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ORIGINAL ARTICLE

Brentuximab vedotin prior to allogeneic stem cell transplantation increases survival in chemorefractory Hodgkin's lymphoma patients

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Abstract

This study reports a retrospective multicenter experience by the Rete Ematologica Pugliese (REP) over the past 16 years, aiming to compare the patients characteristics and outcomes of 21 brentuximab vedotin (BV)–pre-treated patients to 51 patients who received reduced-intensity conditioning (RIC) allogeneic stem cell transplantation (SCT) without prior BV. In total, 72 patients with classical Hodgkin's lymphomas who received allogeneic SCT were retrospectively studied. Prior use of BV had no effect on either engraftment or the incidence and severity of acute graft versus host disease (GVHD). Indeed, a lower incidence of chronic GVHD was observed in the BV group, with a 43% cumulative incidence at 3 years versus 47% in the no BV group, although this was not statistically significant. Despite the low incidence of chronic GVHD, survival was not worse in the BV-treated group: 3-year progression-free survival (PFS) was 53%, 3-year overall survival (OS) was 62%, 3-year non-relapse mortality (NRM) was 24%. In the no BV group, the 3-year PFS was 33%, 3-year OS was 44%, and 3-year NRM was 14%. In chemorefractory patients at the time of transplant, we found a statistically significant difference in PFS between the BV and no BV groups (51% vs. 10%, $p = 0.013$).

Keywords Hodgkin lymphoma · Brentuximab vedotin · Allogeneic stem cell transplant

Introduction

Classical Hodgkin's lymphoma (cHL) remains a chemotherapy-sensitive disease with favorable outcomes. However, the prognosis for many patients who suffer relapse after autologous stem cell transplantation (SCT) is particularly poor, especially for those with chemorefractory disease [1–3].

Treatment options following failure of autologous SCT include the CD30-directed antibody drug conjugate brentuximab vedotin (BV), which can achieve durable responses in this challenging setting [4, 5].

BV is an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E. BV showed a substantial efficacy, including an objective response rate of 75% and a complete remission rate of 34%, in a pivotal phase 2 study of patients with cHL in whom high-dose therapy and autologous SCT had been ineffective [4].

As targeted therapy featuring a low frequency of severe hematologic toxic effects, BV might provide a unique opportunity to deliver preemptive therapy after autologous SCT. BV has also been shown to be an effective option after failure of at least two prior multi-agent chemotherapy regimens for patients with refractory or relapsed cHL who are ineligible for autologous SCT [6, 7] and as consolidation therapy for those at increased risk of relapse or progression following autologous SCT [8]. Other options in this setting include programmed death-1 inhibition with nivolumab [9] or pembrolizumab [10], second autologous SCT, reduced-intensity conditioning allogeneic SCT, salvage chemotherapy/radiotherapy, and trials of new drugs [11].

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This study reports a retrospective multicenter experience by the Rete Ematologica Pugliese (REP) over the past 17 years, aiming to compare the patients characteristics and outcomes of 21 BV-pre-treated patients (29%) to 51 patients (71%) who received reduced-intensity conditioning (RIC) allogeneic SCT without prior BV, in the time period before the drug became available.

Patients and methods

This is a retrospective registry–based multicenter analysis. The REP includes several Italian health centers of excellence and Haematologic and BM Transplant Units, located within a regional area (Apulia), with homogeneous economic resources and scientific and academic background. Audits are routinely performed to determine the accuracy of the data. All transplant centers obtained written informed consent prior to data registration with the REP in accordance with the Helsinki Declaration. Eligibility criteria for this analysis were adult patients (age > 18 years) with cHL who received a first allogeneic SCT between 2010 and 2017 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.

Variables collected included gender, date of diagnosis, lines of therapy prior to allogeneic SCT, previous autologous SCT, duration and number of doses of BV, disease status at transplant, 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, non-relapse mortality (NRM). Chemorefractory disease was defined as no complete remission (CR) or partial remission (PR) with stable disease (SD), primary induction failure, primary refractory, or disease progression (PD).

