


# Brentuximab vedotin prior to allogeneic stem cell transplantation in Hodgkin lymphoma: a report from the EBMT Lymphoma Working Party

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## Summary

Brentuximab vedotin (BV) is an anti-CD30 antibody-drug conjugate. Preliminary data suggest that BV might improve outcomes after allogeneic stem cell transplantation (SCT) for Hodgkin lymphoma (HL) when used as pre-transplant salvage therapy. Between 2010 and 2014, 428 adult patients underwent an allogeneic SCT for classical HL at participating centres of the European Society for Blood and Marrow Transplantation. We compared the outcomes of 210 patients who received BV prior to allogeneic SCT with that of 218 patients who did not receive BV. The median follow-up for survivors was 41 months. Patients in the BV group were more heavily pre-treated (median pre-allograft treatment lines: 4 vs. 3). The two groups were comparable in terms of disease status, performance status, comorbidities, prior autologous SCT, type of donor, conditioning and *in vivo* T cell depletion. In multivariate analysis, pre-allograft BV had no impact on acute graft-versus-host disease (GVHD), non-relapse mortality, cumulative incidence of relapse, progression-free survival or overall survival (OS), but significantly reduced the risk of chronic GVHD (hazard ratio = 0.64; 95% confidence interval = 0.45–0.92;  $P < 0.02$ ). Older age, poor performance status, use of pre-transplant radiotherapy and active disease at SCT adversely affected OS. Patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT except for a lower risk of chronic GVHD. However, BV may improve the outlook of allogeneic SCT by helping otherwise refractory patients to achieve a more favourable disease status, facilitating allotransplant success.

**Keywords:** Hodgkin lymphoma, stem cell transplantation, salvage therapy, allogeneic stem cell transplant.

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Hodgkin lymphoma (HL) is a curable disease with 5-year progression-free survival (PFS) exceeding 80% with standard first line therapy. For primary refractory or relapsed disease after first line treatment, second line salvage chemotherapy followed by autologous stem cell transplantation (SCT) is considered the standard of care, resulting in sustained disease control in more than half of the patients (Linch *et al*, 1993; Andre *et al*, 1999; Schmitz *et al*, 2002; Holmberg & Maloney, 2011). For patients who relapse after autologous SCT, the median survival is 24 months, and allogeneic SCT represents a potentially curative modality (Lazarus *et al*, 1999; Sarina *et al*, 2010; Sureda *et al*, 2012; Kharfan-Dabaja *et al*, 2014).

The success of allogeneic SCT in relapsed/refractory HL is dependent on several factors, including tumour sensitivity to salvage therapy before transplantation (Peggs *et al*, 2005; Alvarez *et al*, 2006; Robinson *et al*, 2009; Moskowitz *et al*, 2012). Unfortunately, a significant number of patients with relapsed/refractory HL have chemo-resistant disease and have received multiple lines of therapy. Therefore, novel monoclonal antibodies, such as brentuximab vedotin (BV), or checkpoint inhibitors are increasingly used as a bridge to transplant (Chen *et al*, 2012a, 2014; Ansell *et al*, 2015; Illidge *et al*, 2015; El Cheikh *et al*, 2017; Hegerova *et al*, 2017; Merzlyan *et al*, 2017).

BV is an anti-CD30 monoclonal antibody linked by a protease-cleavable linker to monomethyl auristatin E, a microtubule-disrupting agent. This antibody-drug conjugate is approved for the treatment of classical HL in relapse either after autologous SCT or after two lines of combination chemotherapy in transplant ineligible patients (Bartlett *et al*, 2008; Forero-Torres *et al*, 2009; Younes *et al*, 2012). The pivotal phase II study using single-agent BV in relapsed/refractory HL revealed an overall response rate of 75%, with 34% complete responses, and a median remission duration of 20 months for complete responders (Younes *et al*, 2012). Side effects are relatively modest, the most clinically significant one being reversible peripheral neuropathy, which often

prohibits long term BV therapy. The AETHERA randomized trial recently demonstrated that consolidation with BV after autologous SCT significantly improved PFS in high-risk HL patients (Moskowitz *et al*, 2015).

Preliminary data suggests that BV may improve the results of allogeneic SCT for HL when used as a bridging agent (Chen *et al*, 2012a, 2014; Illidge *et al*, 2015; Hegerova *et al*, 2017). However, the impact on long-term outcomes remains unknown. This study aimed to assess the impact of pre-transplant BV on subsequent allogeneic SCT by comparing the outcome of patients who received BV before allogeneic SCT with that of patients who did not receive BV before allogeneic SCT, using a large sample from the European Society for Blood and Marrow Transplantation (EBMT) registry.

## Patients and methods

### Study design and data collection

This is a retrospective registry-based multicentre analysis. Data were provided and approved for this study by the Lymphoma Working Party (LWP) of the EBMT. The EBMT is a voluntary working group of more than 600 transplant centres that are required to report all consecutive stem cell transplantations and follow-up once a year. Audits are routinely performed to determine the accuracy of the data. Since January 1 2003, all transplant centres have been required to obtain written informed consent prior to data registration with the EBMT following the Helsinki Declaration 1975. Eligibility criteria for this analysis included adult patients (age >18 years) with classical HL who received a first allogeneic SCT between 2010 and 2014 from a human leucocyte antigen-matched related or unrelated donor with bone marrow (BM) or granulocyte colony-stimulating factor-mobilized peripheral blood (PB) stem cells. Patients who received cord blood, mismatched or haploidentical stem cells and tandem transplants were excluded.

