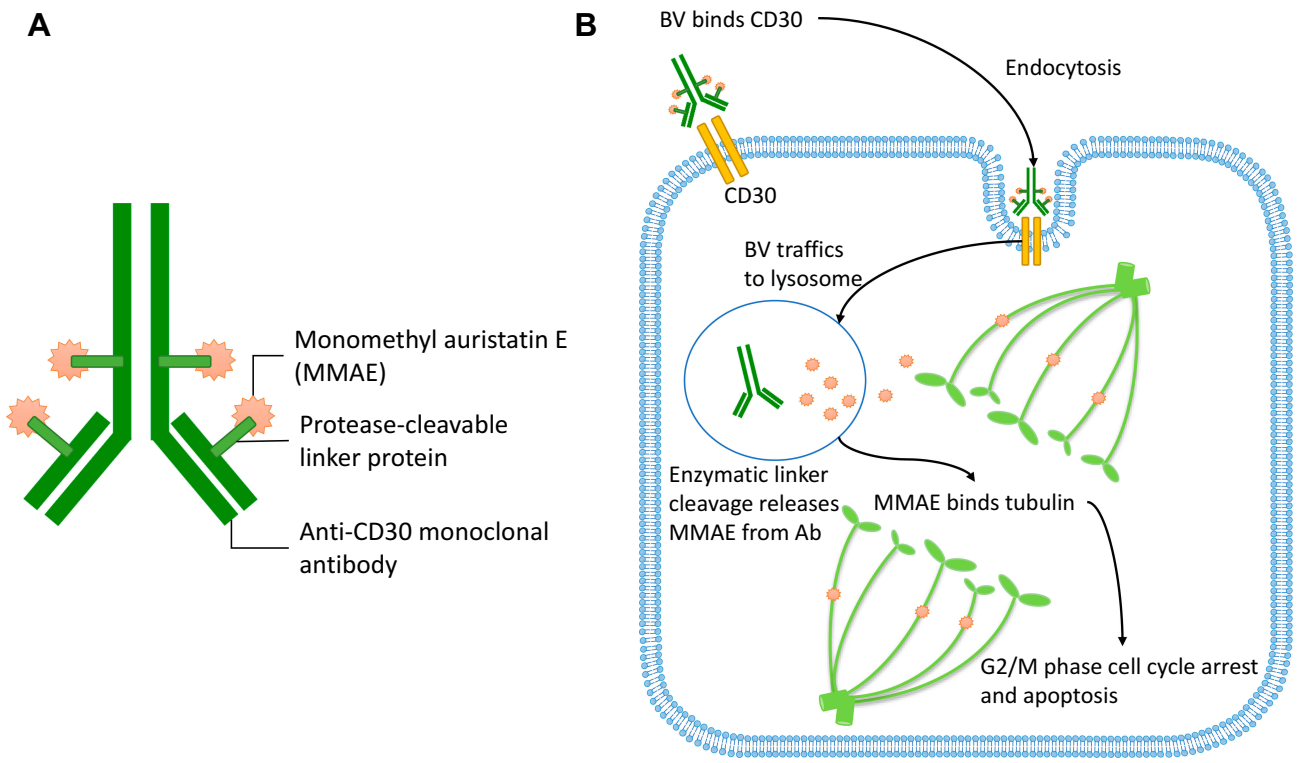


Figure 1 Brentuximab vedotin (BV). BV is an antibody-drug conjugate consisting of an anti-CD30 monoclonal antibody and the microtubule-disrupting agent monomethyl auristatin E (MMAE) (**A**). BV binds to CD30 expressed on the surface of lymphoma cells and is internalized via endocytosis. The cytoplasmic lysosomal enzymes decompose the linker protein that conjugates the CD30 antibody and MMAE. The MMAE released to the cytoplasm inhibits the synthesis of microtubules and leads to apoptosis of lymphoma cells (**B**).

33%), and diarrhea, nausea, neutropenia, and peripheral neuropathy (10 patients, 22% each), but they were grade 1 or 2 in severity and clinically manageable.

Weekly administration of BV (days 1, 8, and 15; 28-day cycle) was also evaluated in another phase I study, and the MTD was judged to be 1.2 mg/kg.[30] However, the incidence of peripheral sensory neuropathy was higher than that of the 21-day cycle schedule.[29] In total, 29 of 44 evaluable patients (66%) experienced peripheral sensory neuropathy in this study. Therefore, subsequent studies of single-agent BV utilized a 21-day cycle administration.

Single-Agent BV for Relapsed/Refractory cHL

A pivotal phase II study of BV in patients with cHL relapsed or refractory after HDC/ASCT was conducted.[31] The primary endpoint was overall ORR, and the planned sample size was 100 based on the assumptions of 29% ORR and that the exact two-sided 95% confidence interval would exclude an ORR of less than 20%. In total, 102 patients were enrolled and treated with BV at a dose of 1.8 mg/kg in a 21-day cycle, for up to 16 cycles. The median number of prior lines of therapy was 3.5, and 42% (43 of 102) of enrolled patients were refractory to the most recent prior therapy. The ORR was 75% (76 of 102), and the primary endpoint was met. The complete response (CR) rate was 34% (35 of 102). The median time to objective response was 5.7 weeks. Although BV was well tolerated, one of the most common treatment-related AEs was a peripheral sensory neuropathy. In total, 42% of patients (43 of 102) experienced sensory neuropathy, and 8% (8 of 102) experienced grade 3. Peripheral motor neuropathy was also observed in 11% (11 of 102). Twenty patients discontinued the treatment because of AE; of them, 9 patients discontinued because of neuropathy.

The estimated 5-year overall survival (OS) and progression-free survival (PFS) rates were 41% and 22%, respectively, with a median follow-up duration of 35.1 months.[32] Notably, 38% (13 of 34) of patients who achieved CR survived without progression for more than 5 years, and 9 of the 13 patients remained in remission without a consolidative allogeneic stem cell transplantation. The data showed that a small subset of patients (9% of the enrolled patients) with relapsed/refractory cHL may be cured with single-agent BV.

Based on the promising results of this pivotal phase II study, the US Food and Drug Administration (FDA) granted accelerated approval of BV in 2011 for cHL that relapsed or became refractory after HDC/ASCT or for after failure of two or more prior lines of multiagent chemotherapy in transplant-ineligible patients. It was the first approval of antibody therapy for cHL.