In the study period, 72 patients underwent RIC allogeneic SCT for cHL. The pre-transplant characteristics are shown in Table 1; 21 patients (29%) received BV prior to transplantation while 51 (71%) did not; clinical features are comparable in the two groups. Median age was 34 years (range 16–57 years) and 37 (51%) were male. The majority of patients (89%) had already undergone prior autologous SCT. At the time of allogeneic SCT, 33 (46%) patients had chemosensitive disease and 39 (54%) were chemorefractory. All the patients received RIC, 50% received grafts from a matched sibling donor (MRD), and 50% from a matched unrelated donor (MUD).

BV was given intravenously at a dosage of 1.8 mg/kg and administered in 250 ml of 0.9% saline over 30 min once every 3 weeks. No routine pre-medication was given, but oral paracetamol and i.v. hydrocortisone were subsequently administered to patients who experienced infusion reactions. BV doses were reduced to 1.2 mg/kg in cases of ≥ grade 3 toxicity.

Conditioning regimens and transplantation details

Conditioning regimens were fludarabine-based. T cell depletion of the graft was performed in 42 (58%) transplants by in vivo T cell depletion using ATG. Post-transplantation GVHD prophylaxis was performed using cyclosporine alone in 21 cases (29%), and cyclosporine and methotrexate in 51 (70%) cases.

Response criteria

Response was assessed by FDG-PET/CT, using the revised Cheson criteria [12]. CR was defined as complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present before therapy. PR was defined as a decrease by at least 50% of measurable disease and no new sites. SD indicates patients failing to attain the criteria for CR or PR but not showing PD. PD defines the appearance of any new lesion or an increase by ≥ 50% of previously involved sites from nadir.

Statistical analysis

Patient and disease characteristics were summarized using descriptive statistics. Chi-square test was employed to assess the main differences between clinical features of the two groups and the *t* test to compare continuous variables. Endpoints included progression-free survival (PFS), overall survival (OS), NRM, and acute and chronic GVHD.

PFS was defined as the time interval between time of allogeneic SCT and treatment failure or last follow-up. Treatment failure was defined as the inability to achieve complete remission requiring a switch to another chemotherapy regimen, or relapse after an initial complete remission.

OS was measured from the date of transplantation until death from any cause or last follow-up.

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 using the Kaplan-Meier estimator. Univariate comparisons were performed using the log-rank test for PFS and OS. Statistical significance was set at 0.05 or less. All tests were two-tailed.

Results

Seventy-two patients with relapsed or refractory cHL were included in this retrospective study. Disease and patient characteristics are summarized in Table 1.

Table 1 Patients characteristics

	No BV	BV	*p*
Tot	51 (71%)	21 (29%)	
Male	27 (53%)	10 (48%)	0.68
Median age at SCT, years (range)	34 (18–57)	35 (16–45)	0.12
Prior autologous SCT	41 (80%)	20 (95%)	0.11
Median time from prior high-dose therapy, months (range)	7 (2–112)	20 (6–32)	0.01
Median pre-allogeneic treatments lines (range)	4 (2–7)	4 (3–8)	0.38
Donor relationship, number (%)			
Matched sibling	27 (53%)	9 (43%)	0.44
Matched unrelated	24 (47%)	12 (57%)	0.44
Stem cell source, number (%)			
PBSC	44 (86%)	18 (86%)	0.95
BM	7 (14%)	3 (14%)	0.95
Status at transplant			
Chemosensitive disease	21 (41%)	12 (57%)	0.22
Chemorefractory disease	30 (59%)	9 (43%)	0.22

BV brentuximab vedotin, *SCT* stem cell transplantation, *PBSC* peripheral blood stem cell, *BM* bone marrow

BV had not been administered to 51 patients (71%) prior to allogeneic SCT (no BV group), while 21 (29%) had received BV as salvage therapy before allogeneic SCT (BV group). A prior autologous SCT had been performed in 61 patients (89%).