Variables collected included recipient and donor age and gender, date of diagnosis, lines and detailed type of therapy prior to allogeneic SCT, response to each individual treatment line, previous autologous SCT, date, duration and number of doses of BV, disease status at transplant [complete remission (CR), partial remission (PR) or active disease], performance status and comorbidity index, transplant related-factors including conditioning regimen, immunosuppression (*in vivo* T cell depletion vs. none), graft-versus-host disease (GVHD) prophylaxis, stem cell source (BM or PB) and donor type. Active disease was defined as not being in CR or PR with stable disease (SD), primary induction failure, primary refractory or disease progression. For patients who received additional treatment after allogeneic SCT, we also collected the date of BV administration, additional cellular therapy, and additional immunotherapy or chemotherapy.

### Definitions

Histological diagnosis was based on local review and patients were staged according to the Ann Arbor system. Disease status at transplantation was classified as chemosensitive disease, which included all patients who had shown at least a PR, chemoresistant disease, which included patients with primary refractory disease, refractory relapse or untreated relapse. Patients who survived more than 90 days after allo-SCT without evidence of tumour were classified as having experienced CR. PR was defined as a  $\geq 50\%$  reduction of all pre-transplantation measurable disease for at least 1 month. Patients achieving less than 50% tumour reduction were considered non-responders. Intensity of conditioning regimens was defined as previously published (Robinson *et al*, 2009).

### Statistical analysis

Endpoints included PFS, overall survival (OS), non-relapse mortality (NRM), cumulative incidence of relapse (CIR) and acute and chronic GVHD. All outcomes were measured from the time of allogeneic SCT. PFS was defined as survival without relapse or progression; patients alive without relapse or progression were censored at the time of last contact. OS was defined as death from any cause. NRM was defined as death without previous relapse. Surviving patients were censored at the time of last contact. The probabilities of OS and PFS were calculated by using the Kaplan-Meier estimator. The probabilities of acute and chronic GVHD, NRM and relapse were calculated by using the cumulative incidence estimator to accommodate competing risks. For NRM, relapse was the competing risk, and for relapse, the competing risk was NRM. For acute and chronic GVHD, death without the event was the competing risk. For all prognostic analyses, continuous variables were categorized and the median used as a cut-off point. Univariate comparisons were performed using the log-rank test for PFS and OS, and Gray's test for cumulative incidences. Chronic GVHD was analysed as a

time-dependent variable. A Cox proportional hazards model was used for multivariate regression. Factors known to influence the outcome and factors associated with a *P*-value less than 0.10 with any endpoint by univariate analysis were included in the model. Results are expressed as hazard ratio (HR) with 95% confidence interval (CI). All tests were two-sided. The type-1 error rate was fixed at 0.05 for determination of factors associated with time to event outcomes.

All analyses were performed using R version 3.1.1 with the R packages survival version 2.38, cmprsk version 2.2-7 and Hmisc version 3.16-0 (R Core Team 2014).

## Results

### Patients' characteristics

A total of 428 patients met the eligibility criteria for this study. 218 patients had not received BV prior to allogeneic SCT (no BV group), and 210 had received BV as salvage therapy before allogeneic SCT (BV group). BV was the most recent regimen before allogeneic SCT (bridge-to-transplant) in 136 of the 210 (65%) BV-exposed patients. Patients' characteristics are listed in Table I. 334 patients (78%) had received a prior autologous SCT. Patients in the BV group had received a median of 5 doses (1–18). Maximum response to BV was CR (34%), PR (41%) and SD (21%). This maximal response was achieved after a median of 4 cycles of BV (1–16). Median time from start of BV to allogeneic SCT was 179 days (Q1 127; Q3 287).

### Transplant characteristics

Transplant characteristics are listed in Table II. Sixty patients in the BV and 30 in the no BV group received BV after allogeneic SCT, predominantly for relapse after allogeneic SCT, after a median of 12 and 22 months post-transplant, respectively.

### Effect of salvage BV prior to allogeneic SCT on transplant outcomes

In univariate analysis, prior use of BV had no effect on either engraftment or on the incidence and severity of acute GVHD (Table III). Indeed, the cumulative incidence of day +100 acute GVHD grade II-IV was 24% in the BV group vs. 31% in the no BV group. Similarly, there was a lower incidence of chronic GVHD in the BV group with a 41% cumulative incidence at 3 years versus 48% in the no BV group, although this was not statistically significant (Table III; Figure S1). Finally, pre-transplant BV was associated with a significantly higher CIR (51% versus 39% at 3 years; *P* = 0.01) (Figure S2A), but had no significant effect on NRM (15% versus 19% at 3 years) (Figure S2C), and OS (60% versus 60% at 3 years) (Figure S2D). The median follow-up for survivors was 41 months (interquartile range [IQR] 28–55 months).

Table I. Patients' characteristics.

