Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression

Running Title: Brentuximab Vedotin in DLBCL

Scientific section: Clinical trials and observations

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Key Points

- Brentuximab vedotin was active in DLBCL (44% ORR) across a range of CD30 expression and responses occurred in 44% of refractory patients.

Keywords:

- Lymphoma, Large B-Cell, Diffuse
- Antigens, CD30
- Antibody-Drug Conjugate
- Antibodies, Monoclonal
- Lymphoma, Non-Hodgkin
- Monomethyl auristatin E
- Drug Therapy
- Immunotherapy
- Hematologic Diseases
- Lymphoma, B-Cell
Abstract
Several non-Hodgkin lymphoma (NHL) subtypes, including diffuse large B-cell lymphoma (DLBCL), varyably express CD30. This phase 2, open-label study evaluated efficacy of brentuximab vedotin, an anti-CD30 antibody-drug conjugate, in relapsed/refractory CD30-positive NHL. This planned subset analysis of B-cell NHLs includes 49 DLBCL patients and 19 with other B-cell NHLs. Objective response rate (ORR) was 44% for DLBCL, including 8 (17%) complete remissions (CR) with a median duration of 16.6 months thus far (range, 2.7 – 22.7+). There was no statistical correlation between response and level of CD30 expression; however, all responding patients had quantifiable CD30 by computer-assisted assessment of immunohistochemistry. DLBCL patients were generally refractory to frontline (76%) and most recent therapies (82%), and 44% of these refractory patients responded (15% CR). Patients with other B-cell lymphomas also responded: 1 CR, 2 PRs of 6 with gray zone, 1 CR of 6 with primary mediastinal B-cell, and 1 CR of 3 with post-transplant lymphoproliferative disorder. Adverse events were consistent with known toxicities. Combining brentuximab vedotin with rituximab was generally well tolerated with similar activity. Overall, significant activity with brentuximab vedotin was observed in refractory DLBCL and responses occurred across a range of CD30 expression. This study was registered at www.clinicaltrials.gov, NCT01421667.
Introduction
Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL). Frontline treatment with R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone) results in long-term disease-free survival in 33 to 96% of patients depending on several prognostic variables; however, about 30% of patients with DLBCL eventually succumb to the disease. A fraction of DLBCL patients (~25%) who recur after or are refractory to frontline therapy are eligible for and will be cured by salvage chemotherapy followed by autologous stem cell transplantation (SCT). There is no standard therapy for patients who fail to respond to salvage regimens or who are ineligible for transplant. Response rates are poor in this setting and novel approaches are needed. Similarly, effective salvage therapies are lacking for DLBCL subsets, such as the mediastinal variant of DLBCL, and other aggressive NHLs, such as gray zone lymphomas (B-cell lymphoma unclassifiable with features intermediate between DLBCL and classical Hodgkin lymphoma [HL]) and post-transplant lymphoproliferative disorders (PTLD).

CD30 is expressed on a variety of malignancies and is present in 14% to 25% of DLBCL cases depending on the cut-off utilized to assign positivity. Hu et al. reported a unique gene expression profile for de novo DLBCL expressing CD30 in greater than 20% of cells. Although this study suggested that CD30 expression imparts a more favorable prognosis with frontline R-CHOP therapy, other studies have not universally confirmed this finding and the prognostic implications of CD30 expression at relapse are unclear.
Brentuximab vedotin (ADCETRIS®) is a CD30-directed antibody-drug conjugate (ADC). After binding to CD30 on the tumor cell surface, preclinical data suggest that the ADC internalizes leading to release of monomethyl auristatin E (MMAE) via proteolytic cleavage and induction of cell-cycle arrest and apoptosis. This trial was initiated to evaluate the efficacy and safety of single-agent brentuximab vedotin in relapsed/refractory mature T-cell and B-cell lymphomas with variable CD30 expression (NCT01421667). Results from the T-cell cohort have been previously published. The protocol was amended to include an additional group of DLBCL patients to be treated with brentuximab vedotin and rituximab with the intent of assessing the safety of this combination.

**Patients and methods**

This is a phase 2, open-label, multicenter study designed to evaluate the efficacy and safety of brentuximab vedotin in relapsed/refractory NHL, including both World Health Organization (WHO) classifications of mature T-/NK-cell and B-cell neoplasms. Presented are the results for the planned subset analysis of patients with CD30-positive B-cell lymphomas, including DLBCL and other B-cell lymphomas.

