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# A multi-center and non-interventional registry of brentuximab vedotin in patients with relapsed or refractory CD30-positive lymphoma: the CISL1803/BRAVO study

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## Background
Brentuximab vedotin (BV), a potent antibody-drug conjugate, targets the CD30 antigen. In Korea, BV has been approved for the treatment of relapsed or refractory Hodgkin lymphoma (HL), anaplastic large-cell lymphoma (ALCL), and cutaneous T-cell lymphomas, including mycosis fungoides (MF). However, there are limited data reflecting real-world experiences with BV treatment for HL, ALCL, and MF.

## Methods
This was a multicenter, non-interventional registry study of the efficacy and safety of BV in patients with relapsed or refractory CD30-positive lymphoma (CISL1803/BRAVO). Outcomes were determined based on the occurrence of relapse or progression and overall survival after BV treatment.

## Results
A total of 85 patients were enrolled in this study. The median number of BV cycles was 10 (range, 2–16) in the patients with HL. The objective response rate (ORR) of patients with HL to BV was 85.4% (41/48), comprising 27 complete responses (CRs) and 14 partial responses (PRs). The ORR of ALCL was 88% (22/25), consisting of 17 CRs and five PRs, whereas the ORR of MF was 92% (11/12). At the median follow-up of 44.6 months after BV treatment, the median post-BV progression-free survival of HL, ALCL, and MF patients was 23.6 months, 29.0 months, and 16.7 months, respectively ($P$=0.641). The most common side effect of BV was peripheral neuropathy; 22 patients (25.9%, 22/85) experienced peripheral neuropathy (all grades).

## Conclusion
The treatment outcomes of patients with relapsed or refractory CD30-positive lymphoma improved with BV treatment, and the safety profile was manageable.

**Key Words** Brentuximab vedotin, CD30, Lymphoma, Outcome

## INTRODUCTION

Brentuximab vedotin (BV) is an anti-CD30 monoclonal antibody-drug conjugate (ADC) containing the microtubule-disrupting agent monomethyl auristatin E (MMAE) [1]. After BV binds to CD30 on the cell surface, BV initiates its internalization into CD30-positive cells. Upon internalization into CD30-expressing tumor cells, MMAE exerts its potent cytostatic effect as it is linked via a protease-cleavable linker. Finally, BV induces apoptotic cell death by preventing cell cycle progression from the G2 to M phase through the disruption of the cytosolic microtubule network. CD30 expression is confined to activated lymphocytes and eosinophils, usually in lymphoid tissues, and not in peripheral blood cells, making it an attractive therapeutic target. CD30 is preferentially expressed in several lymphoid neoplasms such as classical Hodgkin's lymphoma (HL) and anaplastic large cell lymphoma (ALCL) [2]. Thus, BV has been approved for the treatment of relapsed or refractory HL and systemic ALCL based on high objective response rates of 75% and 86%, respectively [3, 4]. After approval, the efficacy of BV was demonstrated in mycosis fungoides (MF) and various cutaneous T-cell lymphomas [5-7]. Owing to its remarkable efficacy against CD30-positive lymphomas, BV has been used as a salvage therapy for relapsed or refractory HL, ALCL, and cutaneous T-cell lymphomas, including MF, in Korea. Since the introduction of BV as a salvage therapy for CD30-positive lymphomas, the number of patients receiving BV has grown. However, there are limited data regarding real-world experiences with patients receiving BV as salvage therapy for various CD30-positive lymphomas. Thus, our study group, the Consortium for Improving Survival of Lymphoma (CISL), conducted a nationwide registry.