Variable	No BV n (%)	BV n (%)	P
Patients	218	210	
Age at allogeneic SCT, years; median (range)	33 (18–71)	30 (18–68)	0.07
Female	82 (38)	87 (41)	0.48
SCT-Comorbidity index	0 (0–6)	0 (0–6)	0.91
Karnofsky score 90, 100	158 (73)	158 (79)	0.34
Lines before SCT; median (range)	3 (1–9)	4 (1–12)	<0.001
4 or more treatment lines	71 (40%)	121 (69%)	<0.001
ABVD as first line treatment	156 (72)	153 (73)	0.8
Second line			
DHAP	43 (20)	43 (20)	0.82
ESHAP	30 (14)	19 (9)	
ICE	15 (7)	23 (11)	
IGEV	23 (11)	27 (13)	
Radiotherapy before transplant	104 (48)	104 (49)	0.78
Prior autologous SCT	171 (78)	163 (78)	0.93
Disease status at SCT			
Not available (N)	1	2	0.33
Active disease	76 (35)	91 (42)	
CR > 1	102 (47)	83 (40)	
PR > 1	39 (18)	34 (16)	
Median interval from diagnosis to allogeneic SCT (months, range)	31 (11–336)	35 (7–23)	0.002
Median follow up for alive patients (months, IQR)	50 (42–60)	33 (25–41)	<0.001

ABVD, Adriamycin, bleomycin, vinblastine and dacarbazine; BV, brentuximab-vedotin; CR, complete response; DHAP, dexamethasone, high dose cytarabine and cisplatin; ESHAP, etoposide, solumedrol, high dose cytarabine and cisplatin; ICE, ifosfamide, carboplatin and etoposide; IGEV, ifosfamide, gemcitabine and vinorelbine; IQR, interquartile range; PR, partial response; SCT, allogeneic stem cell transplant; SD, stable disease.

Similar results were observed when the 136 patients who received BV as last therapy before allo-SCT were compared with the 218 patients who did not receive pre-transplant BV (Table III; Figs 1 and 2), except that there was no difference in the CIR (45% versus 39% at 3 years;  $P = 0.38$ ) (Fig 2A). For these patients, response to BV predicted post-transplant outcomes (Fig 3). Indeed, 57 patients allografted in CR after BV had significantly improved PFS as compared to patients in PR ( $N = 80$ ) or more advanced disease ( $N = 56$ ) (Fig 3A), although OS was not significantly different (Fig 3B). Furthermore, patients allografted in CR or PR had improved PFS (Fig 3C) and OS (Fig 3D) as compared to patients allografted with more advanced disease.

### Multivariate analysis

In multivariate analysis, pre-allograft BV had no significant effect on NRM, CIR, PFS, or OS, but significantly reduced the incidence of chronic GVHD (Table IV). Use of pre-transplant radiotherapy adversely affected chronic GVHD and OS, poor performance status (Karnofsky score <90) adversely affected PFS and OS, older age (>40 years) adversely affected NRM, PFS and OS, whereas active disease status at the time of allogeneic SCT adversely affected chronic GVHD, CIR, NRM, PFS and OS, and finally, a higher number of treatment lines increased the incidence of chronic GVHD (Table IV). Again, similar results were observed when the

multivariate analysis included only the 136 patients who received BV as last therapy before allo-SCT and the 218 patients who did not receive pre-transplant BV (Table V). In this analysis, pre-allograft BV significantly reduced the incidence of chronic GVHD without affecting the other outcomes (Table V).

### Discussion

Allogeneic SCT is an effective treatment modality for HL patients who relapse or progress after autologous SCT. However, the success of this treatment modality is largely dependent on the tumour being sensitive to salvage therapy before transplantation (Robinson *et al*, 2009). Unfortunately, patients with relapsed/refractory disease have already received multiple lines of therapy and are quite difficult to salvage. Preliminary data from small series suggest that pre-transplant salvage therapy with BV might improve outcomes after allogeneic SCT for HL (Chen *et al*, 2012a, 2014; Hegerova *et al*, 2017).

Our study included a high-risk population: 78% of the patients had received a prior autologous SCT (of note, some of the patients had received more than one autologous SCT before allogeneic SCT), and the median number of prior treatment lines was 4. Of note, patients in the BV group were more heavily pre-treated than patients in the no BV group, with 69% of the patients in the BV group having

Table II. Transplant characteristics.

Transplant characteristics	No BV <i>n</i> (%)	BV <i>n</i> (%)	<i>P</i>
Patients	218	210	
Number of this SCT			
First SCT	45 (21)	41 (20)	0.58
Second SCT	160 (73)	152 (72)	
Third SCT	12 (6)	17 (8)	
Fourth SCT	1 (0)	0 (0)	
Non-myeloablative or reduced intensity conditioning	169 (78)	158 (75)	0.57
No TBI	174 (80)	167 (79)	1.00
TCD (ATG or Campath)	95 (44)	90 (43)	0.96
No TCD	123 (56)	120 (57)	
Donor type			
MRD	136 (62)	125 (60)	0.74
MUD	82 (38)	85 (40)	
Stem cell source			
BM	44 (20)	41 (20)	0.96
PB	174 (80)	169 (80)	
Treatment post-transplant			
DLI	38 (17)	67 (32)	0.001
Median time from SCT to DLI (months, range)	10 (3–37)	10 (14 days–58 months)	0.78
BV post-transplant	30 (14)	60 (29)	<0.001*
Median months from SCT to BV	22 (3–36)	12 (4 days–52 months)	0.10
Number of post-SCT BV doses			
Missing	9	12	
Median (range)	8 (1–16)	5 (1–16)	0.04
Duration of BV post-SCT, days; median (range)	178 (1–632)	101 (1–507)	0.06