This study was conducted in compliance with the Declaration of Helsinki, the International Conference on Harmonization Good Clinical Practices, and the applicable United States Food and Drug Administration (FDA) regulations. Approval from the Institutional Review Board was received for each site, and all patients gave written informed consent prior to study participation.
Eligibility
Patients could have any subtype of histologically-confirmed B-cell lymphoma with detectable CD30 expression by visual assessment of immunohistochemistry (IHC) on a biopsy of the most recent relapsed/refractory disease per institutional laboratory. All eligible patients had bidimensionally measurable disease of $\geq 1.5$ cm in greatest transverse diameter and no history of another active invasive malignancy within the previous 3 years. Patients had to be $\geq 12$ years of age and have an Eastern Cooperative Oncology Group (ECOG) performance status of $\leq 2$. Previous allogeneic SCT was allowed if $>100$ days had elapsed since SCT and there was no active graft-versus-host disease (GvHD) at the time of screening. Patients were required to have adequate baseline laboratory values for eligibility as previously reported. Exclusion criteria included prior treatment with brentuximab vedotin, evidence of cerebral/meningeal disease, or prior progressive multifocal leukoencephalopathy. Patients with pre-existing peripheral neuropathy were eligible.

Study Design
The study was designed to enroll approximately 65 patients with CD30-positive relapsed/refractory B-cell lymphomas, including approximately 50 DLBCL patients. Patients received 1.8 mg/kg brentuximab vedotin IV every 3 weeks. Those who achieved stable disease (SD) or better could receive continued treatment until disease progression, unacceptable toxicity, or study closure. The primary objective was objective response rate (ORR) as determined by the investigator per the Revised Response Criteria for Malignant Lymphoma. Secondary endpoints included safety, correlation of CD30 expression with response, duration of objective response, and progression-free survival (PFS).
Dose reduction to 1.2 mg/kg and treatment delay of up to 3 weeks was allowed depending on the type and severity of toxicity, including peripheral neuropathy. Support with platelet and/or red blood cell transfusion or granulocyte colony-stimulating factors was allowed. Low dose prednisone (≤20 mg/day or other steroid equivalent) was permitted prior to study entry for GvHD and other indications unrelated to treatment of lymphoma. Immunosuppressive therapy (any dose level) was permitted for the prevention of transplant rejection or management of GvHD.

A separate cohort of patients (planned n=15) received brentuximab vedotin 1.8 mg/kg IV in combination with rituximab (375 mg/m²) on Day 1 of each 3-week cycle. The primary objective was to assess the safety of brentuximab vedotin when given in combination with rituximab. Patients who completed 8 cycles of combination therapy or those who had unacceptable toxicity to rituximab prior to completion of 8 cycles could receive brentuximab vedotin, 1.8 mg/kg, as a single agent on Day 1 of each cycle until disease progression or unacceptable toxicity.

For patients who received at least one dose of brentuximab vedotin, disease status and survival were followed every 3 months for the first 2 years and per institutional standard of care thereafter until study closure or withdrawal of consent. For patients who discontinued study drug for any reason other than disease progression or initiation of a non-protocol therapy, radiographic assessments were done every 6 months for the first year and per institutional standard of care thereafter.

**Study Assessments**
Response assessments were performed using computed tomography (CT) and positron emission tomography (PET) scans of the neck, chest, abdomen, and pelvis at baseline,
following Cycles 2, 4, and every 3 cycles thereafter while on study treatment, at end-of-treatment (EOT), and during follow-up as described above. Restaging assessments were performed using only CT scans of diagnostic quality if disease was not fluorodeoxyglucose (FDG)-avid at baseline. Clinical response per the Revised International Working Group Response Criteria for Malignant Lymphoma 2007 was determined by the investigator. PD included both disease progression by radiographic assessment and clinical disease progression as determined by the investigator. Safety and tolerability were assessed from first dose until approximately 30–37 days after the last dose of study drug. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.3 was used for grading adverse events (AEs). Other study assessments included pharmacokinetic (PK) analyses.

**CD30 Expression and Soluble CD30**
For eligibility, CD30 positivity on lymphoma cells was determined by the institutional laboratory by visual assessment of routine IHC staining using the anti-CD30 BerH2 antibody. Tissue samples were also sent to the central pathology laboratory (Quest Diagnostics) for an independent quantification of CD30 expression by IHC. Central laboratory definition of CD30 positivity was ≥1% expression on neoplastic cells.