Treatment by BV was well tolerated, and patients underwent a median of 6 cycles (range 4–16). Toxicity was mild to moderate, in one patient who experienced grade 3 neuropathy requiring dosage reduction of BV to 1.2 mg/kg in the subsequent cycles.

Response to BV treatment was evaluated after 4 cycles. Ten patients (48%) were in CR while four patients (19%) were in PR, with a 67% ORR.

Maximum response to BV was achieved after a median of 4 cycles. Median time from the start of BV to allogeneic SCT was 5 months (range 4–10).

Of 72 patients, 71 (99%) achieved engraftment and 1 (1%) did not. The median times to neutrophil and platelet engraftment (platelets > 50) were 13 days (range 0–64) and 14 days (range 0–279), respectively. No difference in engraftment speed was observed between the BV and no BV groups.

Graft versus host disease

Acute GVHD was observed in 32 (44%) patients; acute GVHD grades III and IV developed in 8 (11%) patients.

The 67 patients who survived beyond 100 days were evaluable for chronic GVHD; 39 (58%) remained free of cGVHD and 28 (42%) developed cGVHD. Of those developing cGVHD, 15 (22%) developed limited and 13 (20%) extensive cGVHD.

There was a lower incidence of chronic GVHD in the BV group, with a 43% cumulative incidence at 3 years versus 47% in the no BV group, although this was not statistically significant (Table 2).

Non-relapse mortality

Following transplantation, 12 patients (17%) died of NRM (Table 2) at a median of 90 days (range 1 day–20 months). The causes of death included infection ($n = 7$), GVHD ($n = 3$), and multi-organ failure ($n = 2$). Pre-transplant BV treatment had no significant effect on NRM (16% versus 19% at 3 years).

Response to transplantation

The disease status at day 100 post-transplant was evaluated in 67 of 72 evaluable patients. Overall, 29 (43%) patients were in CR, 19 (28%) were in PR, 15 (22%) were

Table 2 Response to transplant and complications

Response	No BV	BV	*p*
Complete remission	21 (41%)	9 (43%)	0.18
Partial remission	15 (29%)	7 (33%)	0.39
Stable disease	12 (24%)	4 (19%)	0.38
Progression disease	3 (6%)	1 (5%)	0.19
cGVHD	24 (47%)	9 (43%)	0.75
TRM	7 (14%)	5 (24%)	0.30
Infections	4 (8%)	3 (14%)	0.40
Multi-organ failure	1 (2%)	1 (5%)	0.51
GVHD	2 (4%)	1 (5%)	0.87

BV brentuximab vedotin, *TRM* treatment-related mortality, *GVHD* graft versus host disease

in SD, and 4 (6%) had PD. Of the 29 patients in CR at the time of transplantation, 24 remained in CR (83%) and 5 (17%) suffered PD. Of the 11 patients in PR at the time of transplantation, 8 obtained CR (73%) and 3 (27%) suffered PD. Of the 39 patients with chemorefractory disease at transplant, 8 achieved CR (20%), 28 had PR or SD (72%), and 3 (8%) had PD. No differences in response were observed between the BV group and no BV group (Table 2).

Overall survival and progression-free survival

After a median follow-up of 60 months (range 3–207 months), 30 patients remain alive and 42 have died. The Kaplan-Meier estimates of OS and PFS at 5 years were 35% and 34%, respectively. Following transplantation, 40 patients (56%) suffered relapse or progression at a median time of 6 months (range 1–59 months) post-transplant.

No differences in PFS and OS were found when comparing the BV group and no BV group (Fig. 1): 3-year PFS in the BV-treated group was 53% (95% CI 28–54) vs. 32% (95% CI 48–104) in the no BV group ($p = 0.171$). 3-year OS was 62% (95% CI 29–55) in the BV group vs. 44% (95% CI 56–106) in the no BV group ($p = 0.335$).