Consolidation Therapy with BV After HDC/ASCT

Salvage therapy followed by HDC/ASCT has been considered the standard treatment modality for relapsed/refractory cHL. Two randomized trials demonstrated the superiority of HDC/ASCT over conventional chemotherapy without HDC/ASCT.[33,34] Further, subsequent studies indicated that about 60% of relapsed patients and 35% of refractory patients can be cured with HDC/ASCT, while the remaining experience cHL relapse.[35] To improve the treatment outcome of patients with relapsed/refractory cHL who underwent HDC/ASCT, a consolidation with BV after HDC/ASCT was evaluated in a double-blind, randomized phase III trial (AETHERA study).[36] In this study, patients with at least one of the following unfavorable risk factors were enrolled: 1) primary refractory disease, 2) relapse within 12 months after the first remission, and 3) extranodal involvement at the start of the second-line chemotherapy. The primary endpoint was PFS, and the secondary endpoints were OS and safety. In total, 329 patients were randomly assigned in a 1:1 ratio to the BV arm (n=165) and the placebo arm (n=164; 160 received allocated intervention). After a median follow-up duration of 30 months, the median PFS by independent review was significantly longer in the BV arm (42.9 months) than that in the placebo-arm (24.1 months), and the study met its primary endpoint (hazard ratio [HR]: 0.57). Interim analysis of OS showed no statistical difference between the two arms. However, the 5-year follow-up data showed that consolidation with BV significantly reduced the need for subsequent therapy compared with placebo (32%, n=53 in the BV arm vs 54%, n=89 in the placebo arm; $P<.0001$) and sustained PFS benefit.[37] Therefore, consolidation with BV after HDC/ASCT is a reasonable treatment option in patients with unfavorable risk factor.

BV in a Second-Line Setting

Improving the efficacy of the second-line salvage chemotherapy is also an important issue in the management of transplant-eligible relapsed/refractory cHL. Several studies indicated that the pre-transplant disease status, particularly when evaluated with positron emission tomography-computed tomography (PET-CT) scan, predicts the outcome following HDC/ASCT.[38–40] The conventional salvage therapies demonstrate substantial efficacy against relapsed/refractory cHL; the ORR is 62%-89%,[41–45] but their CR rates are only 10%–41% (Table 2). Several studies evaluated incorporation of BV into the chemotherapy at the second-line setting to achieve higher PET-negative CR rate before HDC/ASCT (Table 3).[46–53] Moskowitz et al conducted a phase II study to evaluate a PET-adopted sequential combination of BV and augmented ifosfamide, carboplatin, etoposide (ICE) therapy (Figure 2).[46] In this study, patients initially received 2 cycles of weekly BV (1.2 mg/kg, days 1, 8, and 15, 28-day cycle), and the response was evaluated with PET-CT scan. If they achieved complete metabolic response (CMR) (defined as Deauville score 1 or 2 in this study), the patients underwent stem cell mobilization/harvest and subsequent HDC/ASCT. The remaining patients were treated with 2 cycles of augmented ICE therapy and underwent HDC/ASCT if they achieved CMR. Meanwhile, patients who did not achieve CMR after 3 cycles of augmented ICE received other conventional salvage chemotherapy and underwent HDC/HSCT. Of the 45 patients enrolled, 12 (27%) achieved CMR (Deauville score ≤2 in this study) after 2 cycles of weekly BV and received HDC/ASCT without salvage therapy. Actually, 44% (20/45) of patients were Deauville score ≤3 after 2 cycles of weekly BV. The remaining patients who were Deauville score ≥3 after 2 cycles of weekly BV received augmented ICE and 69% (22 of 32) achieved CMR. In total, 76% (34 of 45) achieved CMR in this PET-adopted sequential strategy. Chen et al also evaluated PET-adopted sequential strategy using conventional dosing and schedule of BV for up to 4 cycles.[47] Patients received salvage chemotherapy if they cannot achieve CMR

Table 2 Response of Selected Salvage Chemotherapy for Relapsed/Refractory cHL

Authors	Regimen	No. of Pts	ORR	%CR
Josting et al[41]	DHAP	102	89%	21%
Moskowitz et al[42]	ICE	65	88%	26%
Aparicio et al[43]	ESHAP	22	73%	41%
Bartlett et al[44]	GVD	91	70%	19%
Kuruvilla et al[45]	GDP	34	62%	10%

Abbreviations: CR, complete remission; cHL, classic Hodgkin lymphoma; DHAP, cisplatin, cytarabine, dexamethasone; ESHAP, etoposide, methyl prednisolone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin; GVD, gemcitabine, vinorelbine, pegylated liposomal doxorubicin; ICE, ifosfamide, carboplatin, etoposide; ORR, objective response rate.

Table 3 Selected Clinical Trials of BV Combined with Chemotherapy or Immune Checkpoint Inhibitor for Relapsed/Refractory cHL at the Second-Line Setting

Study Group	Regimen	Type of BV Combination	N	%CMR	ASCT, n (%)	PFS/EFS (ITT)
MSKCC[46]	Weekly BV × 2 +/− AugICE	Response-adapted sequential	45	27%[a] (BV alone) 69%[a] (Including-AugICE)	34 (76%) after BV-AugICE 10 (22%) after additional Tx	80% at 2 years
City of Hope[47]	BV × 4 +/− Salvage	Response-adapted sequential	37	35% (BV alone) 65% (Including salvage)	32 (86%)	71.9% at 18 months
GELTAMO[48]	BRESHAP	Concurrent	66	70%	60 (91%)	71% at 30 months
HOVON[49,50]	BV-DHAP	Concurrent	61	79%	53 (87%)	76% at 2 years
FHCRR[51]	BV-ICE	Concurrent	24	87%	19 (79%)	NR
LaCasce et al[52]	BV-bendamustine	Concurrent	55	74%	40 (72%)	62.6% at 2 years
COG[53]	BV-gemcitabine	Concurrent	42	67%	34 (76%)	NR
Herrera et al[58] Moskowitz et al[59]	BV-Nivolumab	Concurrent	91	67%	67 (74%)	78% at 2 years

Notes: [a]Defined as Deauville score 1 or 2 in this study.

Abbreviations: ASCT, autologous stem cell transplantation; AugICE, augmented ICE; BRESHAP, brentuximab vedotin, etoposide, methyl prednisolone, cytarabine, cisplatin; BV, brentuximab vedotin; CMR, complete metabolic response; COG, Children's Oncology Group; DHAP, dexamethasone, cytarabine, cisplatin; EFS, event-free survival; FHCRC, Fred Hutchinson Cancer Research Center; GELTAMO, Grupo Español de Linfomas/Trasplante Autólogo de Médula Ósea; HOVON, Hemato-Oncologie voor Volwassenen Nederland; ICE, ifosfamide, carboplatin, etoposide; MSKCC, Memorial Sloan-Kettering Cancer Center; Nivo nivolumab; NR, not reported; PFS, progression-free survival; Tx, therapy.

with BV alone. Overall, 13 of 37 enrolled patients (37%) achieved CMR after BV and underwent HDC/ASCT. Collectively, the results of these studies suggest that about 30%–40% of patients with relapsed/refractory cHL can obtain CMR with BV alone. Further, conventional salvage chemotherapy is not required in such population. The response-adapted sequential combination might reduce the risk of subsequent late toxicities associated with intensive cytotoxic chemotherapy. However, caution should be taken because there are no data comparing long-term outcomes after HDC/HSCT with regard to BV monotherapy versus conventional salvage therapy regimens. Further careful evaluation of this strategy is warranted.