ATG, antithymocyte globulin; BM, bone marrow; BV, brentuximab-vedotin; DLI, donor lymphocyte infusion; MRD, matched related donor; MUD, matched unrelated donor; PB, peripheral blood; SCT, allogeneic stem cell transplant; TBI, total body irradiation; TCD, T cell depletion.

\*Gray's test for cumulative incidence of BV post administration taking into account competing risk of death.

Table III. Transplant outcomes.

Transplant outcomes	No BV before allo-SCT <i>n</i> (%)	BV before allo-SCT		BV as last line before allo-SCT	
		<i>n</i> (%)	<i>P</i>	<i>n</i> (%)	<i>P</i>
Patients	218	210		136	
Engrafted	210 (99)	202 (98)	0.8	133 (98)	0.4
Acute GVHD, % (range)					
Grade II–IV	27 (21–33)	24 (18–30)	0.2	27 (20–35)	0.7
Grade III–IV	8 (5–13)	8 (4–12)	0.4	9 (5–15)	0.9
3-year NRM, % (range)	19 (14–25)	15 (10–20)	0.32	19 (13–26)	0.9
3-year CIR, % (range)	39 (33–46)	51 (44–58)	0.01	45 (35–53)	0.38
3-year PFS, % (range)	41 (35–49)	34 (27–41)	0.1	37 (29–47)	0.51
3-year chronic GVHD, % (range)	48 (41–54)	41 (34–48)	0.13	42 (33–51)	0.25
3-year OS, % (range)	60 (54–67)	60 (53–68)	0.83	59 (51–69)	0.99

received 4 or more lines of therapy (including BV) versus 40% in the no BV group ( $P < 0.001$ ). As most of the patients in this study received BV as last treatment before allogeneic SCT, one could argue that BV allowed these high-risk patients to obtain a response good enough to proceed to SCT. Therefore, one important issue of this study lies in the inherent bias of the study population. Given the fact that patients who received BV and those who did not receive BV

were treated in the same time period, and that patients who received BV had a higher number of prior therapies, one could argue that the majority of patients in the BV cohort had disease relapsed/refractory to chemotherapy so, without BV, the outcome after an allogeneic SCT with active disease would have been much worse. Multivariate analysis showed that pre-allograft salvage therapy with BV did not significantly affect NRM, CIR, PFS or OS, even for the 136 patients

Fig 1. Effect of pre-transplant BV as last salvage on post-transplant cumulative incidence of chronic graft-versus-host disease. BV, brentuximab-vedotin; cGVHD, chronic graft-versus-host disease; SCT, allogeneic stem cell transplant.