For exploratory purposes, further analyses of the same samples was performed to quantify CD30 expression by computer-assisted methods using pixel-based image processing techniques to detect CD30 expression on all cells (Flagship Biosciences). Soluble CD30 (sCD30) concentrations were measured in a commercial bead-based sandwich fluoroimmunoassay modified to eliminate interference by brentuximab vedotin;
assays were performed on a Bio-Plex® 200 system (Bio-Rad Laboratories, Inc.) with appropriate calibrators and controls.

**Statistical Analysis**
Pathology was classified as DLBCL or other B-cell lymphomas according to WHO 2008 criteria. Patient disposition, demographics, disease characteristics, safety, disease response, and exposure to study drug were analyzed by disease diagnosis, including DLBCL and other B-cell lymphomas. Primary mediastinal B-cell lymphoma (PMBL) was included in other B-cell lymphomas since the natural history and treatment of PMBL can differ from other DLBCL.\(^{23,24}\)

ORR was defined as the proportion of patients with CR or PR as best clinical response according to the Revised Response Criteria for Malignant Lymphoma.\(^{22}\) For the primary objective for the DLBCL subgroup, observation of 10 or more objective responses (≥20% ORR) in efficacy-evaluable patients allowed rejection of the null hypothesis and a claim that the true ORR is greater than 10% (with a one-sided significance level of 0.05). The efficacy-evaluable analysis set included all patients who received any amount of brentuximab vedotin or combination therapy and who had both a baseline and at least one post-baseline disease assessment (radiographic response assessment or clinical disease progression) up to the closure of the study or prior to the start of new anti-cancer treatment. No formal hypothesis was specified for the other B-cell lymphoma subgroup.

The medians and two-sided 95% confidence-intervals (CIs) for duration of response, duration of CR, and PFS were estimated using Kaplan-Meier methodology. Duration of response for this study was defined as the time from start of the first documentation of objective response (CR or PR) to the first documentation of tumor progression or to death.
due to any cause. PFS was defined as the time from start of study treatment to first documentation of tumor progression or death due to any cause. Patients who initiated a non-protocol antitumor treatment prior to documented PD or death (excluding stem cell transplant) were censored at the date of the last disease assessment prior to start of new therapy. The correlation of CD30 expression with response was assessed using a generalized linear model. The pharmacokinetic (PK) parameters of brentuximab vedotin, MMAE, and total antibody were estimated and summarized with descriptive statistics.

No formal hypotheses were specified for combination therapy. The intent of this cohort was to describe the type, incidence, severity, seriousness, and relatedness of adverse events and laboratory abnormalities in patients treated with brentuximab vedotin in combination with rituximab.

Results

Patients
Sixty-eight patients with B-cell lymphomas (49 DLBCL and 19 other B-cell lymphomas) were treated between August 2011 and August 2013 at 26 sites in the United States. Patient demographics, baseline disease characteristics, and prior cancer-related therapies are presented in Table 1. Most patients had Stage III or IV disease and 12 DLBCL patients (24%) had transformed disease from a prior indolent NHL. More than half of all patients had received 3 or more prior systemic therapies (range, 1–19) and nearly all had received prior rituximab. Most patients had refractory disease defined by less than CR or relapse from CR within 3 months of completion of frontline therapy or lack of an objective response with most recent therapy in patients who had received >1 prior therapy. Thirteen of the 68 patients (19%) had a prior SCT. Patients who had not
undergone prior SCT were considered by the treating investigator to be ineligible for SST based upon age, co-morbidities, and/or lack of response.

Efficacy
Of the 48 efficacy-evaluable DLBCL patients, the ORR was 44% (Table 2). Eight patients (17%) achieved a CR and 13 (27%) a PR. One patient was excluded because the patient received a non-protocol anticancer treatment prior to EOT restaging. The ORR was 44% in patients with refractory disease (15% CR), and 38% in patients with relapsed disease (25% CR) (Table 2). The ORR was 50% for the 12 DLBCL patients with transformed disease (3 CRs, 3 PRs).