## MATERIALS AND METHODS

### Patients and study design

This was a multicenter, non-interventional, registry study of BV in patients with relapsed or refractory CD30-positive lymphoma (CISL1803/BRAVO study). This study aimed to evaluate the efficacy and safety of BV in patients with relapsed or refractory HL, ALCL, or cutaneous T-cell lymphoma. Thus, the eligibility criteria were as follows: (1) patients who had CD30-positive lymphomas, including HL, ALCL, and MF; (2) patients receiving at least one dose of BV as salvage therapy after relapse or progression after previous treatments; and (3) written informed consent for registration in this study. After registration, data were collected for the analysis of the efficacy and safety of BV, including age, sex, ECOG performance status, disease type, and stage. The expression of CD30 was determined via immunohistochemistry using antibodies against CD30 (Dako, Copenhagen, Denmark). Immunohistochemical analyses were performed using a modified avidin-biotin peroxidase complex amplification and detection system. The outcomes were determined based on the occurrence of relapse, progression, and overall survival. The objective was to determine the overall disease control rate, defined as complete response (CR), partial response (PR), or stable disease (SD). Patients received 1.8 mg/kg BV intravenously every 3 weeks. Those who achieved SD or better continued to receive treatment for up to a maximum of 16 cycles, according to the current guidelines for reimbursement of the Korean National Health Insurance. However, in the event of progressive disease (PD) or unacceptable toxicity, BV administration was discontinued.

The response evaluation was completed by the investigator according to the 2007 Revised International Working Group Response Criteria for Malignant Lymphoma [8]. Baseline assessments were performed using computed tomography (CT) and fluorine-18 deoxyglucose (FDG) positron emission tomography/CT (PET/CT) of the neck, chest, abdomen, and pelvis before the first treatment cycle. Restaging assessments were performed using CT and PET/CT after the fourth, eighth, twelfth, and sixteenth cycles by CT scan. For presumed new lesions that were not observed on pretreatment or other post-treatment scans, PET/CT was performed to confirm disease progression. As this was a registry study, toxicity was assessed in clinical practice according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version. 4.0). Disease and survival status were assessed every three months according to the institutional standards of care and thereafter until study closure or withdrawal of consent for patients who received at least one dose of BV.

### Statistical methods

Patients' clinical characteristics, demographics, and treatment outcomes were analyzed, and Chi-square tests were used to evaluate their relationships with the outcomes. Post-BV overall survival (OS) was calculated from the first date of BV infusion to the final follow-up or death from any cause. Post-BV progression-free survival (PFS) was calculated from the first date of BV infusion to the date of disease progression or death from any cause. The median potential follow-up time with a 95% confidence interval (CI) was determined using the Kaplan-Meier method [9]. Survival was estimated based on Kaplan-Meier curves and compared using the log-rank test. Two-sided $P<0.05$ was considered statistically significant.

## RESULTS

### Patients

Researchers from 12 hospitals in the CISL participated in the study, and 85 patients were registered between 2018 and 2022. In total, 48 patients had HL, 25 patients had systemic ALCL; and 12, MF (Table 1). The median age of all patients at the time of BV treatment was 48 years (range, 18–84 yr). As patients with HL were younger than patients with ALCL and MF at diagnosis, the median age at BV administration was also significantly lower (34 yr) than that