Other studies demonstrated higher efficacy (with respect to the CR rate) of concurrent combination of BV and salvage therapy. A Spanish study group conducted a phase I/II study of etoposide methylprednisolone, cytarabine, and cisplatin (ESHAP) in combination with BV on day 1 (BRESHAP

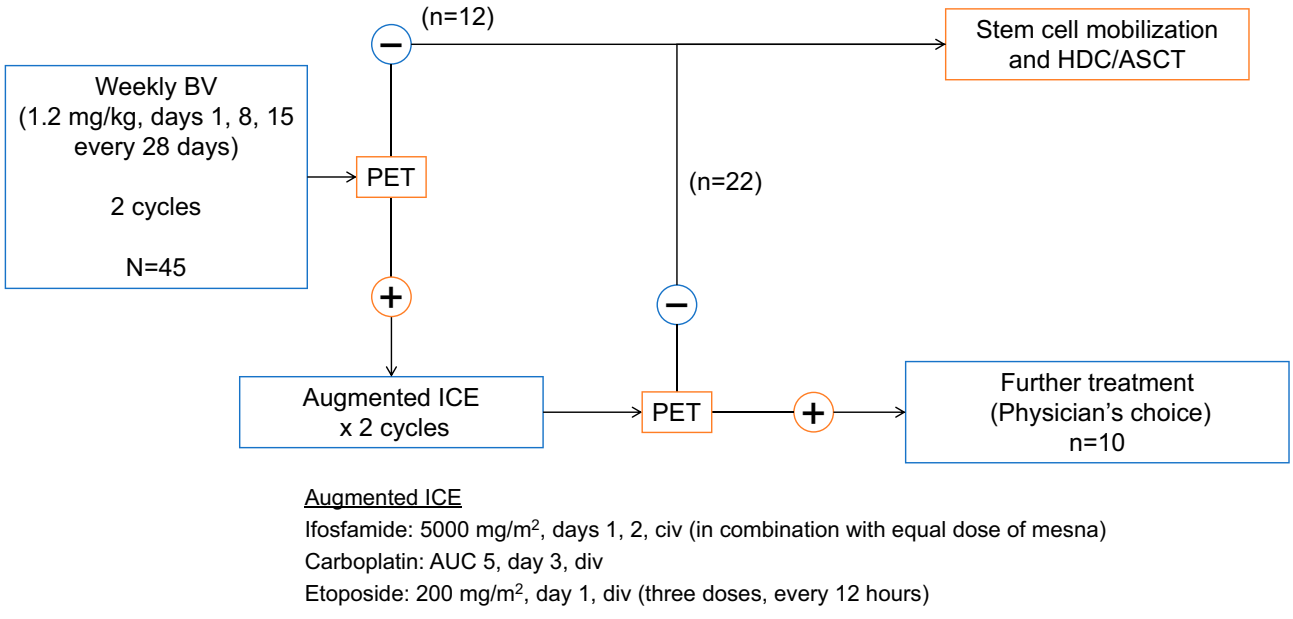


Figure 2 Example of sequential combination of BV and salvage chemotherapy: Weekly BV followed by augmented ICE.

Abbreviations: BV, brentuximab vedotin; HDC/ASCT, high-dose chemotherapy with autologous stem cell transplantation; ICE, ifosfamide, carboplatin, and etoposide; PET, positron emission tomography.

therapy) (Figure 3).[48] In the phase I portion, 3 dose levels (0.9, 1.2, and 1.8 mg/kg) of BV were evaluated, and no DLT was observed. The recommended phase II dose of BV was established as 1.8 mg/kg, which is the same dose of single-agent use. In total, 66 patients were assessed for efficacy, and the ORR and CR rates before HDC/ASCT were 91% and 70%, respectively. Preliminary studies of BV in combination with other salvage therapies such as dexamethasone, cytarabine, and cisplatin and ICE also reported high CR rates of 79%-87%.[49–51] Although these concurrent combination regimens appear highly effective, hematologic toxicities remain a concern. For example, the incidence of grade 3–4 hematologic toxicities in BRESHAP was approximately 50% (neutropenia, 50%; thrombocytopenia, 47%),[48] while that in ESHAP was 10%–20% (neutropenia, 10%-17%; thrombocytopenia 17%–24%).[54,55]

The combination of bendamustine with BV was also evaluated. A certain efficacy of single-agent bendamustine (120 mg/m^2, 28-day cycle) for heavily pretreated cHL has already been reported in a single-institute phase II study. The ORR by intent-to-treat analysis was 53% (19/36), and the CR rate was 33% (12/36).[56] O'Connor et al conducted a phase I/II study of BV plus bendamustine (90 mg/m^2, 21-day cycle) in heavily pretreated cHL.[57] The median number of prior therapies was 5 (range, 2–12) in the phase I portion (n=28) and 3 (range 1–8) in the phase II portion (n=37). The ORR was 71% (46 of 65), and the CR rate was 32% (21 of 65). A phase II study conducted by LaCasce et al using this combination as a bridging therapy for HDC/ASCT at the second-line setting showed a higher ORR of 92% (49 of 53) and CR of 74% (39 of 53), which is comparable to that of BRESHAP.[52]

BV plus nivolumab might be one of the most promising salvage therapies.[58,59] Preclinical studies suggested that the MMAE-based antibody-drug conjugates induce endoplasmic reticulum (ER) stress, which leads to immunogenic cell death and antigen presenting cell (APC) activation. As activated APCs promote innate antitumor immune responses, synergistic effects of BV and immune checkpoint inhibitors are expected.[60,61] A phase I/II study of BV in combination with nivolumab in a second-line setting was conducted (NCT02572167); the treatment comprised BV (1.8 mg/kg) and nivolumab (3.0 mg/kg) in 3-week cycles for up to 12 weeks (4 cycles). After the investigators assessed the response, patients could undergo HDC/ASCT. In total, 91 patients were enrolled in this study; the median age 34 years (range; 18–69), 42% with primary refractory disease, and 30% experienced relapse within 1 year of frontline therapy. The ORR for all treated patients was 85% (77/91) and the CR rate was 67% (61/91). The most common AEs were nausea (52%) and infusion-related reaction (IRR) (43%). However, IRR was typically only grade 1–2. Immune-related adverse events (IrAE) that required systemic steroid treatment occurred in 14% of patients; these including rash (8%), pneumonitis (4%), increased AST (1%), diarrhea (1%), and Guillain-Barre syndrome (1%). With a median follow-up duration of 22.6 months, the estimated 2-year PFS rate in all treated patients was 78%, and for patients who underwent HDC/ASCT after BV + nivolumab, it was 91%.