At the time of this analysis, the median follow-up time from first dose was 4.6 months (range, 0.6 – 29.5) and the median PFS for the DLBCL patients was 4 months (range, 0.6+ – 24+). The median duration of objective response was 5.6 months (range, 0+ – 22.7+) in all responders and 16.6 months (range, 2.7 – 22.7+ months) in patients with a CR (Figure 1). Median duration of PR was 3.9 months (range, 0+ – 8.7 months). Two patients who achieved an objective response discontinued treatment to proceed to transplant. One achieved a PR and underwent autologous SCT after 2 cycles of treatment and the other patient achieved a PR and underwent allogeneic SCT after 7 cycles of treatment.

Five of the 19 efficacy-evaluable patients with other B-cell lymphomas (26%) had either CR or PR: 3 of 6 patients with gray zone lymphoma (1 CR, 2 PR), 1 of 6 patients with PMBL (1 CR), and 1 of 3 patients with PTLD (1 CR) (see Supplemental Table 1 found at the Supplemental Data link at the top of the online article on the Blood website). One
PTLD patient’s response was determined to be not evaluable because the patient had no measureable baseline lesions.

**Soluble CD30 and CD30 Expression in Responding DLBCL Patients**
A summary of baseline CD30 expression by visual central review and by computer-assisted methods as well as a summary of baseline sCD30 is presented in Table 3. Five CD30-positive DLBCL patients per the enrolling institution were reclassified as having undetectable CD30 expression by central laboratory review and were included in analyses as having 0% CD30 expression. Five patients with DLBCL and 1 patient with PTLD had inadequate tissue for central review; these patients were excluded from analyses where quantitative CD30 expression level was required.

No statistical correlation was observed between response and CD30 expression as assessed by visual central review (Figure 3A) or by computer-assisted central review of IHC (Figure 3B), nor was there a correlation between CR and CD30 expression. There was also no statistical correlation between sCD30 and response or CR. However, all responding patients had elevated sCD30 at baseline and all had quantifiable CD30 expression per computer-assisted assessment of IHC. As expected, the majority of patients had a higher CD30 expression level by computer-assisted analysis because this method detects low intensity staining and analyzes all cells within the tumor whereas the central pathologist manually scores CD30 visual presence only on neoplastic cells. One DLBCL patient who achieved a CR was determined to have 0% CD30 expression by central visual review, but had detectable CD30 expression (1.4%) by subsequent computer-assisted evaluation (Figure 2A). Another DLBCL patient who achieved a CR had 1% CD30 expression detected by visual central review, but had 34% CD30 by
computer-assisted methods (Figure 2B). Best clinical response, % CD30 expression by
visual assessment of neoplastic cells, % CD30 expression by computer-assisted methods
on all cells within tumor, and baseline sCD30 levels are shown for each of the responding
DLBCL patients in Supplemental Table 2.

Safety
All patients with B-cell lymphomas who received at least one dose of brentuximab
vedotin were included in the safety analysis. Patients received a median of 4 cycles of
treatment (range, 1–19 cycles). Neutropenia and peripheral sensory neuropathy were the
primary AEs leading to dose modifications. Forty percent of patients had dose delays and
13% had dose reductions. Disease progression was the most common reason for
treatment discontinuation (71%). Six (12%) DLBCL patients discontinued treatment due
to AEs, including peripheral sensory neuropathy (PSN, n=3), peripheral motor
neuropathy, hypoxia, and elevated alanine aminotransferase (n=1 each). Five of these 6
patients were in CR and 1 had SD at the time treatment was discontinued. Three of the
15 patients with pre-existing PSN (20%) either experienced a worsening of the event on
treatment or were dose reduced due to PSN. Two of the 6 patients in the combination
cohort with pre-existing PSN (33%) experienced a worsening of the event on treatment.
These patients did not require dose reduction.

Overall, the safety data in the present trial is comparable to the safety data reported in the
pivotal phase 2 study of single-agent brentuximab vedotin treatment in systemic ALCL.25
Treatment-emergent AEs (TEAEs) occurring in ≥25% of patients are shown in Table 4.
Serious adverse events (SAEs) of pyrexia and pneumonia were the most frequently
occurring SAEs observed (10% and 9%, respectively). All 5 deaths within 30 days of the last study treatment were disease related.