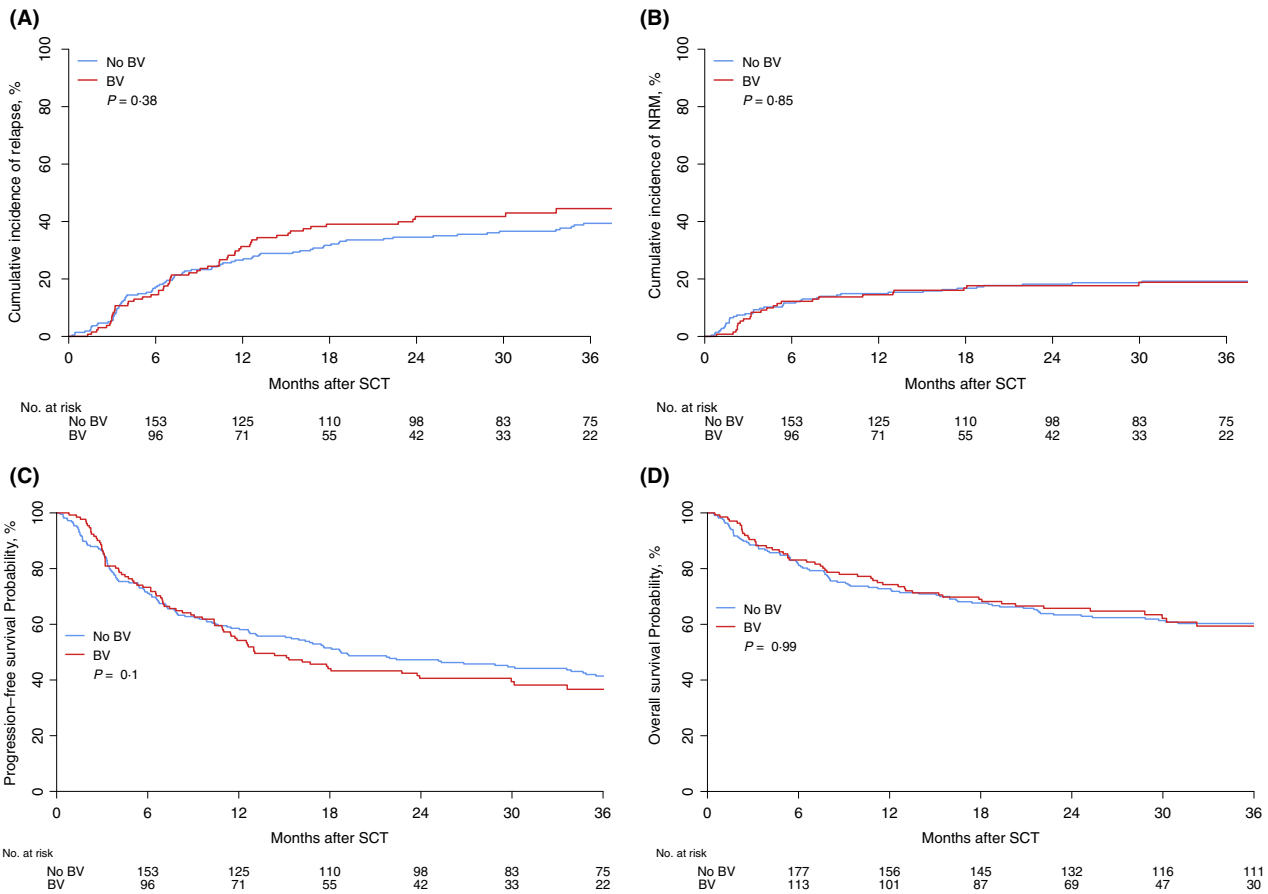
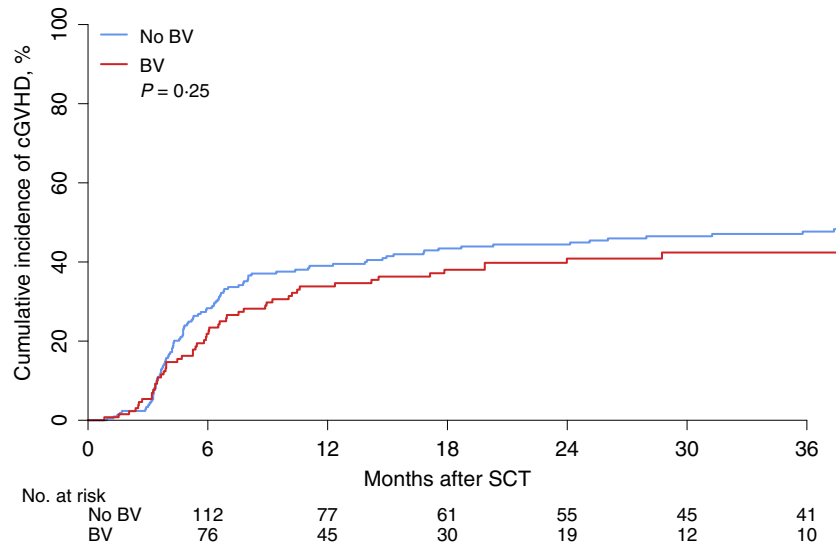
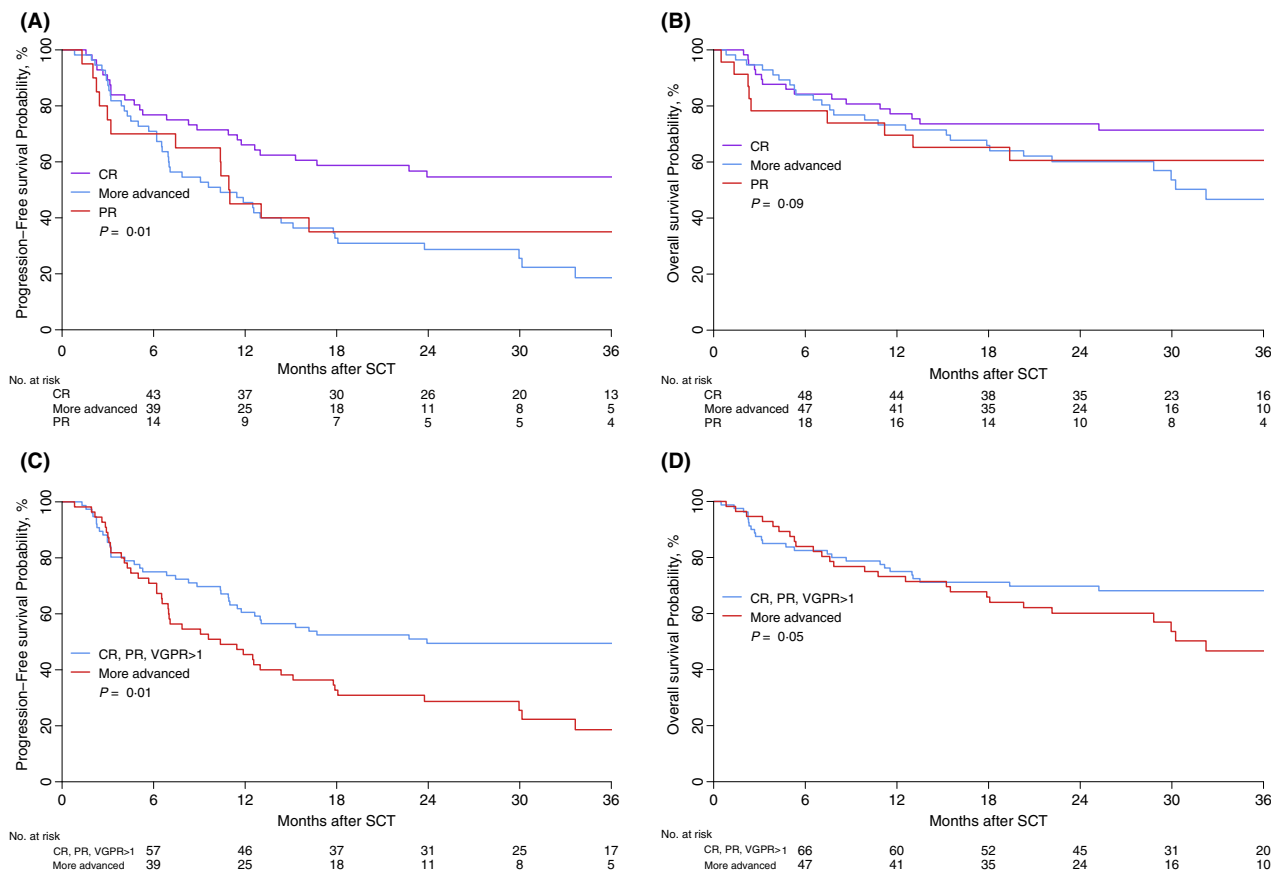