In chemorefractory patients at the time of transplant, we found a statistically significant difference in PFS when comparing the BV vs no BV group (Fig. 2): 3-year PFS in the BV-treated group was 51% (95% CI 19–59) vs. 10% (95% CI 7–9) in the no BV group ($p = 0.013$); 3-year OS was 59% (95% CI 19–50) in the BV group vs. 20% (95% CI 21–61) in the no BV group ($p = 0.149$).

Discussion

Allogeneic SCT is an effective treatment modality for cHL patients suffering relapse or progression after autologous SCT. However, the success of this treatment modality is largely dependent on the tumor being sensitive to salvage therapy before transplantation [13].

Unfortunately, a significant number of patients with relapsed/refractory cHL have chemo-resistant disease and have received multiple lines of therapy. Therefore, novel monoclonal antibodies, such as BV, or checkpoint inhibitors, are increasingly being used as a bridge to transplant [4–10].

The role of BV as a bridge to allogeneic SCT has been examined in multiple small studies. Chen et al. analyzed the results in 19 patients who had received BV for relapsed/refractory cHL before reduced-intensity allogeneic SCT. The 1-year OS and PFS after allogeneic SCT were 100% and 92.3%, respectively, and the 2-year PFS was 59.3% [14].

Similarly impressive results were also obtained in a small study by Garciaz et al., with no NRM identified by 100 days and 100% OS at a median of 20 months in 12 patients with cHL who had undergone allogeneic SCT after BV salvage [15]. Therefore, BV appears to function as a highly effective bridge to allogeneic SCT for patients relapsing after autologous SCT.

Preliminary data from small series suggest that pre-transplant salvage therapy with BV might improve outcomes after allogeneic SCT for cHL [14, 16].

A report by the EBMT Lymphoma Working Party on 428 adult cHL patients treated between 2010 and 2014 (210 receiving BV prior to allogeneic SCT vs 218 who did not receive BV) indicated that exposure to BV prior to allogeneic SCT did not have a favorable impact on relapse rate, PFS, and

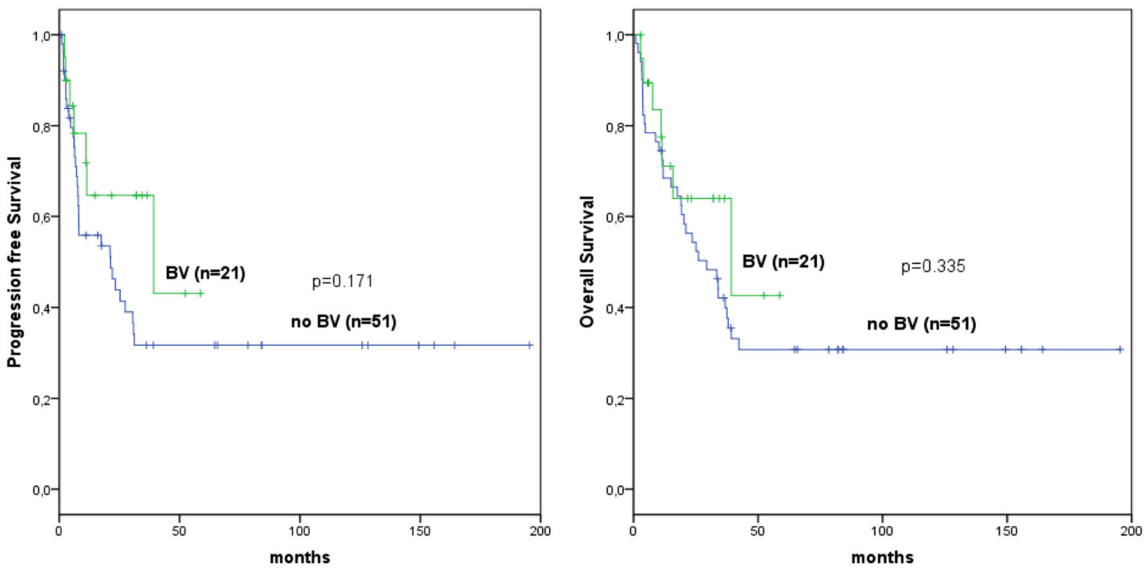

Fig. 1 Progression-free survival and overall survival according to prior brentuximab vedotin (BV) treatment