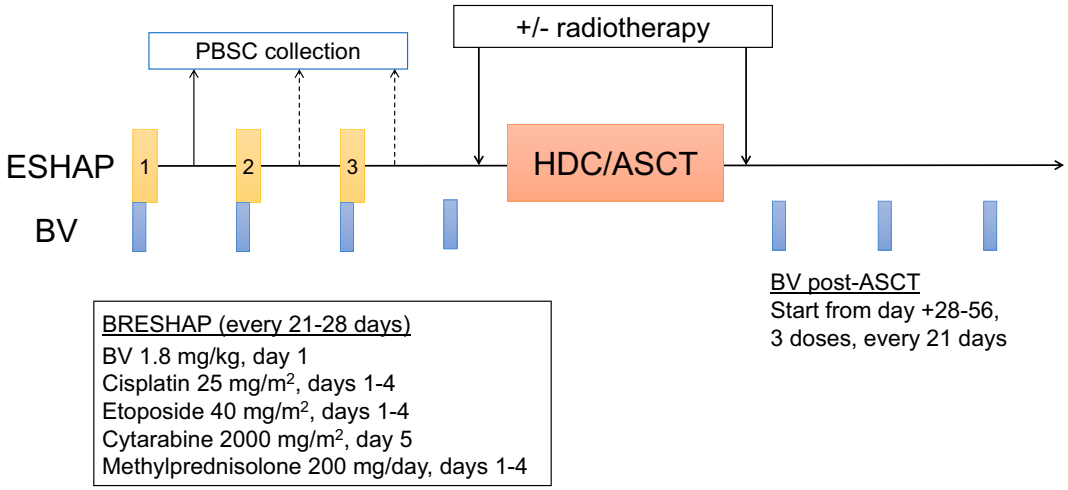


Figure 3 Example of concurrent combination of BV and salvage chemotherapy: BRESHAP.
Abbreviations: BV, brentuximab vedotin; ESHAP, etoposide, methylprednisolone, cytarabine, and cisplatin; HDC/ASCT, high-dose chemotherapy with autologous stem cell transplantation; PBSC, peripheral blood stem cell.

BV in Combination with Chemotherapy for Untreated Advanced-Stage cHL

Although cHL is one of the most curable malignancies, patients in the advanced stage have poorer prognosis compared to those with early-stage cHL.[2] Therefore, several approaches have been evaluated to improve the treatment outcome of these patients.[62] One approach is a PET-adopted dose-intensified strategy based on the interim PET-CT performed after 2 cycles (iPET2) of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD). Gallamini et al reported that positive iPET2 is a strong and independent predictor of poor outcomes in patients with advanced-stage cHL. The 2-year PFS of iPET2-negative patients was 95.0%, whereas that of iPET2-positive patients was 12.8%.[63] Based on these results, several study groups conducted an iPET2-guided response-adapted therapy for advanced-stage cHL (Table 4).[64–68] Overall, approximately 20% of patients with advanced-stage cHL will be iPET2 positive, and a dose-intensified conventional chemotherapy (eg, escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone [escalated BEACOPP] therapy) may improve their PFS to up to 60%-70%. An iPET2-guided response-adapted strategy appears feasible, and it is one of the reasonable treatment options in this population. However, the negative predictive value of iPET2 does not appear to be superior to that reported by Gallamini et al.[63] In the early report of iPET2, 95% of patients with negative-iPET2 achieve progression-free with ABVD,[63] whereas approximately 20% of iPET2-negative patients experience relapse in subsequent prospective studies.[64–68] In addition, the dose-intensified treatment for iPET2-positive patients is not feasible for elderly patients, often requires inpatient treatment, may increase the risk of second primary malignancy,[65] and has a high risk for gonadotoxicity.[69]

Another approach is a BV-containing chemotherapy. The effectiveness and tolerability of BV for cHL in the relapsed/refractory setting encouraged it to incorporate in the frontline setting. Younes et al conducted a phase I study to evaluate the safety and preliminary efficacy of BV in combination with ABVD therapy for advanced-stage cHL.[70] Initially, BV was combined with standard ABVD on days 1 and 15 of a 28-day cycle, and 3 dose levels (0.6, 0.9, and 1.2 mg/kg) were evaluated. Although no DLT was observed during the DLT assessment period and the MTD was not reached, 44% (11 of 25 patients) experienced pulmonary toxicity, which frequently occurred during cycles 3–4. Meanwhile, patients treated with BV + AVD (bleomycin was omitted) (n=26) experienced no pulmonary toxicities. The results suggested that concomitant administration of bleomycin and BV should be avoided. The CR rate in patients with BV + ABVD was 95% (21 of 22) and that of BV + AVD was 96% (24 of 25). According to the long-term follow-up data, the 5-year failure-free survival in the BV + ABVD group and the BV + AVD groups were 79% and 92%, respectively.[71]

Based on this promising efficacy, an international, open-label, randomized phase III study comparing BV + AVD with standard ABVD in patients with advanced-stage cHL (ECHELON-1) was conducted.[72] The primary endpoint was "modified" PFS, defined as (1) a progressive disease, (2) a non-CR to front-line therapy (Deauville 3–5 at the end-of-treatment PET scan by independent review committee) followed by the delivery of subsequent treatment (including radiotherapy), and (3) any-cause death. In

Table 4 ABVD-Based Response-Adapted Therapy for Advanced-Stage cHL

Study	N	Study Design	Tx Before iPET2	Tx for iPET2 Negative	Tx for iPET2 Positive	%iPET2 Positive	PFS of iPET2 Positive	PFS of iPET2 Negative
S0816 (SWOG)[64,65]	336	Phase II	ABVD×2	ABVD×4	eBEACOPP×6	18%	66% at 5 years	76% at 5 years
HD0607 (GITIL)[66]	782	Phase II	ABVD×2	ABVD×4	eBEACOPP×4 (+R) → bBEACOPP×4 (+R)	19%	60% at 3 years	87% at 3 years
RATHL (CR-UK)[67]	1214	Phase III	ABVD×2	ABVD×4 vs AVD×4	BEACOPP14×6 or eBEACOPP×4	16%	67.5% at 3 years	85.7% at 3 years 84.4% at 3 years
HD0801 (FIL)[68]	520	Phase II/III	ABVD×2	ABVD×4 +/− IFRT[a]	IGEV×4 → HDC/ASCT	20%	76% at 2 years	81% at 2 years

Note: [a]Patients with bulky disease were randomly assigned to the RT arm or the no-RT arm.

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; bBEACOPP, baseline BEACOPP; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; CR-UK, Cancer Research UK; eBEACOPP, escalated BEACOPP; FIL, Fondazione Italiana Linfomi; GITIL, Gruppo Italiano Terapie Innovative nei Linfomi; HDC/ASCT, high dose chemotherapy with autologous hematopoietic stem cell transplantation; IGEV, ifosfamide, gemcitabine, etoposide, vinorelbine; iPET2, interim positron emission tomography scan after 2 cycles of ABVD; PFS, progression-free survival; SWOG, Southwest Oncology Group; Tx, therapy.

total, 1334 patients with stage III or IV cHL were randomly assigned to the BV + AVD-arm (n=664) and the ABVD arm (n=670). The study met its primary endpoint, with the 2-year modified PFS being 82.1% in the BV + AVD-arm vs 77.2% in the ABVD arm (HR: 0.77 [95% CI: 0.60-0.98]; p=0.04) after a median follow-up duration of 24.6 months. However, the difference was modest, and the 95% CI upper margin was near to 1. Further, the OS was not significantly different between the two arms (2-year OS: 96.6% [BV+AVD] vs 94.2% [ABVD]).