Fig 2. Effect of pre-transplant BV as last salvage therapy before allo-SCT on post-transplant outcomes. (A) Cumulative incidence of relapse; (B) Cumulative incidence of non-relapse mortality; (C) Progression-free survival; (D) Overall survival. BV, brentuximab-vedotin; NRM, non-relapse mortality; SCT, allogeneic stem cell transplant.

who received BV as last treatment before allo-SCT. These results disagree with a previous report from (Chen *et al*, 2014), which suggested that the use of BV as a bridge to

allogeneic SCT improves post-transplant outcomes. However, the two studies had significant differences. The sample size in the study reported by Chen *et al* (2014) was much smaller



**Fig 3.** Effect of response to BV as last salvage therapy before allo-SCT on post-transplant outcomes. (A, C) Cumulative incidence of Progression-free survival; (B, D) Overall survival. CR, complete response; PR, partial response; SCT, allogeneic stem cell transplant; VGPR, very good partial response.

but patients were much more homogenous on both arms (everyone received reduced intensity conditioning with fludarabine/melphalan, and the number of prior regimen on both arms was 4). Furthermore, all patients in our series were transplanted between 2010 and 2014, whereas in the earlier study (Chen *et al*, 2014), patients who did not receive BV were transplanted between 2003 and 2009, implying that general improvements in SCT technology rather than BV itself might have contributed to the superior outcome of the BV group in that study.

Interestingly, we clearly show that pre-allograft salvage therapy with BV significantly decreased the cumulative incidence of chronic GVHD in multivariate analysis. This was even though 32% of patients in the BV group received post transplant donor lymphocyte infusion versus only 17% in the no-BV group ( $P = 0.002$ ). Importantly, the two groups were comparable in terms of *in vivo* T cell depletion because anti-thymocyte globulin and alemtuzumab were used in 24% and 26%, respectively, of the patients in the BV group, versus 25% and 30%, respectively, in the no BV group. This reduced incidence of chronic GVHD makes BV an attractive bridge to allo-SCT in comparison with checkpoint inhibitors, which may

increase the post transplant morbidity and incidence of severe GVHD (Merryman *et al*, 2017).

While there is no clear explanation for this BV-associated reduction of chronic GVHD, it may be due to the immunomodulatory effects of BV, which need to be further studied. In this context, BV has been shown to induce remission in rheumatoid arthritis (Vachhani *et al*, 2014). CD30 is a cell membrane protein of the tumour necrosis factor superfamily expressed on activated CD3<sup>+</sup> T cells and upregulated in T cells when exposed to allogeneic antigens. Malard *et al* (2013) reported that the absolute number of CD30<sup>+</sup> lymphocytes is significantly higher in the dermal infiltrate of the skin of the patients with acute GVHD, compared with those without it, indicating that the accumulation of cytotoxic and activated CD30<sup>+</sup> T cells reflected an activated immune status in the skin of the patients with acute GVHD. Chen *et al* (2012b) showed that patients with acute GVHD have a higher percentage of CD30 expressing CD8<sup>+</sup> T cells with a particularly pronounced difference in the central memory subset (CD8<sup>+</sup> CD45RO<sup>+</sup> CD62L<sup>+</sup>). The same group recently reported the results of a Phase I study in steroid-refractory acute GVHD, showing that BV induces

**Table IV.** Multivariate analysis including 210 patients who received BV before allo-SCT and 218 patients who did not receive BV pre-transplant.