**Table 1.** Characteristics of patients.

| | Total (N=85) | Hodgkin lymphoma (N=48) | Anaplastic large cell lymphoma (N=25) | Mycosis fungoides (N=12) |
|---|---|---|---|---|
| Median age at BV (range, yr) | 48 (18–84) | 34 (19–83) | 55 (18–84) | 62 (32–84) |
| Age at BV treatment | | | | |
| Age ≤60 years | 56 (66) | 37 (77) | 14 (56) | 5 (42) |
| Age >60 years | 29 (34) | 11 (23) | 11 (44) | 7 (58) |
| Sex | | | | |
| Male | 51 (60) | 34 (71) | 13 (52) | 4 (33) |
| Female | 34 (40) | 14 (29) | 12 (48) | 8 (67) |
| ECOG PS prior to BV | | | | |
| 0 | 61 (72) | 32 (67) | 19 (76) | 10 (83) |
| 1 | 15 (18) | 11 (23) | 2 (8) | 2 (17) |
| 2 | 9 (10) | 5 (10) | 4 (16) | 0 (0) |
| Stage at diagnosis | | | | |
| I/II | 8/33 (48) | 4/23 (56) | 3/4 (28) | 1/6 (58) |
| III/IV | 18/26 (52) | 6/15 (44) | 7/11 (72) | 5/0 (42) |
| Stage prior to BV | | | | |
| I/II | 4/35 (46) | 2/22 (50) | 1/7 (28) | 1/6 (58) |
| III/IV | 18/28 (54) | 9/15 (50) | 5/12 (72) | 4/1 (42) |
| Mediastinum | | | | |
| Not involved | 50 (59) | 15 (31) | 23 (92) | 12 (100) |
| Involved | 35 (41) | 33 (69) | 2 (8) | 0 (0) |
| IPS at diagnosis | | | | |
| Low (0–3 points) | | 35 (73) | | |
| High (4–7 points) | | 13 (27) | | |
| IPS prior to BV | | | | |
| Low (0–3 points) | | 37 (77) | | |
| High (4–7 points) | | 11 (23) | | |
| Refractory to 1st-line Tx | | | | |
| No | 46 (54) | 27 (56) | 14 (56) | 5 (42) |
| Yes | 39 (46) | 21 (44) | 11 (44) | 7 (58) |
| Previous RT before BV | | | | |
| Not done | 73 (86) | 38 (79) | 25 (100) | 10 (83) |
| Done | 12 (14) | 10 (81) | 0 (0) | 2 (17) |
| Previous ASCT before BV | | | | |
| Not done | 70 (82) | 36 (75) | 22 (88) | 12 (100) |
| Done | 15 (18) | 12 (25) | 3 (12) | 0 (0) |
| Previous Tx before BV | | | | |
| One line | 32 (38) | 8 (17) | 17 (68) | 7 (58) |
| Two lines | 33 (39) | 23 (48) | 7 (28) | 3 (25) |
| More than two lines | 20 (23) | 17 (35) | 1 (4) | 2 (17) |
| Time between Dx and BV | | | | |
| <12 months | 26 (30) | 10 (21) | 12 (48) | 4 (33) |
| 12–36 months | 32 (38) | 21 (44) | 6 (24) | 5 (42) |
| >36 months | 27 (32) | 17 (35) | 7 (28) | 3 (25) |

Abbreviations: ASCT, autologous stem cell transplantation; BV, brentuximab vedotin; Dx, diagnosis; ECOG, Eastern Cooperative Oncology Group; IPS, International Prognostic Score; PS, performance status.

of patients with ALCL (55 yr) or MF (62 yr) (Table 1).

After diagnosis, patients with HL were initially treated with combination chemotherapy consisting of Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD); 21 patients were refractory to ABVD (Table 1). Refractoriness to ABVD was defined as follows: (1) primary refractory to ABVD and (2) relapse within 6 months after the completion of ABVD. The median time between diagnosis and BV treatment was 21.9 months (range, 6–147 mo), and 31 patients with HL received BV within 3 years of the initial diagnosis (Table 1). When HL patients were initially diagnosed, 44% of the patients had stage III/IV disease, and 13 patients were at high risk according to the International Prognostic Score (IPS, Table 1). Of these 13 patients, 10 (77%, 10/13) were refractory to ABVD, whereas only 11 patients of the 35 low-risk IPS patients (31%) were refractory to ABVD.

Of the 25 patients with systemic ALCL, 23 had ALK-negative ALCL and only two had ALK-positive ALCL. Most

patients with ALCL received anthracycline-based chemotherapy, such as cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP), as first-line treatment, and 44% of the patients were refractory to first-line therapy (Table 1). At the time of BV administration, more than 70% of patients had stage III/IV disease, and around 32% (8/25) of patients received ≥2 lines of therapy prior to BV treatment. Accordingly, 48% of patients with ALCL received BV as salvage therapy within 1 year of diagnosis (Table 1). On the other hand, national health insurance reimbursement for MF was only recently approved, leading to a smaller sample size compared to other subtypes. Of the 12 patients with MF, seven were refractory to first-line therapy, and 9 patients received BV within 36 months after diagnosis (Table 1).