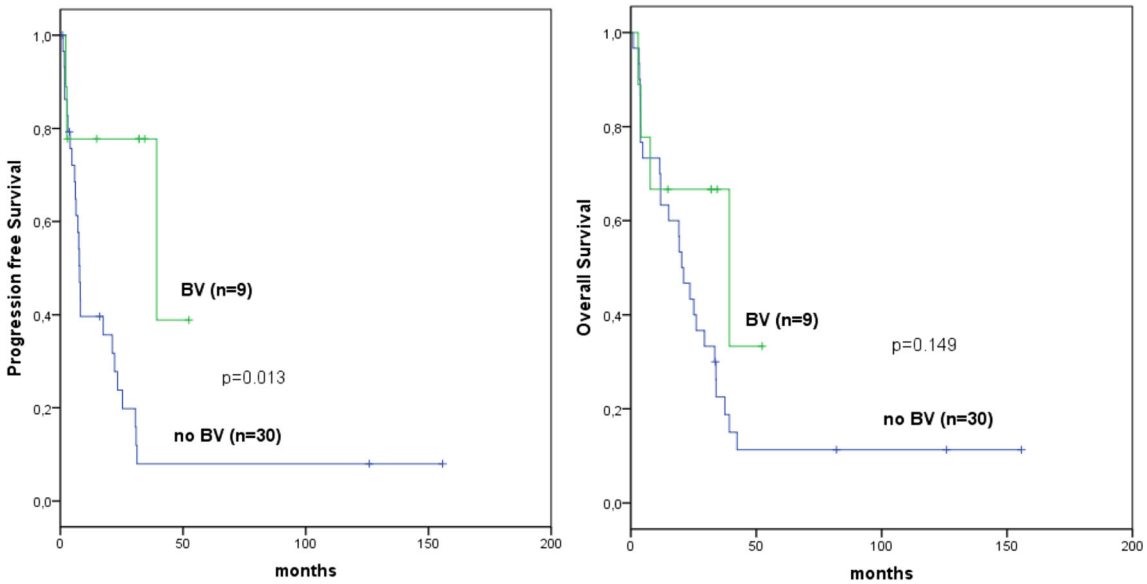

Fig. 2 Progression-free survival and overall survival of chemorefractory patients according to prior brentuximab vedotin (BV) treatment

OS. In that study, the authors hypothesized that BV may improve the allogeneic SCT outlook in otherwise refractory patients, helping them to achieve a more favorable disease status, and thus facilitating the success of the allotransplant [17].

Our study included a high-risk population: 89% of the patients had received a prior autologous SCT. We found that pre-allograft salvage therapy with BV did not significantly affect PFS or OS (Fig. 1).

Interestingly, we found that pre-allograft salvage therapy with BV decreased the cumulative incidence of chronic GVHD. This reduced incidence of chronic GVHD makes BV an attractive bridge to allogeneic SCT in comparison with checkpoint inhibitors, which may increase the post-transplant morbidity and the incidence of severe GVHD [18]. While there is no clear explanation for this BV-associated reduction of chronic GVHD, it could be due to the immunomodulatory effects of BV, which need to be further studied.

CD30 is a cell membrane protein of the tumor necrosis factor superfamily expressed on activated CD3+ T cells and upregulated in T cells when exposed to allogeneic antigens. In non pathologic conditions, CD30 expression is generally restricted to activated B and T lymphocytes and NK cells, showing lower levels in activated monocytes and eosinophils.

As shown in other members of the TNFR family, CD30 engagement may regulate T cell survival [19–21].

Malard et al. [22] reported that the absolute number of CD30+ lymphocytes is significantly higher in the dermal infiltrate of the skin in patients with acute GVHD, compared with those without, indicating that the accumulation of cytotoxic and activated CD30+ T cells reflected an activated immune status in the skin of the patients with acute GVHD. Chen et al. [23] showed that patients with acute GVHD have a higher percentage of CD30 expressing CD8+ T cells, with a particularly pronounced difference in the central memory subset (CD8+ CD45RO+ CD62L+).