	cGVHD	NRM	CIR	PFS	OS
Variables	HR (95% CI) <i>P</i>	HR (95% CI) <i>P</i>	HR (95% CI) <i>P</i>	HR (95% CI) <i>P</i>	HR (95% CI) <i>P</i>
BV salvage pre-SCT vs. no	<b>0.64 (0.45–0.92)</b> <i>P</i> = <b>0.016</b>	0.91 (0.53–1.55) <i>P</i> = 0.7192	1.29 (0.91–1.82) <i>P</i> = 0.1524	1.16 (0.87–1.55) <i>P</i> = 0.3179	0.88 (0.62–1.26) <i>P</i> = 0.5014
Age (10-year increase)	1.01 (0.87–1.16) <i>P</i> = 0.933	1.1 (0.87–1.38) <i>P</i> = 0.4336	1.04 (0.9–1.21) <i>P</i> = 0.5791	1.06 (0.94–1.2) <i>P</i> = 0.3599	<b>1.2 (1.04–1.39)</b> <i>P</i> = <b>0.0137</b>
Male vs. female	1.29 (0.92–1.8) <i>P</i> = 0.1375	1.11 (0.66–1.87) <i>P</i> = 0.6878	1.24 (0.89–1.73) <i>P</i> = 0.2066	1.2 (0.91–1.59) <i>P</i> = 0.1959	1.32 (0.94–1.87) <i>P</i> = 0.1088
Karnofsky 90, 100 vs. under 80	0.96 (0.65–1.41) <i>P</i> = 0.8218	0.61 (0.35–1.06) <i>P</i> = 0.0799	<b>0.7 (0.48–1.01)</b> <i>P</i> = <b>0.0581</b>	<b>0.67 (0.49–0.91)</b> <i>P</i> = <b>0.0103</b>	<b>0.57 (0.4–0.81)</b> <i>P</i> = <b>0.0019</b>
≥4 lines before SCT vs. ≤3	<b>1.52 (1.06–2.17)</b> <i>P</i> = <b>0.0236</b>	1.16 (0.67–2) <i>P</i> = 0.5947	1.15 (0.81–1.63) <i>P</i> = 0.4286	1.16 (0.87–1.56) <i>P</i> = 0.3169	1.28 (0.89–1.83) <i>P</i> = 0.1791
Advanced disease vs. CR, PR	1.62 (1.15–2.28) <i>P</i> = 0.0054	<b>2.68 (1.58–4.54)</b> <i>P</i> = <b>0.0003</b>	<b>2.34 (1.68–3.26)</b> <i>P</i> < <b>0.0001</b>	<b>2.44 (1.84–3.22)</b> <i>P</i> < <b>0.0001</b>	<b>2.55 (1.8–3.6)</b> <i>P</i> < <b>0.001</b>
Radiotherapy before SCT vs. no	1.38 (0.99–1.92) <i>P</i> = 0.0551	1.43 (0.85–2.4) <i>P</i> = 0.1756	0.91 (0.66–1.26) <i>P</i> = 0.5798	1.04 (0.79–1.37) <i>P</i> = 0.7893	1.34 (0.96–1.88) <i>P</i> = 0.0867
MUD vs. identical sibling	<b>1.8 (1.29–2.5)</b> <i>P</i> = <b>0.0005</b>	1.09 (0.65–1.84) <i>P</i> = 0.7335	0.71 (0.5–1.01) <i>P</i> = 0.0541	0.81 (0.61–1.08) <i>P</i> = 0.1461	1.11 (0.79–1.56) <i>P</i> = 0.5517

BV, brentuximab-vedotin; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; HR, hazard ratio; MUD, matched unrelated donor; NRM, non relapse mortality; OS, overall survival; PFS, progression free survival; PR, partial remission; SCT, allogeneic stem cell transplant. Statistically significant results are in bold font.

**Table V.** Multivariate analysis including 136 patients who received BV as last therapy before allo-SCT and 218 patients who did not receive BV pre-transplant.