## Response to BV

The median number of BV cycles was 10 (range, 2–16) in patients with HL. The objective response rate (ORR) of patients with HL to BV was 85.4% (41/48), consisting of 27 CRs and 14 PRs; only three patients showed SD and four patients failed to respond to BV. The ORR of patients with ALCL to BV was 88% (22/25), consisting of 17 CRs and 5 PRs. Only two patients with SD and one with PD were found during BV treatment among patients with ALCL. The ORR of patients with MF was 92% (11/12); thus, the response to BV according to diagnosis was similar among patients with HL, ALCL, and MF (Fig. 1A), as was the number of BV treatment cycles (Fig. 1B). Additional consolidation treatments, including ASCT, were not performed in all responders to BV. When the response to BV was analyzed

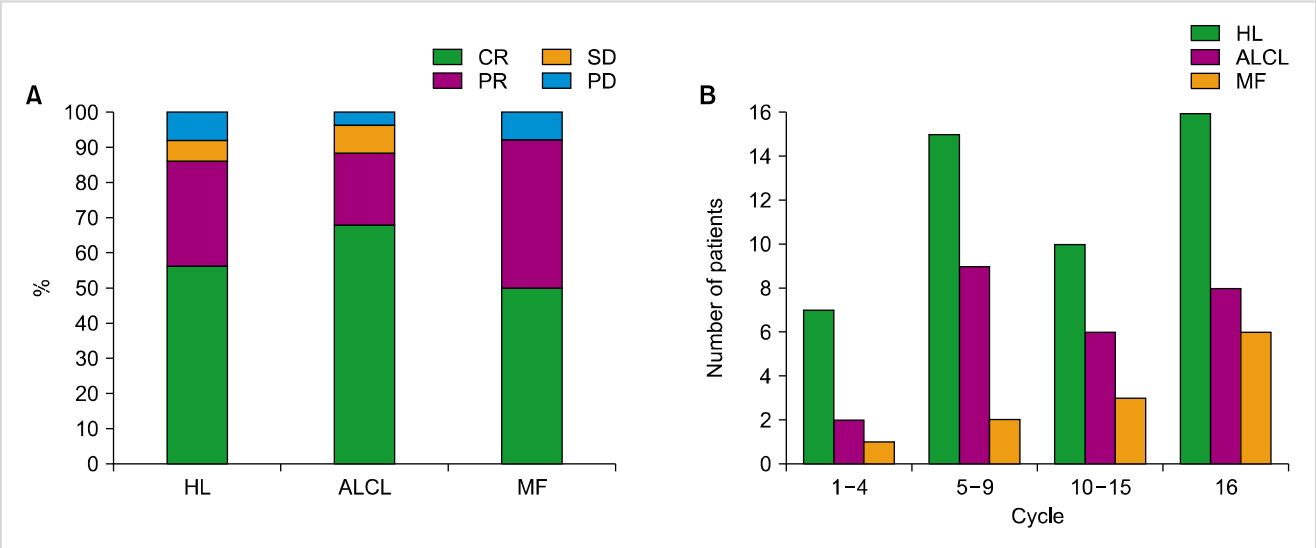


**Fig. 1.** Response to brentuximab vedotin and treatment duration. **(A)** Comparison of response to brentuximab vedotin based on diagnosis. **(B)** Comparison of number of treatment cycles based on diagnosis.