For patients with refractory disease at the time of allogeneic SCT, the risk of subsequent relapse is substantial and alternative strategies need to be considered.

In this study, we further stratified patients with chemorefractory disease, highlighting that the survival of patients shown to be chemorefractory at the time of transplantation could improve with BV pretreatment. This increase in survival may be due to the arrival of a greater number of patients with responsive disease at the time of SCT, as previous authors have hypothesized, but also to a possible further immunomodulatory effect.

Novel agents such as BV and checkpoint inhibitors have truly changed the management of relapsed/refractory cHL. In the Checkmate 205 study, nivolumab yielded a 12 months OS of 95% [24], as compared to 78% reached with BV [4]. With these encouraging study results and new preliminary data, the hope is rising that these agents may soon change the frontline management and produce a real paradigm shift in treating cHL. We need to answer the question as to how many cycles are needed before we can safely stop checkpoint inhibitors. The cost of such treatment, currently approved until disease progression, is undoubtedly a major burden on the global healthcare system. However, the big unanswered question is whether this class of drugs can be curative. Although published checkpoint inhibitors data in cHL are lacking in such evidence, long-term data on new immune-therapy agents such as BV [25], demonstrating long-lasting remissions, and results of recent clinical studies with tremendous efficacy of checkpoint inhibitors in heavily pre-treated cHL patients, are raising our anticipations for the future of this new treatment option. Although the role of allogeneic transplantation after anti-PD1

treatment in a heavily pre-treated population with few treatment options remains to be seen, it is important to note that transplantation continues to be an option for these patients. At this stage, it is too early to draw any conclusions regarding the use of nivolumab as a bridge to allogeneic SCT.