**Combination with Rituximab**

To explore the safety of combining brentuximab vedotin and rituximab, this study was amended in January 2013 to add approximately 15 patients with histologically-confirmed DLBCL. Sixteen DLBCL patients were enrolled in this cohort as one patient withdrew consent after only one dose of treatment and was replaced with an additional patient to ensure sufficient collection of safety data. Baseline disease characteristics in this cohort were similar to those of the monotherapy DLBCL patients (Table 1). Disposition and exposure are presented in Supplemental Table 3. TEAEs occurring in ≥25% of patients were similar to those reported in the monotherapy cohort (Table 5). Neutropenia incidence appeared to be lower in patients treated with the combination potentially due to the better ECOG performance status (Table 1), as well as a shorter duration of drug exposure (13% received >5 cycles versus 43% on monotherapy). SAEs were consistent with what would be expected for the study agents and patient population (Supplemental Table 4). For the efficacy-evaluable patients (n=13), the ORR was 46% (2 CR, 4 PR) with a median follow-up of 2.8 months thus far (Supplemental Table 5).

**Pharmacokinetics**

Pharmacokinetic (PK) parameters for monotherapy were determined using concentrations of serum brentuximab vedotin ADC and plasma MMAE, and actual sampling times relative to the start of infusion. The estimated AUC, Cmax, and Tmax of brentuximab vedotin and MMAE were consistent with those from historic data for brentuximab.
vedotin. Based on current analyses, there did not appear to be a significant correlation between response and exposure of ADC or MMAE.

**Discussion**

The cell surface antigen CD30 is a well-established target for the targeted delivery of MMAE to lymphoma cells via the ADC brentuximab vedotin as evidenced by an ORR of 86% (CR 59%) in patients with relapsed systemic ALCL and 75% (CR 34%) in patients with relapsed HL in pivotal studies. Both diseases are characterized by high CD30 expression. CD30 is also frequently expressed on other T- and B-cell malignancies making brentuximab vedotin a potential therapeutic option in these diseases. In this phase 2 study of brentuximab vedotin, reduction in tumor volume was observed in the majority of patients enrolled with B-cell NHLs that had CD30 expression as determined by standard IHC per local laboratory (Figure 4). In addition, 44% of all patients with DLBCL (n=27/61) regardless of treatment regimen (monotherapy or combination therapy) achieved an objective response (Supplemental Table 4).

The ORR of single-agent brentuximab in DLBCL was 44% (n=21/48), including 8 (17%) CRs. Complete remissions were durable with a median duration of 16.6 months. At a median follow-up time of 4.6 months, the median PFS in DLBCL patients is 4 months. Most DLBCL patients had refractory disease and the ORR was no different in refractory DLBCL patients than in relapsed DLBCL patients. There was no correlation of disease or demographic characteristics with response to treatment.

Objective responses were observed in patients across a wide range of CD30 expression by central IHC. One unanticipated finding was that neither the degree of surface expression of CD30 nor sCD30 levels correlated with the likelihood of response.
However, all responding DLBCL patients had elevated sCD30 at baseline and also proved to have a quantifiable level of CD30 expression by computer-assisted methods, even if the visual assessment of IHC on central review did not suggest CD30 expression. The lack of correlation between the level of surface or soluble CD30 and response may have a number of potential explanations. CD30 expression within the tumor could be heterogeneous and not fully represented by random samples selected for IHC. Another possibility is that some minimal threshold of CD30 is required for response; this was not apparent in the pivotal studies in relapsed HL and ALCL, diseases with uniformly high CD30 expression, where brentuximab vedotin can be an effective therapy.26,27 This would explain responses in patients with no CD30 expression by visual assessment of IHC but with low level expression detected by optical methods. A bystander effect is also plausible, with uptake in the tumor microenvironment and subsequent release of MMAE to the tumor cells. To further understand the activity of brentuximab vedotin in patients with low levels of CD30 expression, this study was amended in July 2013 to evaluate the efficacy of monotherapy in DLBCL patients with undetectable CD30 expression by visual assessment of IHC. Results from this cohort are forthcoming.