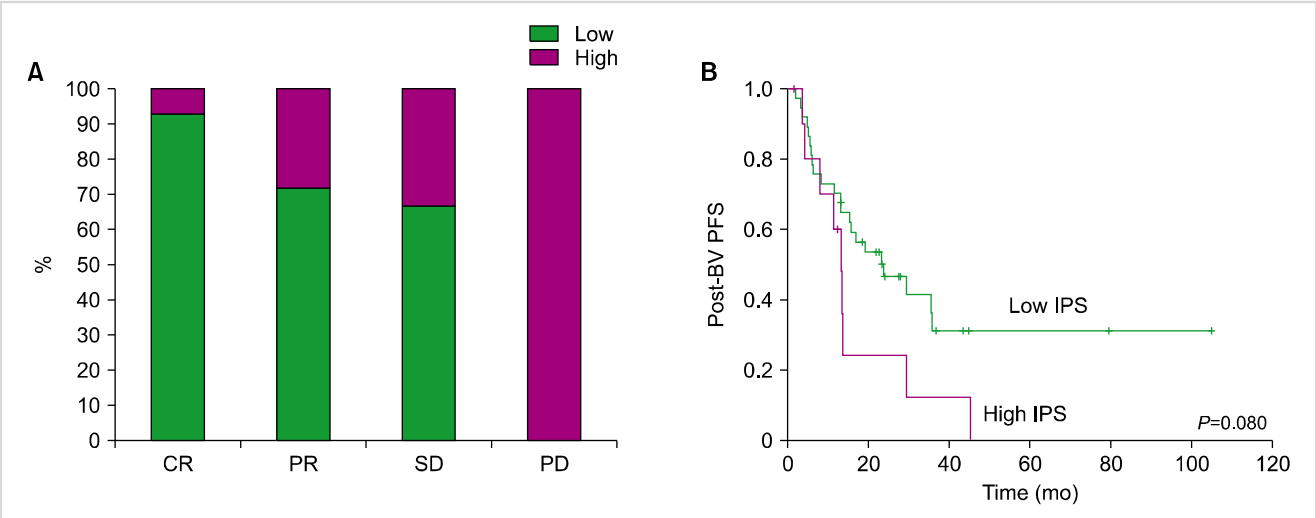


**Fig. 2.** Response and survival outcomes in Hodgkin lymphoma patients. **(A)** Comparison of response to brentuximab vedotin (BV) based on the risk of Internal Prognostic Score (IPS). **(B)** Comparison of post-BV progression-free survival based on risk of IPS.

according to IPS risk prior to the initiation of BV, the low-risk IPS group was significantly more likely to respond to BV than the high-risk IPS group (Fig. 2A). Thus, the post-BV PFS was significantly lower in the high-risk group than in the low-risk group (Fig. 2B).

## Survival outcomes after BV treatment

At the median follow-up of 44.6 months (95% CI, 40.5–48.7 mo) after the first day of the first cycle of BV treatment, 34 patients with HL had relapsed (71%, 34/48) with a median post-BV PFS of 23.6 months (95% CI, 17.3–29.8 mo; Fig. 3A). Among the patients with ALCL, 11 relapsed after BV treatment, representing a median post-BV PFS of 29.0 months (Fig. 3A). Eight patients with MF relapsed after BV treatment, with a median post-bevacizumab PFS of 16.7 months (Fig. 3A). Because all patients received BV in a state of relapsed or refractory disease, the occurrence of disease relapse or progression was observed after BV treatment, regardless of the histologic type. PFS showed a similar pattern across the three groups ($P$=0.641, Fig. 3A). More than 70% of the patients with HL experience relapse or progression during or after BV treatment; however, most patients are rescued by subsequent salvage treatment. Thus, only three HL patients had died at the time of analysis, and the post-BV OS showed a plateau in the survival curve (Fig. 3B). The relatively high number of relapses or progression in patients with HL after BV treatment may be related to the following factors: First, most patients received two or more lines of therapy before BV treatment. Second, only 25% of patients received ASCT before BV treatment. This may indicate that the patients failed to achieve a sufficient response to ASCT. This could imply that our patients with HL might have had a more aggressive disease, because our study represents a real-world situation. In contrast, eight of 11 relapsed patients with ALCL died; thus, the post-BV OS of patients with ALCL was significantly worse than that of HL patients (Fig. 3B). This poor outcome in our patients with ALCL might be related to the fact that most of the patients had ALK-negative ALCL. Four patients with relapsed MF died (Fig. 3B). Therefore, the OS was worse in patients with ALCL and MF than patients those with HL ($P$=0.001, Fig. 3B).

## Safety

The most common side effect of BV was peripheral neuropathy; 22 patients (25.9%, 22/85) experienced peripheral neuropathy of any grade (Table 2). However, most cases were manageable, except for two cases with grade 4 peripheral neuropathy, in which BV was discontinued owing to toxicity. Hematological toxicity, particularly neutropenia (N=13,