In conclusion, despite the limits of the study (small numbers and some unbalance in subset analyses, as well as the extensive enrollment period including general improvements in SCT technology, heterogeneous treatments, and disease characteristics before alloSCT), we found that patients allografted for cHL after prior exposure to BV do not have a superior outcome after allogeneic SCT. However, chemorefractory patients pre-treated with BV prior to transplant have a better survival, implying that BV can improve the outlook after allogeneic SCT. The decrease in chronic GVHD is an interesting finding that needs to be further studied in the allogeneic SCT setting.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Sweetenham JW, Carella AM, Taghipou G, Cunningham D, Marcus R, Della Volpe A et al (1999) High-dose therapy and autologous stem-cell transplantation for adult patients with Hodgkin's disease who do not enter remission after induction chemotherapy: results in 175 patients reported to the European Group for Blood and Marrow Transplantation. J Clin Oncol 17:3101–3109
2. Gajewski JL, Phillips GL, Sobocinski KA, Armitage JO, Gale RP, Champlin RE, Herzig RH, Hurd DD, Jagannath S, Klein JP, Lazarus HM, McCarthy PL Jr, Pavlovsky S, Peterson FB, Rowlings PA, Russell JA, Silver SM, Vose JM, Wiernik PH, Bortin MM, Horowitz MM (1996) Bone marrow transplants from HLA-identical siblings in advanced Hodgkin's disease. J Clin Oncol 14:572–578
3. Visani G, Malerba L, Stefani PM, Capria S, Galieni P, Gaudio F, Specchia G, Meloni G, Gherlinzoni F, Giardini C, Falcioni S, Cuberli F, Gobbi M, Sarina B, Santoro A, Ferrara F, Rocchi M, Ocio EM, Caballero MD, Isidori A (2011) BeEAM (bendamustine, etoposide, cytarabine, melphalan) before autologous stem cell transplantation is safe and effective for resistant/relapsed lymphoma patients. Blood 118(12):3419–3425
4. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Ramchandren R, Bartlett NL, Cheson BD, de Vos S, Forero-Torres A, Moskowitz CH, Connors JM, Engert A, Larsen EK, Kennedy DA, Sievers EL, Chen R (2012) Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 30:2183–2189
5. Pellegrini C, Broccoli A, Pulsoni A, Rigacci L, Patti C, Gini G, Mannina D, Tani M, Rusconi C, Romano A, Vanazzi A, Botto B, Santoro A, Hoaus S, Rigolin GM, Musto P, Mazza P, Molica S, Corradini P, Fama A, Gaudio F, Merli M, Ronconi F, Gritti G, Vallisa D, Tosi P, Liberati AM, Pinto A, Pavone V, Gherlinzoni F, Bianchi MP, Volpetti S, Trentin L, Goldaniga MC, Bonfichi M, De Renzo A, Schiavotto C, Spina M, Carella AM, Stefoni V, Argnani L, Zinzani PL (2017) Italian real life experience with brentuximab vedotin: results of a large observational study on 234 relapsed/refractory Hodgkin's lymphoma. Oncotarget 8(53):91703–91710
6. Forero-Torres A, Fanale M, Advani R, Bartlett NL, Rosenblatt JD, Kennedy DA, Younes A (2012) Brentuximab vedotin in transplant-naive patients with relapsed or refractory hodgkin lymphoma: analysis of two phase I studies. Oncologist 17:1073–1080
7. Pavone V, Mele A, Carlino D, Specchia G, Gaudio F, Perrone T, Mazza P, Palazzo G, Guarini A, Loseto G, Eleonora P, Cascavilla N, Scalzulli P, Melpignano A, Quintana G, Di Renzo N, Tarantini G, Capalbo S (2018 Oct) Brentuximab vedotin as salvage treatment in Hodgkin lymphoma naïve transplant patients or failing ASCT: the real life experience of Rete Ematologica Pugliese (REP). Ann Hematol 97(10):1817–1824
8. Moskowitz CH, Nademanee A, Masszi T, Agura E, Holowiecki J, Abidi MH, Chen AI, Stiff P, Gianni AM, Carella A, Osmanov D, Bachanova V, Sweetenham J, Sureda A, Huebner D, Sievers EL, Chi A, Larsen EK, Hunder NN, Walewski J (2015) Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo controlled, phase 3 trial. Lancet. 385:1853–1862
9. Ansell SM, Lesokhin AM, Borrello I, Halwani A, Scott EC, Gutierrez M, Schuster SJ, Millenson MM, Cattry D, Freeman GJ, Rodig SJ, Chapuy B, Ligon AH, Zhu L, Grosso JF, Kim SY, Timmerman JM, Shipp MA, Armand P (2015) PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med 372:311–319
10. Armand P, Shipp MA, Ribrag V, Michot JM, Zinzani PL, Kuruvilla J, Snyder ES, Ricart AD, Balakumaran A, Rose S, Moskowitz CH (2016) Programmed death-1 blockade with pembrolizumab in patients with classical Hodgkin lymphoma after brentuximab vedotin failure. J Clin Oncol 34:3733–3739
11. Sureda A, Domenech E, Schmitz N et al (2014) The role of allogeneic stem cell transplantation in Hodgkin's lymphoma. Curr Treat Options in Oncol 15:238–247
12. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V, International Harmonization Project on Lymphoma (2007) Revised response criteria for malignant lymphoma. J Clin Oncol 25(5):579–586
13. Gaudio F, Mazza P, Carella AM, Mele A, Palazzo G, Pisapia G, Carluccio P, Pastore D, Cascavilla N, Specchia G, Pavone V (2019) Outcomes of reduced intensity conditioning allogeneic hematopoietic stem cell transplantation for Hodgkin lymphomas: a retrospective multicenter experience by the Rete Ematologica Pugliese (REP). Clin Lymphoma Myeloma Leuk 19(1):35–40
14. Chen R, Palmer JM, Thomas SH, Tsai NC, Farol L, Nademanee A, Forman SJ, Gopal AK (2012) Brentuximab vedotin enables successful reduced-intensity allogeneic hematopoietic cell transplantation in patients with relapsed or refractory Hodgkin lymphoma. Blood 119:6379–6381