	cGVHD	NRM	CIR	PFS	OS
Variables	(95% CI) <i>P</i>	(95% CI) <i>P</i>	(95% CI) <i>P</i>	(95% CI) <i>P</i>	(95% CI) <i>P</i>
BV salvage pre-SCT vs. no	<b>0.67 (0.45–0.99)</b> <i>P</i> = <b>0.0448</b>	0.98 (0.55–1.74) <i>P</i> = 0.9372	1.03 (0.69–1.54) <i>P</i> = 0.8755	1.01 (0.73–1.4) <i>P</i> = 0.9404	0.93 (0.62–1.38) <i>P</i> = 0.7204
Age (10-year increase)	0.98 (0.83–1.15) <i>P</i> = 0.7643	1.12 (0.87–1.43) <i>P</i> = 0.3836	1.12 (0.94–1.33) <i>P</i> = 0.2048	1.12 (0.97–1.29) <i>P</i> = 0.1247	<b>1.22 (1.04–1.43)</b> <i>P</i> = <b>0.0164</b>
Male vs. female	1.3 (0.9–1.87) <i>P</i> = 0.1622	1.22 (0.7–2.13) <i>P</i> = 0.49	1.38 (0.94–2.03) <i>P</i> = 0.1042	1.32 (0.96–1.81) <i>P</i> = 0.0859	1.41 (0.96–2.06) <i>P</i> = 0.0792
Karnofsky 90, 100 vs. under 80	0.91 (0.6–1.4) <i>P</i> = 0.6788	0.59 (0.33–1.06) <i>P</i> = 0.08	0.81 (0.52–1.25) <i>P</i> = 0.3342	0.73 (0.51–1.03) <i>P</i> = 0.0706	<b>0.61 (0.41–0.9)</b> <i>P</i> = <b>0.0119</b>
≥4 lines before SCT vs. ≤3	<b>1.49 (1.02–2.16)</b> <i>P</i> = <b>0.0385</b>	1.25 (0.71–2.19) <i>P</i> = 0.4443	1.26 (0.86–1.86) <i>P</i> = 0.2403	1.26 (0.91–1.73) <i>P</i> = 0.1574	1.36 (0.93–1.98) <i>P</i> = 0.1134
Advanced disease vs. CR, PR	1.42 (0.98–2.06) <i>P</i> = 0.0656	<b>2.35 (1.33–4.13)</b> <i>P</i> = <b>0.0031</b>	<b>2.7 (1.83–3.97)</b> <i>P</i> < <b>0.0001</b>	<b>2.59 (1.89–3.57)</b> <i>P</i> < <b>0.0001</b>	<b>2.5 (1.71–3.65)</b> <i>P</i> < <b>0.0001</b>
Radiotherapy before SCT vs. no	1.33 (0.93–1.91) <i>P</i> = 0.1161	1.44 (0.83–2.5) <i>P</i> = 0.1962	0.89 (0.61–1.3) <i>P</i> = 0.553	1.04 (0.76–1.41) <i>P</i> = 0.8052	1.32 (0.92–1.91) <i>P</i> = 0.132
MUD vs. identical sibling	<b>1.81 (1.27–2.58)</b> <i>P</i> = <b>0.0011</b>	1.15 (0.66–1.98) <i>P</i> = 0.6247	0.73 (0.49–1.08) <i>P</i> = 0.1165	0.85 (0.62–1.16) <i>P</i> = 0.3022	1.16 (0.81–1.68) <i>P</i> = 0.4178

BV, brentuximab-vedotin; cGVHD, chronic graft-versus-host disease; CI, confidence interval; CIR, cumulative incidence of relapse; CR, complete remission; HR, hazard ratio; MUD, matched unrelated donor; NRM, non relapse mortality; OS, overall survival; PFS, progression free survival; PR, partial remission; SCT, allogeneic stem cell transplant. Statistically significant results are in bold font.

an overall response rate of 38.2% at day 28 including 14.7% CR and 23.5% very good partial responses (Chen *et al*, 2017).

The 5-year end-of-study results from the pivotal phase 2 trial of BV in patients with relapsed/refractory HL after failed autologous SCT showed that 9% (9/102) of the enrolled

study population enjoyed long-term remission exceeding 5 years in response to single-agent BV without any additional therapy, challenging the notion that allogeneic SCT is the only option for long-term disease control in this setting (Chen *et al*, 2016). However, this long-term disease control with BV alone was restricted to a minority of patients who

achieved CR (9/34) and therefore allogeneic SCT remains a widely used treatment modality after failed autologous SCT.

One important limitation of our registry study is its retrospective nature, and the heterogeneous population in the both arms. Another limitation is the use of a registry-based approach to look at the effect of a treatment given before transplant among transplanted patients only. Indeed, the decision to give the treatment is not random, and is clearly affected by date and number of previous therapies. Both of these are confounder factors, acting in different directions. Another confounder is that, by looking at transplanted patients only, we cannot determine if the decision to transplant is based upon the availability of, suitability of or response to BV. Ideally, this question should be answered by a prospective randomized trial comparing allogeneic SCT after prior salvage with or without BV. However, this type of study is ethically questionable because of the limited alternative options in these, often chemoresistant, patients. Therefore, and despite the above-mentioned weaknesses, we believe that this study is the first and largest analysis to tackle this topic.

In conclusion, and in contrast to previous much smaller studies, patients allografted for HL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, patients with BV-induced remissions prior to transplant do not do worse than chemosensitive patients, implying that BV can improve the outlook of allogeneic SCT by helping otherwise refractory patients to achieve a more advantageous disease status as a prerequisite for a successful allotransplant. Indeed, patients in the BV cohort would otherwise have been transplanted with active disease and therefore should have had a much worse outcome. The decrease in chronic GVHD is an interesting finding that needs to be further studied in the setting of allogeneic SCT, even beyond HL.

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## Author contributions

ABa proposed the study, interpreted the data and wrote the manuscript. AS, MM and PD participated in study design, interpreted the data and edited the manuscript. SM interpreted the data and edited the manuscript. ABo helped with the design and was responsible for statistical analysis. HF was the study coordinator. All other authors reported updated patient data and read and commented on the manuscript. All authors proofread the manuscript and agreed on the data presented.

## Conflict of Interest

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Figure S1.** Effect of pre-transplant BV salvage on post transplant cumulative incidence of chronic graft versus host disease.

**Figure S2.** Effect of pre-transplant BV salvage on post transplant outcomes.

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