**Table 2.** Safety profile.

| | Patients (N=85) | | |
|---|---|---|---|
| | All grades | G3 | G4 |
| Anemia | 7 | 3 | 0 |
| Anorexia | 7 | 0 | 0 |
| Constipation | 8 | 3 | 0 |
| Diarrhea | 5 | 2 | 1 |
| Fatigue | 10 | 0 | 0 |
| Febrile neutropenia | 11 | 5 | 0 |
| Fever | 11 | 4 | 0 |
| Insomnia | 3 | 0 | 0 |
| Nausea | 10 | 0 | 0 |
| Neutropenia | 13 | 4 | 1 |
| Peripheral neuropathy | 22 | 5 | 2 |
| Pneumonia | 4 | 2 | 0 |
| Skin rash | 4 | 0 | 0 |
| Thrombocytopenia | 12 | 5 | 0 |
| Vomiting | 2 | 0 | 0 |

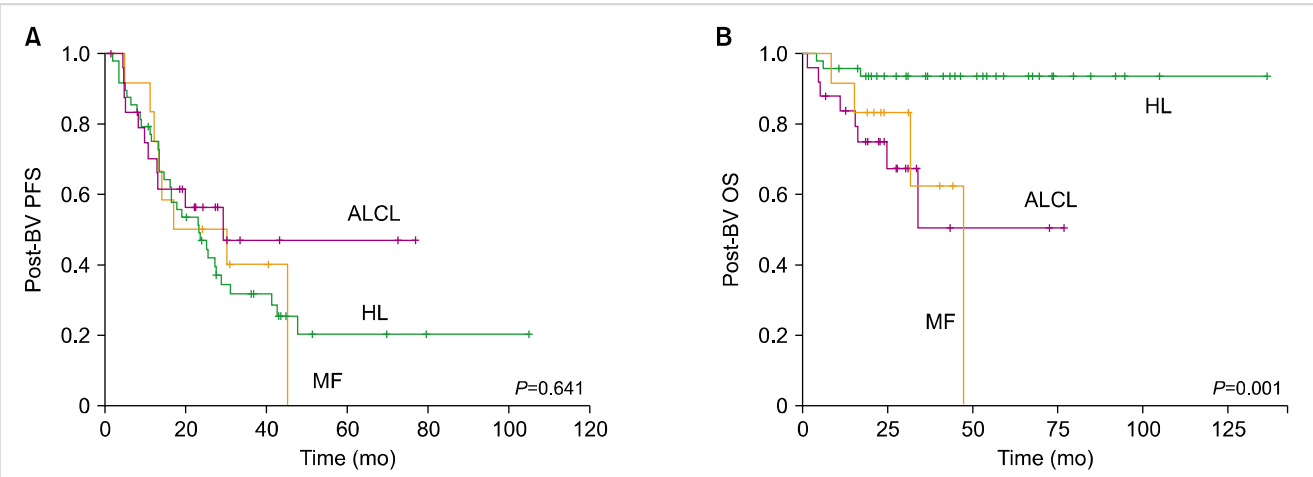


**Fig. 3.** Survival outcomes after brentuximab vedotin treatment. **(A)** Progression-free survival and **(B)** overall survival after brentuximab vedotin treatment.

15.3%) and thrombocytopenia (N=12, 14.1%), was also observed. Of the 13 patients with neutropenia, febrile neutropenia was documented in 11, but there was no treatment-related mortality. Non-hematological toxicities, such as nausea and vomiting, were manageable. Although grade 3 constipation and diarrhea were observed in three and two patients, respectively, they were manageable with supportive care.

## DISCUSSION

CD30, also known as Ki-1 or tumor necrosis factor receptor superfamily member 8 (TNFRSF8), was first found to be specific to Reed-Sternberg cells in patients with Hodgkin lymphoma [10]. The efficacy of BV has been demonstrated in patients with relapsed or refractory HL who failed autologous stem cell transplantation (ASCT) in a 5-year end-of-study, reporting an estimated OS rate of 41% (95% CI, 31–51) and a PFS rate of 22% (95% CI, 13–31) [11]. The AETHERA randomized, double-blind phase III trial also demonstrated the efficacy of BV as a consolidation therapy after ASCT in patients with relapsed or refractory HL because BV significantly prolonged PFS to 42.9 months relative to the PFS of only 24.1 months in the placebo group [12]. Based on its favorable outcomes in relapsed or refractory HL, the use of BV has expanded to include a first-line treatment. Thus, the randomized ECHELON-1 trial demonstrated a favorable outcome of the combination of BV with a doxorubicin, vinblastine, and dacarbazine (AVD) regimen compared to that of ABVD in newly diagnosed stage III or IV HL patients [13]. Likewise, a 5-year update of the ECHELON-2 trial comparing BV plus cyclophosphamide, doxorubicin, and prednisolone (CHP) with CHOP as a frontline treatment for patients with peripheral T-cell lymphoma, including systemic ALCL, showed that BV plus CHP provided clinically meaningful improvements in PFS and OS compared to CHOP, with a manageable safety profile [14].