15. Garciaz S, Coso D, Peyrade F, Fürst S, Duran S, Chetaille B, Brenot-Rossi I, Devillier R, Granata A, Blaise D, Bouabdallah R (2014) Brentuximab vedotin followed by allogeneic transplantation as salvage regimen in patients with relapsed and/or refractory Hodgkin's lymphoma. Hematol Oncol 32:187–191
16. Hegerova L, Cao Q, Lazaryan A, McClune BL, Weisdorf DJ, Brunstein CG, Bacha- nova V (2017) Improving outcomes after allogeneic hematopoietic cell transplantation for Hodgkin lymphoma in the brentuximab vedotin era. Bone Marrow Transplant 52: 697–703
17. Bazarbachi A, Boumendil A, Finel H, Mohty M, Castagna L, Peggs KS, Blaise D, Afanasyev B, Diez-Martin JL, Sierra J, Bloor A, Martinez C, Robinson S, Malladi R, El-Cheikh J, Corradini P, Montoto S, Dreger P, Sureda A (2018 Apr) Brentuximab vedotin prior to allogeneic stem cell transplantation in Hodgkin lymphoma: a report from the EBMT Lymphoma Working Party. Br J Haematol 181(1):86–96
18. Merryman RW, Kim HT, Zinzani PL, Carlo-Stella C, Ansell SM, Perales MA, Avigdor A, Halwani AS, Houot R, Marchand T, Dhedin N, Lescaut W, Thiebaut-Bertrand A, Francois S, Stamatoullas-Bastard A, Rohrlich PS, Labussiere Wallet H, Castagna L, Santoro A, Bachanova V, Bresler SC, Srivastava A, Kim H, Pesek E, Chammas M, Reynolds C, Ho VT, Antin JH, Ritz J, Soiffer RJ, Armand P (2017) Safety and efficacy of allogeneic hematopoietic stem cell transplant after PD-1 blockade in relapsed/ refractory lymphoma. Blood 129:1380–1388
19. Agrawal B, Reddish M, Longenecker BM (1996) CD30 expression on human CD8+ T cells isolated from peripheral blood lymphocytes of normal donors. J Immunol 157(8):3229–3234
20. Muta H, Boise LH, Fang L, Podack ER (2000) CD30 signals integrate expression of cytotoxic effector molecules, lymphocyte trafficking signals, and signals for proliferation and apoptosis. J Immunol 165:5105–5111
21. Chiarle R, Podda A, Prolla G, Gong J, Thorbecke GJ, Inghirami G (1999) CD30 in normal and neoplastic cells. Clin Immunol 90(2): 157–164
22. Malard F, Bossard C, Brissot E, Chevallier P, Guillaume T, Delaunay J, Mosnier JF, Mor- eau P, Gregoire M, Gaugler B, Mohty M (2013) Increased plasmacytoid dendritic cells and RORgammat-expressing immune effectors in cutaneous acute graft-versus-host disease. J Leukoc Biol 94:1337–1343
23. Chen YB, McDonough S, Hasserjian R, Chen H, Coughlin E, Illiano C, Park IS, Jagasia M, Spitzer TR, Cutler CS, Soiffer RJ, Ritz J (2012b) Expression of CD30 in patients with acute graft-versus-host disease. Blood 120:691–696
24. Armand P, Engert A, Younes A, Fanale M, Santoro A, Zinzani PL, Timmerman JM, Collins GP, Ramchandren R, Cohen JB, De Boer JP, Kuruvilla J, Savage KJ, Trneny M, Shipp MA, Kato K, Sumbul A, Farsaci B, Ansell SM (2018) Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II checkMate 205 trial. J Clin Oncol 36(14): 1428–1439
25. Chen R, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, Connors JM, Engert A, Larsen EK, Huebner D, Fong A, Younes A (2016 Sep 22) Five-year survival and durability results of brentuximab vedotin in patients with relapsed or refractory Hodgkin lymphoma. Blood. 128(12):1562–1566