Concerning toxicities, febrile neutropenia was observed in 19% in the BV+AVD arm and in 8% in the ABVD arm. In addition, 7 of 9 deaths in BV+AVD arm were associated with neutropenia. Therefore, primary prophylaxis with granulocyte colony-stimulating factor was recommended after the protocol amendment. Meanwhile, pulmonary toxicity was higher in the ABVD arm (2% in BV + AVD vs 7% in ABVD). Based on the results, BV + AVD was approved for previously untreated advanced-stage cHL by the US FDA in 2018. However, although this large-scale multicenter phase III study met its primary endpoint, the clinical benefit of BV + AVD remains arguable, partly because of the following points. First is a complex endpoint that might have been affected by observer bias associated with the unblinded study design. Physicians knew whether their patients received ABVD or the new BV + AVD treatment, and it could have impacted the decision on whether additional therapy was needed or not in patients with non-CR. In fact, among the 144 patients (65 with BV + AVD and 79 with ABVD) with Deauville 3–5 at the end-of-treatment PET scan, 14% (9 of 65) in the BV + AVD arm received subsequent therapy, whereas 28% (22 of 79) in the ABVD arm received such treatment. Second is the over-recruitment compared to the planned number of patients, and this might affect the relevance of P value. Initially, the study was designed to show a 7.5% difference of modified PFS (82.5% vs 75%, HR 0.67) at 3 years with 1,040 patients. However, the study was amended to evaluate the primary endpoint at 2 years, and 1,240 patients would have been needed to show an 8% difference (81% vs 73%, HR 0.67). As such, 1,334 patients were enrolled in ECHELON-1. The actual HR was 0.77, but the difference of modified PFS was smaller than expected (4.9%). Third is a relatively short follow-up duration, and fourth is controversial clinical benefit of BV + AVD in patients with stage III disease and elderly age.

To reveal the actual role of BV in the first-line setting, OS data with further long-term follow-up data are required.

While BV + AVD was compared against the international standard ABVD, escalated BEACOPP has also demonstrated superior efficacy in advanced-stage cHL when compared to ABVD.[73–76] Escalated BEACOPP is not utilized internationally as a routine first-line therapy for advanced-stage cHL because of its high incidence of acute and/or late toxicities including second primary malignancies, and lack of benefit in terms of long-term clinical outcome when HDC/ASCT is planned at the relapsed setting.[77] However, considering better initial tumor control, it is regarded as a standard of care for advanced-stage cHL in the German Hodgkin Study Group (GHSG). The investigators of GHSG are evaluating the incorporation of BV into a BEACOPP backbone. Two types of BV-containing regimens have been developed; BrECAPP and BrECADD regimens (BV, etoposide, cyclophosphamide, doxorubicin and procarbazine/prednisone or dacarbazine/dexamethasone). Because concomitant administration of bleomycin and BV increase the risk of pulmonary toxicity, bleomycin was replaced with BV in both regimens. Vincristine was also omitted because both vincristine and MMAE inhibit tubulin polymerization and may result in unacceptable neurotoxicity. In a randomized phase II study comparing BrECAPP and BrECADD, both regimens were equally effective. However, BrECADD was associated with a more favourable toxicity profile.[78] Therefore, BrECADD was selected to be compared with the standard of care in the subsequent phase III study. Currently, a phase III study comparing BrECADD with escalated BEACOPP in patients with advanced-stage cHL is ongoing (HD21, NCT02661503).

Untreated Advanced-Stage cHL in Elderly Patients

Elderly patients with cHL (usually age over 60 years) account for 20%-30% of cHL.[79] The elderly patients with cHL have poorer treatment outcome compared with that of younger patients. The 5-year PFS and OS rates are 30%-48% and 40%-58%, respectively.[80–84] This is partly because of treatment-related toxicities associated with comorbidities and the high incidence of bleomycin lung toxicity. As BV demonstrated high efficacy with minimal toxicities in relapsed/refractory patients with cHL, BV was tested in the front-line setting of elderly patients with cHL (Table 5). Forero-Torres et al tested single-agent BV in elderly patients with cHL.[85] Twenty-seven patients with untreated cHL aged 60 years or older were enrolled in this study. The ORR among the 26 efficacy-evaluable patients

Table 5 Selected Studies of BV-Containing Regimen for Untreated Elderly Patients with cHL

Treatment	Study Design	N	ORR	CR rate	PFS
BV	Phase II	27	92%	73%	Median 10.5 months
BV + dacarbazine	Phase II	22	100%	62%	Median 17.9 months
BV + bendamustine	Phase II	20	100%	88%	Median not reached
Sequential BV and AVD	Phase II	48	95%	93%	84% at 2 years
BV + nivolumab	Phase II	18	100%	72%	ND

Abbreviations: AVD, doxorubicin, vinblastine, dacarbazine; BV, brentuximab vedotin; CR, complete response; ND, no available data; ORR, objective response rate; PFS, progression-free survival.

was 92% (24 of 26), with 73% of patients (19 of 26) achieving CR. However, the median PFS was only 10.5 months. Subsequently, frontline BV in combination with dacarbazine or bendamustine was tested in a phase II study.[86] In this study, 22 patients received 1.8 mg/kg BV and 375 mg/m^2 dacarbazine for up to 12 cycles, and 20 more patients received 1.8 mg/kg BV plus 90 (or 70) mg/m^2 bendamustine for up to 6 cycles. All the patients in both treatment regimens achieved objective responses, but the CR rate was higher in patients treated with bendamustine-based regimen (62% in BV + dacarbazine vs 88% in BV + bendamustine). Nevertheless, despite encouraging efficacy, patients treated with BV + bendamustine tended to experience more severe adverse events, and the regimen was determined to be too toxic in this population.

Another approach for using BV with conventional chemotherapy in elderly patients is a sequential combination. A subgroup analysis of elderly patients treated in the ECHELON-1 study did not find the superiority of concurrent combination of BV-AVD over ABVD with respect to both PFS and modified PFS. Further, the incidence of febrile neutropenia (FN) was higher in the BV + AVD arm than that in the ABVD arm (37% vs 17%).[87] To reduce the toxicities associated with concurrent combination of BV with cytotoxic chemotherapy, Evens et al conducted a phase II study of a sequential combination of BV and AVD for elderly patients with untreated cHL.[88] The study treatment comprised 2 cycles of lead-in BV (1.8 mg/kg, 21-day cycle) followed by 6 cycles of AVD and 4 subsequent cycles of consolidation BV. In total, of the 48 patients enrolled, 42 patients were evaluable for the efficacy. The ORR was 95% (40 of 42), and the CR rate was 93% (39 of 42). Of note, the incidence of FN was only 8%. Although this was a small-scale, single-arm study, the results show that sequential BV combination is more tolerable with sufficient efficacy in older patients with cHL.