Accordingly, the introduction of BV led to several successful changes in treatment paradigms. First, the development of BV established CD30 as a new druggable target in patients with lymphomas, although the frequency of CD30 expression is lower than that of other CD antigens in lymphomas, such as CD19 and 20. Indeed, since the therapeutic role of BV was established, efforts have been made to detect CD30 in other lymphomas, and BV has been tested in various CD30-positive lymphomas, including diffuse large B-cell lymphoma, mediastinal large B-cell lymphoma, and NK/T-cell lymphomas [15, 16]. Second, BV was the first ADC used in patients with lymphoma in clinical practice. This has led to increased research interest in the development of ADCs targeting various antigens with novel drug conjugates for patients with lymphomas [17].

Our study analyzed the efficacy and safety of BV in patients with various CD30-positive lymphomas in a real-world setting. Compared to clinical trials, in clinical practice, the health condition and laboratory findings, such as bone marrow function, might deteriorate more in patients receiving BV. Thus, our results reflect the real-world experience of patients receiving BV as a salvage therapy for relapsed or refractory diseases. In our study, most patients responded to BV treatment; however, relapse after BV treatment was frequently observed. In particular, our study showed that patients belonged to the high-risk IPS group prior to BV treatment showed a greater number of relapses after BV treatment (Fig. 2). Thus, the risk of IPS might also influence the outcome of BV because patients with a high risk of IPS might exhibit a disease with more aggressive biological characteristics. Indeed, our study included a higher proportion of patients with refractory HL because 21 patients were refractory to ABVD. Considering the favorable outcomes of patients with HL, our study population might be more aggressive and might be influenced by selection bias. Furthermore, out of 48 patients with HL in our study, 13 patients were initially belonged to the high risk of IPS at diagnosis (Table 1). These results imply that patients at a high risk of IPS might be more likely to experience failure after standard ABVD treatment, and they might also be at risk of treatment failure when they are treated with BV at the time of relapse or progression. Thus, patients with HL with high-risk IPS should receive more aggressive treatments than those with ABVD.

Patients with ALCL and MF also experience relapses after BV treatment. This suggests the occurrence of a resistant clone during BV treatment; however, the mechanism of BV resistance and how to overcome it remain unresolved. A recent in vitro study suggested that CD30 downregulation, MMAE resistance, and MDR1 overexpression are the potential mechanisms [18]. In this study, the most common adverse events that occurred in ≥20% of the patients included neutropenia and peripheral sensory neuropathy, which is consistent with previous studies [19, 20]. Although two patients had grade 4 peripheral neuropathy where BV was discontinued due to toxicity, other non-hematologic side effects were manageable despite the enrollment of heavily pretreated patients with relapsed or refractory lymphomas (Table 2). Although this cannot be fully explained, the relatively small proportion of elderly and frail patients might have influenced the lower frequency of toxicity profiles. Furthermore, the assessment of toxicity might not be less strict than that of clinical trials, because this study analyzed the data of patients who were monitored in clinical practice. This may also have led to an underestimation of non-hematological side effects, particularly peripheral neuropathy.

In conclusion, although this study analyzed heavily pre-treated patients with relapsed or refractory HL, ALCL, and MF, our results could show novel findings reflecting the real-world situation because there are few data about real-world experiences with patients receiving BV as a salvage therapy for various CD30-positive lymphomas. The treatment outcomes in the present study were comparable with those of previous clinical trials across the subtypes. Safety profiles were manageable across disease subtypes, and peripheral neuropathy was the most common adverse event,

which is consistent with the results of previous clinical trials.

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## Authors' Disclosures of Potential Conflicts of Interest

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

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