Brentuximab vedotin was also active in other B-cell lymphomas. Three of the 6 patients with gray zone lymphoma achieved an objective response and 1 patient with PTLD achieved a CR. One unexpected finding was the relatively low response rate in PMBL (1 CR out of 6 patients, 17% ORR), which is typically characterized by high CD30 expression. However, given the small numbers of each of these B-cell NHL subtypes, it is difficult to establish meaningful conclusions on the activity of brentuximab vedotin in these.
The results of brentuximab vedotin monotherapy in CD30-positive DLBCL are comparable to other agents studied in relapsed/refractory DLBCL. Lenalidomide alone or in combination with rituximab has ORRs of 33% to 40% with a median duration of response of 8 to 10 months. The ORR differs by cell of origin and is 53% in the activated B-cell subtype (ABC) versus 9% in the germinal center B-cell (GCB) subtype. Similarly, ibrutinib had a single-agent ORR of 40% and PFS of 5.5 months in the ABC subtype, but an ORR of only 5% in the GCB subtype. The combination of bendamustine and rituximab resulted in an ORR of 45.8% (CR 15%; PR 31%) in DLBCL. One limitation of that study, similar to ours, is that responses were not analyzed by cell of origin. Assessing responses to brentuximab vedotin by cell of origin of DLBCL would be an interesting exploratory analysis, though CD30 expression does not clearly correspond to the GCB or the ABC subtype of DLBCL. Other limitations of the present study are the lack of a comparator arm, absence of central review of response, and lack of analysis of response by other potentially important prognostic markers, such as Bcl-2 or c-Myc. We also cannot exclude the possibility that relapsed CD30-positive DLBCL has a better prognosis than relapsed CD30-negative DLBCL since there are no studies examining CD30 as a prognostic factor at relapse.

Brentuximab vedotin as a single agent and in combination with rituximab was generally well tolerated in these heavily pretreated patients with advanced disease. Adverse events were generally consistent with the known toxicity profile of brentuximab vedotin based upon prior studies.

In summary, brentuximab vedotin demonstrated noteworthy activity in relapsed/refractory DLBCL patients, and complete remissions were durable. Antitumor
activity was not associated with CD30 expression levels by IHC or baseline sCD30. The activity of brentuximab vedotin in this study warrants further investigation. Additional combination studies are being considered for the treatment of relapsed/refractory DLBCL and for frontline treatment of DLBCL.

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Authorship Contributions
Contribution: EDJ and NLB contributed to the analysis and interpretation of data and wrote the manuscript. JPS, YO, RHA, JNW, CMB, and GS contributed to the acquisition of the data and critically reviewed the manuscript. MCP, DAK, PL, and JY contributed to the analysis and interpretation of the data and critically reviewed the manuscript. All authors contributed to the concept and design of the study. The final manuscript was approved by all authors.

Conflict-of-interest disclosure: Seattle Genetics, Inc. provided research funding to the institutions of EDJ, JPS, YO, RHA, JNW, CMB, GS and NLB. NLB and GS have acted as consultants for Seattle Genetics, Inc. CMB has participated in a Seattle Genetics, Inc. speakers’ bureau. Seattle Genetics Inc. has provided JPS, RHA, and NLB with funds for travel expenses. MCP, DAK, PL and JY are employees of and have equity ownership in Seattle Genetics, Inc.

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References


## Tables

### Table 1. Demographics and Baseline Disease Characteristics

<table>
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<tr>
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<th>Single-Agent Brentuximab Vedotin</th>
<th>Brentuximab Vedotin + Rituximab</th>
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<td>DLBCL (N=49)</td>
<td>Other B-Cell (N=19)</td>
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<tr>
<td>Median age in years (min, max)</td>
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<td>Male, n (%)</td>
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<td>Baseline ECOG performance status, n (%)</td>
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<td>IPI Score, n (%)</td>
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<td>Plasmablastic lymphoma</td>
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<td>Transformed disease, n (%)</td>
<td>12 (24)</td>
<td>1 (5)</td>
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<td>Bulky disease, ≥5 cm on at least one baseline index lesion, n (%)</td>
<td>19 (39)</td>
<td>8 (42)</td>
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<td>Median time from diagnosis to first dose, months (min, max)</td>
<td>14.0 (0.8, 124.4)</td>
<td>13.2 (1.7, 191.2)</td>
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<td>Median % CD30+ malignant cells (min, max)</td>
<td>25 (0, 100)</td>
<td>47.5 (4, 100)</td>
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<td>Median soluble CD30, ng/mL, (min, max)</td>
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<td></td>
<td>(35.6, 9428.6)</td>
<td>(33.2, 21277.7)</td>
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<td>Stage at initial diagnosis, n (%)</td>
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<td>Stage III-IV</td>
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<td>Refractory to most recent prior therapy, n (%)</td>
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<td>14 (74)</td>
</tr>
<tr>
<td>Refractory to frontline therapy, n (%)</td>
<td>37 (76)</td>
<td>17 (89)</td>
</tr>
<tr>
<td>Median number of prior cancer-related systemic therapy</td>
<td>3 (1, 6)</td>
<td>3 (1, 19)</td>
</tr>
</tbody>
</table>
Patients with prior rituximab exposure, n (%)  
47 (96)  
18 (95)  
15 (94)  