BV plus nivolumab is thought to be an attractive treatment option in this setting. Recently, results of a phase II study of BV plus nivolumab in patients with classic Hodgkin lymphoma aged ≥60 years were reported.[89] In total, 21 patients received BV (1.8 mg/kg) and nivolumab (3 mg/kg) on day 1 of each 21-day cycle for up to 16 cycles. The median age was 72 years (range, 60–88); the majority had ECOG-PS 0–1 (95%) and stage III–IV disease (77%). Among the 18 response-evaluable patients, all achieved objective responses, including 13 patients (72%) with CR. The median duration of the response was not yet reached, and the maximum duration of the response was 22 months and ongoing. The most common treatment-related AEs of any grade were fatigue (48%), peripheral sensory neuropathy (38%), diarrhea, IRR, and pyrexia (24% each). The most common AEs of grade 3 or higher were lipase increases (19%) and peripheral motor neuropathy (14%).

Considering the encouraging efficacy and tolerability of BV + nivolumab, it might be a potential treatment option in this setting, especially for patients who are unfit for cytotoxic chemotherapy. Validation in a large sample of patients with longer follow-up data is warranted.

BV in Combination with Chemotherapy for Early-Stage Untreated cHL

As most early-stage cHL can be cured with chemoradiotherapy, determining methods to reduce the risk of late toxicities such as second primary malignancy or cardiovascular toxicity is a major purpose of clinical development in this population. The late toxicities are mostly associated with radiotherapy. Therefore, several treatment strategies to omit radiotherapy have been evaluated. The H10 trial conducted by EORTC/LYSA/FIL and the RAPID trial conducted by a UK study group evaluated a PET-adapted strategy to omit radiotherapy in the PET-negative population.[90–92] However, both studies failed to show non-inferiority of omission of radiotherapy.

The GHSG previously demonstrated that in early-stage cHL patients without unfavorable risk factors (so-called

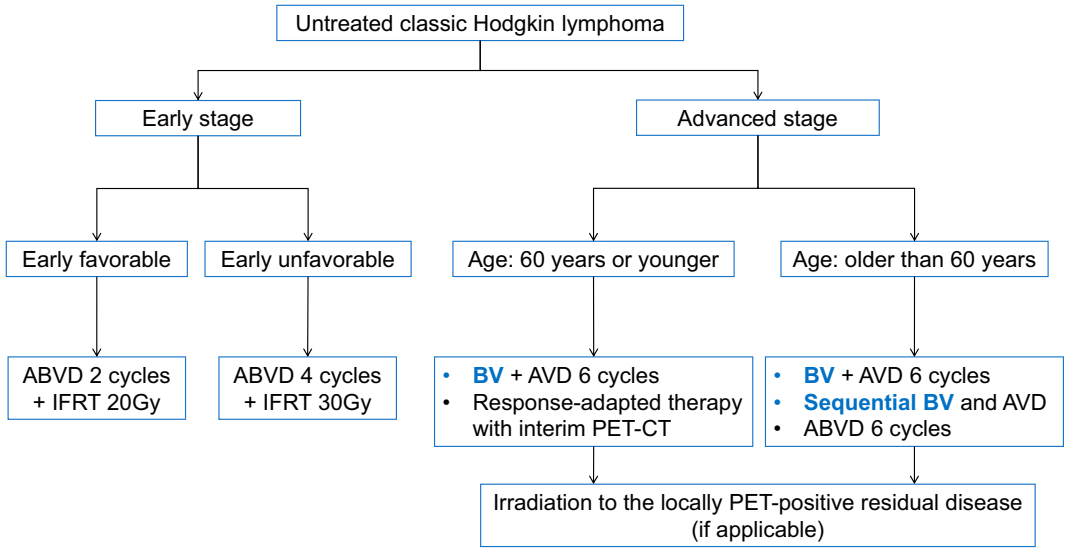


Figure 4 Current treatment strategy for untreated classic Hodgkin lymphoma.
Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BV brentuximab vedotin; IFRT, involved-field radiotherapy; PET-CT, positron emission tomography-computed tomography.

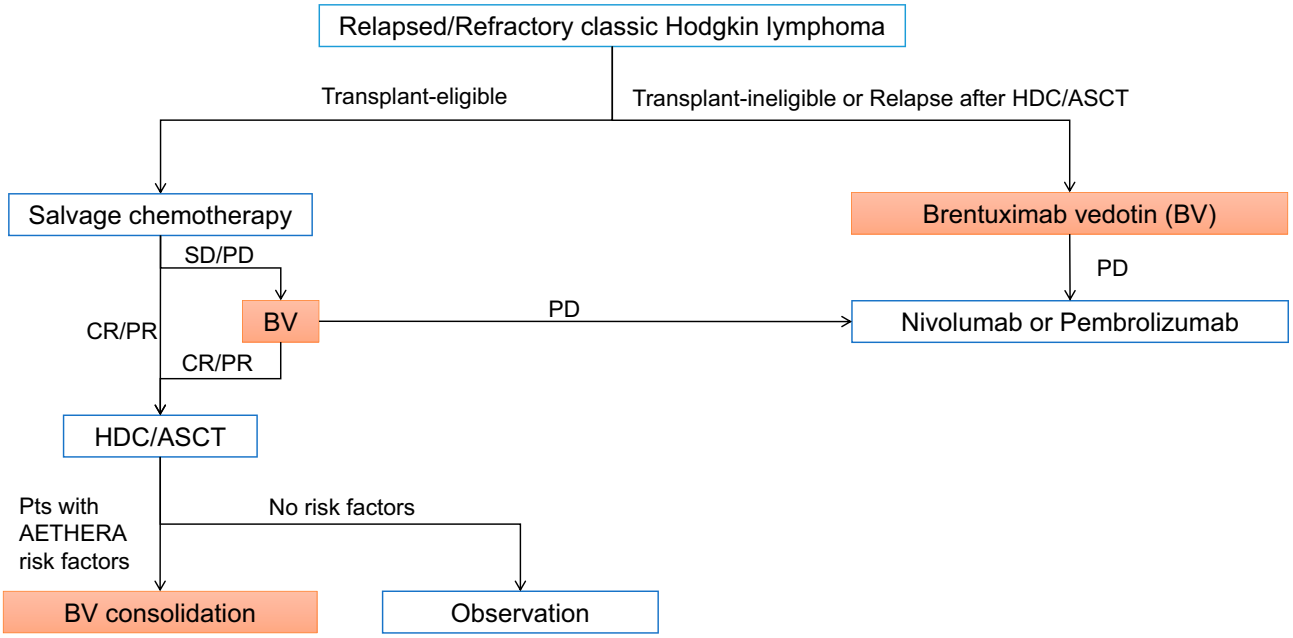


Figure 5 Current treatment strategy for relapsed/refractory classic Hodgkin lymphoma.
Abbreviations: BV, brentuximab vedotin; CR, complete response; HDC/ASCT, high-dose chemotherapy with autologous stem cell transplantation; PD, progressive disease; PR, partial response; SD, stable disease.

"early-favorable"), the number of cycles of ABVD can be reduced with preserving efficacy from 4 to 2 cycles and the dose of radiotherapy can also be reduced (30 to 20 Gy).[93,94] Subsequently, they have tested to omit radiotherapy for those who demonstrated PET-negative scan after 2 cycles of ABVD in patients with early-favorable cHL. However, non-inferiority has not been confirmed even in this population (the 5-year PFS was 93.4% for those who received ABVD followed by radiotherapy vs 86.1% in ABVD alone).[95]

Recently, Abramson et al evaluated BV + AVD without consolidative radiotherapy in patients with early-stage non-bulky cHL.[96] In this phase II study, 34 patients with early-stage cHL were enrolled. The best CR rate was 100%, and the 3-year PFS and OS were 94% and 97%, respectively, with

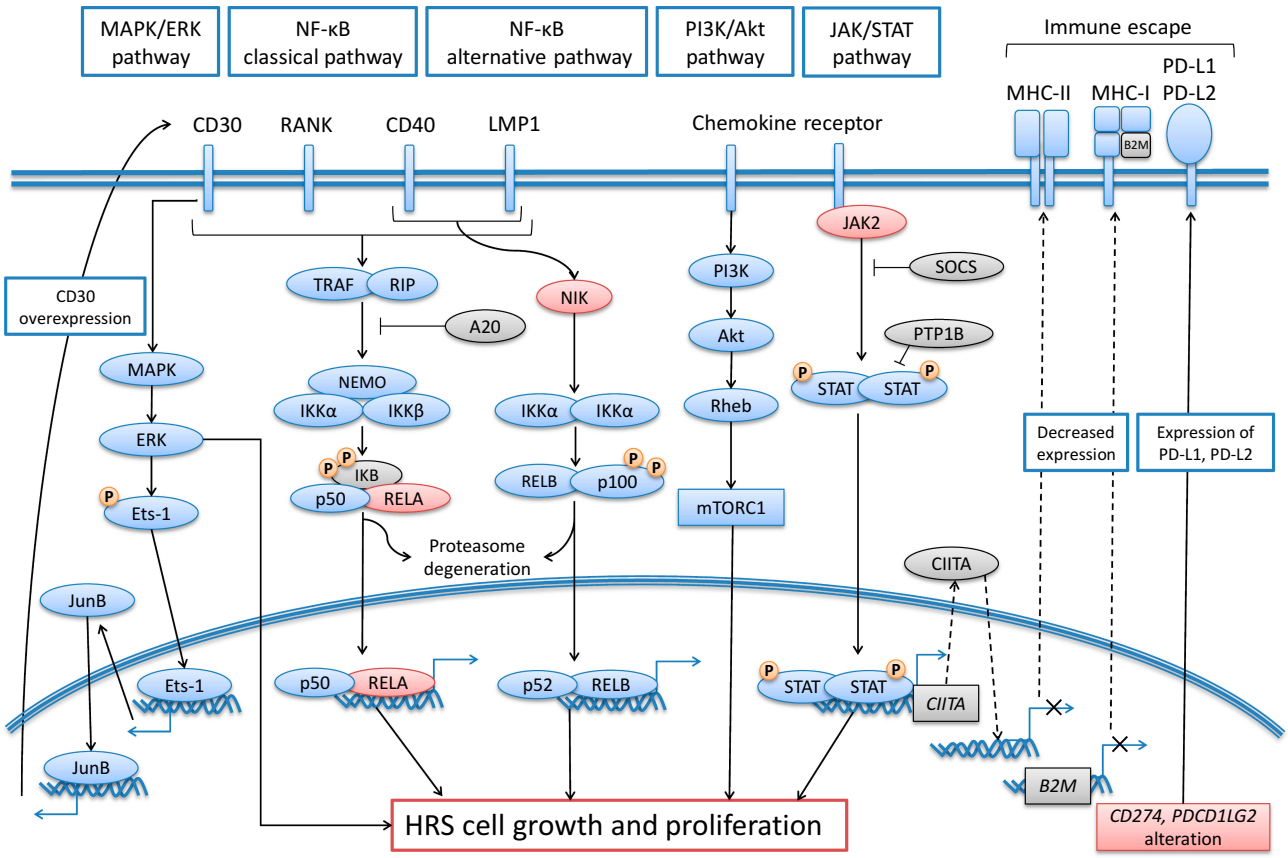


Figure 6 Signaling pathways and genomic alterations in Hodgkin Reed Sternberg cell Activating mutations are highlighted in red, and loss-of-function mutations are highlighted in gray.

Abbreviations: B2M, beta-2 microglobulin; CIITA, class II major histocompatibility complex transactivator; ERK, extracellular signal-regulated kinase; HLA, major histocompatibility complex; IKK, I kappa kinase; JAK, Janus kinase; LMP1, latent membrane protein 1; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NEMO, NF-κB essential modulator; NF-κB, nuclear factor kappa B; NIK, NF-κB-inducing kinase; PDCD1LG2, programmed cell death 1 ligand 2; PD-L1/-L2, programmed cell death-ligand 1/-ligand 2; PI3K, phosphatidylinositol 3-kinase; PTP1B, protein tyrosine phosphatase 1B; RANK, receptor activator of nuclear factor kappa B; RIP, receptor interacting protein; Rheb, Ras homolog enriched in brain; SOCS, suppressor of cytokine signaling; STAT, signal transducers and activator of transcription; TRAF, TNF receptor associated factor.

a median follow-up duration of 38 months. The results indicate that BV + AVD without consolidative radiotherapy yields similar benefit with that of chemoradiotherapy. However, it remains unclear whether radiotherapy can be omitted by using BV-containing chemotherapy in early-stage patients because this was a small-scale, single-arm phase II study with a relatively short follow-up duration. As early-stage cHL is a highly curable disease when treated with standard chemoradiotherapy, omission of radiotherapy should be carefully evaluated. For the treatment course, radiotherapy should never be omitted in the first-line treatment for early-stage cHL outside the clinical trials.

Resistance Mechanisms Against BV

The actual mechanism by which cHL patients become refractory to BV remains unclear. In ALCL patients, CD30 downregulation was observed when exposed to BV both in vitro and in vivo.[97,98] However, CD30 expression remains preserved in patients with BV-refractory cHL.[99] Instead, MMAE resistance and upregulation of multi drug resistance mutation 1 (MDR1), which pumps MMAE out of the tumor cells, are thought to play major roles in the refractory mechanism of cHL patients to BV.[97] Currently, a phase I study of BV in combination with cyclosporine or verapamil, which are substrates for MDR1 and may prevent the export of MMAE by overwhelming the transporter, is ongoing (NCT03013933).

Conclusions and Future Directions

Current treatment strategies for cHL and the role of BV are summarized in Figures 4 and 5. BV plays important roles both in the relapsed/refractory and in front-line settings.