Patients with prior anthracycline-containing regimen, n (%)  
45 (92)  
17 (89)  
14 (88)  

Patients with prior platinum-based systemic therapy, n (%)  
34 (65)  
12 (63)  
10 (63)  

Patients with prior cancer-related radiotherapy, n (%)  
14 (29)  
6 (32)  
5 (31)  

Patients with prior stem cell transplant, n (%)  
10 (20)  
3 (16)\(^d\)  
4 (25)  

   10 (20)  
   2 (11)  
   4 (25)  

   0  
   2 (11)  
   0  

\(^a\) Per visual central review; single-agent DLBCL n=44, other B-cell n=18; combination n=12  
\(^b\) Single-agent DLBCL n=46, other B-cell n=18; combination n=12  
\(^c\) Four patients had unknown disease stage at study entry; 2 each single-agent DLBCL and other B-cell  
\(^d\) One patient had both a prior autologous and allogeneic SCT  

**Table 2. Best Clinical Response**  

<table>
<thead>
<tr>
<th></th>
<th>Single-Agent Brentuximab Vedotin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refractory (N=39)</td>
</tr>
</tbody>
</table>
| **Objective response rate, n (%)**  
|                          | 17 (44) | 3 (38) | 21 (44) | 5 (26) |  
| 95% CI\(^c\)  
|                          | 27.8, 60.4 | 8.5, 75.5 | 29.5, 58.8 | 9.1, 51.2 |  
| **Best clinical response, n (%)\(^d\)**  
| Complete remission (CR)  
|                          | 6 (15) | 2 (25) | 8 (17) | 3 (16) |  
| Partial remission (PR)  
|                          | 11 (28) | 1 (13) | 13 (27\(^a\)) | 2 (11) |  
| Stable disease (SD)  
|                          | 8 (21) | 3 (38) | 11 (23) | 7 (37) |  
| Progressive disease (PD)  
|                          | 14 (36) | 2 (25) | 16 (33) | 6 (32) |  
| Disease control rate\(^e\), n (%)  
|                          | 25 (64) | 6 (75) | 32 (67) | 12 (63) |  

\(^a\) One patient missing disease status, but efficacy evaluable  
\(^b\) One response was determined to be not evaluable because the patient had no measureable baseline lesions.  
\(^c\) Two-sided 95% exact confidence interval  
\(^d\) Per Cheson, as assessed by the investigator  
\(^e\) CR+PR+SD
### Table 3. Summary of Baseline CD30 Expression in DLBCL by Central Review and Computer-Assisted Methods and Summary of Baseline Soluble CD30

<table>
<thead>
<tr>
<th></th>
<th>Single-Agent Brentuximab Vedotin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR (N=8)</td>
<td>CR + PR (N=21)</td>
</tr>
<tr>
<td>Median soluble CD30 expression at baseline, ng/mL (min, max)</td>
<td>103 (44, 485)</td>
<td>121 (44, 1341)</td>
</tr>
<tr>
<td>Median % CD30+ malignant cells by visual central review, % (min, max)</td>
<td>11 (0, 90)</td>
<td>25 (0, 90)</td>
</tr>
<tr>
<td>Patients with &lt;10% CD30+ malignant cells by visual central review, n (%)</td>
<td>4 (50)</td>
<td>8 (21)</td>
</tr>
<tr>
<td>Median % CD30+ all cells by computer-assisted methods, % (min, max)</td>
<td>58.5 (1, 95)</td>
<td>37.4 (1, 95)</td>
</tr>
</tbody>
</table>

a Normal range <29 ng/mL
b N=24; there were 3 non-responders who did not have data available

### Table 4. Treatment-Emergent Adverse Events Occurring in ≥25% of B-cell Patients Treated with Monotherapy

<table>
<thead>
<tr>
<th></th>
<th>Single-Agent Brentuximab Vedotin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DLBCL (N=49)</td>
<td>Other B-Cell (N=19)</td>
</tr>
<tr>
<td></td>
<td>G1/2</td>
<td>G3/4a</td>
</tr>
<tr>
<td>Fatigue</td>
<td>21 (43)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18 (37)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>2 (4)</td>
<td>18 (37)</td>
</tr>
<tr>
<td>Nausea</td>
<td>13 (27)</td>
<td>6 (12)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11 (22)</td>
<td>4 (8)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13 (27)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>12 (24)</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

a All events were Grade 3 in severity with the exception of Grade 4 events of neutropenia in 9 (18%) patients.
b All events were Grade 3 in severity with the exception of Grade 4 events of neutropenia in 2 (11%) patients.
Table 5. Treatment-Emergent Adverse Events Occurring in ≥25% of DLBCL Patients Treated with Combination Therapy

<table>
<thead>
<tr>
<th>Condition</th>
<th>Brentuximab Vedotin + Rituximab</th>
<th>DLBCL (N=16)</th>
<th>G1/2</th>
<th>G3/4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6 (38)</td>
<td></td>
<td>0</td>
<td>6 (38)</td>
<td></td>
</tr>
<tr>
<td>Peripheral sensory neuropathy</td>
<td>5 (31)</td>
<td></td>
<td>0</td>
<td>5 (31)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5 (31)</td>
<td></td>
<td>0</td>
<td>5 (31)</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>4 (25)</td>
<td></td>
<td>0</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>4 (25)</td>
<td></td>
<td>0</td>
<td>4 (25)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1 (6)</td>
<td>3 (19)</td>
<td>4 (25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (19)</td>
<td>1 (6)</td>
<td>4 (25)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- a All Grade 4 in severity
- b Grade 3 in severity
Figure legends

Figure 1. Duration of Objective Response and Complete Remission in DLBCL

Patients – Analyzed using Kaplan-Meier methodology; censored patients are indicated.

Figure 2. CD30 Expression per IHC assessed by Visual and Computer-Assisted Methods – 83-year-old male with relapsed DLBCL: achieved a CR after 2 cycles of treatment, had 0% CD30 expression by visual central review (A), had 1.4% CD30 expression by computer-assisted methods (B), discontinued treatment after 7 cycles of therapy due to Grade 2 peripheral sensory neuropathy, and subsequently progressed (response duration ~4 months). 76-year-old male with refractory DLBCL: achieved a CR after 2 cycles of treatment, had 1% CD30 expression by visual central review (C), had 34% CD30 expression by computer-assisted methods (D), discontinued treatment after 17 cycles of therapy due to disease progression (response duration ~11 months).

Figure 3. Maximum Tumor Size Reduction by Quantitative CD30 Expression in DLBCL Patients – Blue shaded area represents the 95% confidence band around the point estimates; solid line is a smooth curve based on non-parametric regression. Figure includes patients who have both post-baseline radiographic response assessments and CD30 IHC expression data; (A) maximum tumor size decrease by CD30 expression as assessed by central visual review, (B) maximum tumor size decrease by CD30 expression as assessed by computer-assisted methods.

Figure 4. Maximum Tumor Size Reduction from Baseline – Includes patients with post-baseline tumor measurements (n=74). Five patients are not included in the figure for the following reasons: 1 patient with plasmablastic lymphoma was determined to have clinical disease progression per investigator and had no post-baseline scans; 1 PTLD
patient’s response was determined to be not evaluable because the patient had no measureable baseline lesions; and 3 patients in the combination therapy cohort were excluded because 1 patient received 1 cycle of treatment, then withdrew consent; 1 died due to related TEN after 2 cycles with no response assessment; and 1 was excluded because of prohibited therapy prior to ending treatment for progression (no post-baseline scans).
Figure 2

CR in 83-Year-Old Male with Relapsed DLBCL

(A) 0% CD30 expression on neoplastic cells

Visual Assessment

CR in 76-Year-Old Male with Refractory DLBCL

(C) 1% CD30 expression on neoplastic cells

Computer-Assisted Assessment

(B) 1.4% CD30 expression on all cells

(D) 34% CD30 expression on all cells
Figure 4

77% of patients achieved tumor reduction

Tumor Size (% Change from Baseline)

Individual Patients (N=74)
Brentuximab vedotin demonstrates objective responses in a phase 2 study of relapsed/refractory DLBCL with variable CD30 expression

Eric D. Jacobsen, Jeff P. Sharman, Yasuhiro Oki, Ranjana H. Advani, Jane N. Winter, Celeste M. Bello, Gary Spitzer, Maria Corinna Palanca-Wessels, Dana A. Kennedy, Pamela Levine, Jing Yang and Nancy L. Bartlett