Among patients who experience relapsed/refractory cHL after HDC/ASCT, single-agent BV has demonstrated

Table 6 Selected Targeted Therapies for Relapsed/Refractory Classic Hodgkin Lymphoma

Agent	Target	Study Design	Number of Patients	ORR	Reference
Bortezomib	NF-κB	Phase II	30	0%	Blum et al Leuk Lymphoma 2007[103]
SB1518	JAK2	Phase I	14	0%	Younes et al J Clin Oncol 2012[104]
Ruxolitinib	JAK1/2	Phase II	32	18.8	Van Den Neste et al Haematologica 2018[105]
Everolimus	mTOR	Phase II	19	47%	Johnston et al Am J Hematol 2010[106]
Idelalisib	PI3Kδ	Phase II	25	20%	Gopal et al Ann Oncol 2017[107]
MK2206	AKT	Phase II	25	23%	Oki et al Br J Haematol 2015[108]
Panobinostat	HDAC	Phase II	129	27%	Younes et al J Clin Oncol 2012[109]
Mocetinostat	HDAC	Phase II	23 (85 mg cohort)	26%	Younes et al Lancet Oncol 2011[110]
Entinostat	HDAC	Phase II	49	12%	Batlevi et al Haematologica 2016[111]
Resminostat	HDAC	Phase II	37	34%	Walewski et al Leuk Lymphoma 2019[112]

Abbreviations: AKT, protein kinase B; HDAC, histone deacetylase; JAK, Janus kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase.

substantial efficacy with a favorable toxicity profile. However, more than half of patients experience disease progression and there is clearly room for further improvement.

BV in combination with immune checkpoint inhibitors is actively being developed in this setting. The Eastern Cooperative Oncology Group (ECOG) and the American College of Radiology Imaging Network (ACRIN) Cancer Research Group conducted a phase I/II study (E4412) comparing two doublet regimens and one triplet regimens: BV + ipilimumab (anti-cytotoxic T lymphocyte antigen 4 [CTLA-4] antibody), BV + nivolumab, and BV + nivolumab + ipilimumab in patients with relapsed/refractory cHL.[100] The ORR/CR rates in these regimens were 67%/55%, 95%/65%, and 95/79%, respectively. Despite the highest efficacy identified for the triplet regimen, 4 of 5 DLTs in this study were observed in the triplet arm including grade 4 diabetic ketoacidosis, hyperglycemia, grade 3 transaminitis, and grade 4 graft versus host disease (in a patient with a previous history of allogeneic HSCT). Currently, a randomized phase II part comparing a BV-nivolumab doublet regimen with triplet regimen is ongoing.

BV combined with small-molecule treatment is another expected approach. Recent advances in basic research have revealed molecular pathogenesis of cHL (Figure 6)[101,102] leading to the clinical development of several targeted small molecules (Table 6).[103–112] However, the development of these small molecules fell out of favor because of their moderate efficacy with single-agent use. Currently, the combination of BV and/or immune checkpoint inhibitors with small molecules is being tested in early phase trials.

In the second-line setting, seeking a novel optimal salvage regimen before HDC/ASCT is warranted. Based on several single-arm studies of BV-containing cytotoxic regimens, incorporation of BV into this setting appears to be reasonable. Further, conventional-cytotoxic-free strategies, such as PET-adapted sequential BV-salvage and BV in combination with immune checkpoint inhibitors are actively being tested. However, careful evaluation in a randomized trial with long-term follow-up is warranted to further evaluate the role of BV in this setting.

The role of BV in the first-line setting may be more controversial than that in other settings. Despite positive results of the ECHELON-1 study, the actual clinical benefit of BV-AVD remains arguable. The final results should help to determine whether the curve separation will be consistent with longer follow-up. In addition, a randomized phase III study comparing AVD in combination with nivolumab with BV-AVD in patients with untreated advanced-stage cHL is ongoing (SWOG S1826, NCT03907488). The results of this study might change the role of BV in this setting in the future.

Introduction of BV into the first-line setting will make the application of previous evidence of BV for relapsed/refractory cHL difficult. However, as increasing data support the efficacy of BV re-treatment,[113,114] patients who initially respond to BV and subsequently experience relapse may be considered for BV-containing treatment strategy.

Considering the high efficacy and low toxicity of BV, it is a suitable agent for the treatment of elderly patients with cHL, particularly in the front-line setting. Although Evens et al demonstrated the safety and efficacy of sequential BV with AVD, the strategy is applicable only to patients who are fit for an anthracycline-containing regimen. Further studies to optimize the use of BV in this population, including BV + nivolumab is expected.

In conclusion, BV has opened a new horizon for the management of cHL and has provided a novel treatment paradigm since the first FDA approval. However, there remains several arguable discussion points, especially in the first-line setting. Further accumulation of data with well-designed clinical trials is warranted to identify the exact role of BV in our daily clinical practice.

Abbreviations

ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AE, adverse events; ALCL, anaplastic large cell lymphoma; ASCT, autologous stem cell transplantation; APC, antigen presenting cell; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisolone; BV, brentuximab vedotin; cAC10, chimeric anti-CD30 monoclonal antibody; cHL, Classic Hodgkin lymphoma; CMR, complete metabolic response; CR, complete response; CTLA-4, cytotoxic T lymphocyte antigen 4; DHAP, dexamethasone, cytarabine, and cisplatin; DLT, dose-limiting toxicities; ER, endoplasmic reticulum; ESHAP, etoposide methylprednisolone, cytarabine, and cisplatin; BRESHAP, ESHAP in combination with BV; FN, febrile neutropenia; FDA, Food and Drug Administration; HR, hazard ratio; HDC, high-dose chemotherapy; ICE, ifosfamide, carboplatin, etoposide; IrAE, immune-related adverse events; IRR, infusion-related reaction; iPET2, interim PET-CT performed after 2 cycles; MTD, maximum-tolerated dose; MMAE, monomethyl auristatin E; MDR1, multidrug resistance mutation 1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RIP, ribosome-inactivating proteins.

Disclosure

SM received honoraria from Takeda, Novartis, Eisai, and Celgene. DM received honoraria from Ono Pharmaceutical, Celgene, Takeda, Janssen, Eisai, Chugai Pharma, Kyowa Hakko Kirin, Zenyaku Kogyo, Bristol-Myers Squibb, Synmosa Biopharma Corporation, Nippon Shinyaku, and research funding from Merck, Amgen Astellas BioPharma, Astellas Pharma, Sanofi, Celgene, Novartis Pharma, Bristol-Myers Squibb, Janssen, Ono Pharmaceutical, Otsuka, Chugai Pharma, and Takeda. KT received honoraria from Zenyaku Kogyo, Eisai, Takeda, Mundipharma, HUYA Bioscience International, Kyowa Hakko Kirin, Celgene, Chugai Pharma, Ono Pharmaceutical, Yakult, Daiichi Sankyo, Bristol-Meyers Squibb, Meiji Seika Kaisha, Solacia Pharma, Verastem, and serving consulting or advisory role in Celgene, Zenyaku Kogyo, Huya Bioscience, Daiichi Sankyo, Takeda, Mundipharma, Ono Pharmaceutical, and received research funding from Chugai Pharma, Kyowa Hakko Kirin, Ono Pharmaceutical, Celgene, Janssen, Eisai, Mundi Pharma, Takeda, and Abbvie. The authors report no other conflicts of interest in this work.

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