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RESEARCH LETTER

Bendamustine supercharge plus brentuximab vedotin as early salvage therapy following failure to obtain complete metabolic remission after two cycles of adriamycin–bleomycin–vinblastine–dacarbazine for classic Hodgkin lymphoma in patients aged ≤ 60 years: Long-term efficacy results of a retrospective multicentre study

To the editor,

Treatment intensification with salvage therapy, high-dose chemotherapy (HDT) and autologous stem cell transplantation (ASCT) is the best course of action for patients ≤60 years with classic Hodgkin lymphoma (c-HL) failing to obtain complete metabolic remission (CMR) to adriamycin–bleomycin–vinblastine–dacarbazine (ABVD). However, its clinical impact in patients showing *interim* 2-deoxy-2[F-18] fluoro-D-glucose positron emission tomography (*i*-FDG-PET) positive scans after only two cycles remains to be confirmed.[1,2] In these patients with primary chemo-refractory illness, the prognosis is dismal with disease progression within 12 months from ASCT; the reported 2-year progression-free survival (PFS) reaches the rates of 28%–66% following conventional salvage regimens.[1,2] Thus, optimizing the results of salvage regimens before ASCT is still essential to provide the best chance of recovery for most patients with refractory c-HL.[1] The combination of bendamustine (B) at 90 mg/m^2 iv on days 1–2 and brentuximab vedotin (Bv) at 1.8 mg/kg iv on day 1 of a 21-day cycle has been investigated, and clinical trials with cohorts of refractory/relapsed patients showed a manageable toxicity profile and an overall response rate (ORR) of 80% (average CMR, 70%) following a median of four cycles.[3–5] Follow-up data tempered the expectations: pooled 2-year PFS rate of about 50%. Emerging in vitro data allowed the speculation that high-dose B, administered right after Bv, facilitated the anti-CD30–auristatin conjugates pharmacodynamics and thus targeted delivery of anticancer therapeutics.[6–8] Phase II and real-life studies in this setting presented convincing evidence that an increasing dosage of B held promising anticancer activity with no dose-limiting toxicity.[9–12] Thus, a compelling case is presented for using early treatment intensification with bendamustine supercharge (Bs) that maximizes the synergistic effects with Bv and raises the remission rates obtained with either drug in the pre-ASCT setting after failure of front-line ABVD. Therefore, we undertook a multicentre retrospective study involving large southern Italy tertiary centres with long-standing experience in HL cure: the Hematology Unit of the Federico II University, Oncology Unit of the Federico II University Medical School of Naples and Hematology Unit of the Antonio Cardarelli Hospital of National Importance in Naples, Italy.

We acquired consistent information about a selected population of patients aged ≥18 and ≤60 years with c-HL and positive FDG-PET scans following two courses of ABVD from 1 September 2013 to 1 September 2023 (view study design and inclusion criteria in the Data S1). The sequential combination (every 3 weeks) of Bv standard dose and Bs, named 'Bv + Bs$_{21}$' regimen, for four courses as early salvage treatment intensification (Bv + Bs$_{21}$ regimen and relative prophylaxis is shown in the Data S1 and in Figure S1) followed by HDT and ASCT was used as the routine first-line salvage regimen in the three hospital units for patients aged ≤60 years with c-HL and *i*-FDG-PET positivity.[9,12] The primary objective of the study was the 5-year PFS of Bv + Bs$_{21}$ regimen followed by HDT and ASCT in a selected population of high-risk c-HL adult patients who were primary refractory to ABVD, as timely identified by *i*-FDG-PET scans interpreted with the Deauville scale (DS) 5-point scoring system .[13] Secondary end-points were overall survival (OS), end-of-treatment (EoT) response and toxicity following the fourth cycle of Bv + Bs$_{21}$,[14] peripheral blood stem cell (PBSC) collection and bridge to transplant, and feasibility of the Bv + Bs$_{21}$ regimen (outcomes analysis in the Data S1). As routinely performed in the participating Institutions, all patients underwent PBSC collection after two Bv + Bs$_{21}$ courses. At any time beyond cycle 4, those who achieved at least a partial metabolic response (PMR) at FDG-PET scans according to the Lugano criteria proceeded to ASCT (Figure S1). Statistical analysis details are in the Data S1.

On initial review of the medical records or database of the three haematology units, 50 consecutive patients ≤60 years with c-HL and no response/stable disease or progression after two cycles of front-line ABVD were identified among 330 newly diagnosed c-HL patients (≥18 years aged) treated from 1 September 2013 to 1 September 2023; 8% were excluded due to other salvage regimens and/or insufficient information. The remaining 46 patients constituted the entire population included in the final assessment; a diagram in Figure 1 summarizes the flow of patients throughout the study. Patients' characteristics are detailed in Table 1. All patients had positive FDG-PET with DS scores of 4 ($n=12$) or 5 ($n=34$) and were scheduled to receive four courses of Bv + Bs_{21} as 3-day outpatient iv infusions of 1.8 mg/kg Bv on day 1 and of B at a fixed dose of 120 mg/m^2/day (days 2 and 3), and all received routine prophylaxis (Figure S1). Regarding Bv + Bs_{21} regimen feasibility, all patients received more than 85% of the planned treatment: the median dose intensity was 100% (range: 88.6–102.4%) for Bv and 100% (range: 88.7%–102.4%) for B. After four cycles of Bv + Bs_{21}, all patients ($n=46$) were assessable for disease response (Table S1). The ORR was 100% with 42 patients obtaining CMR (91%) and four obtaining PMR (9%). The full courses of the salvage regimen served as a bridge to ASCT in 42 patients (91%) while four patients (9%) did not proceed to ASCT due to patient preference (Figure 1). All patients had successful engraftment. During post-transplant follow-up, five patients relapsed; the four patients refusing the procedure were in CMR after Bv + Bs_{21} but then 50% relapsed. Four patients died during post-salvage follow-up at a median time of 20 months (see Data S1). The 5-year PFS rate at a median follow-up of 60 months (range: 6–132 months) from Bv + Bs_{21} administration for the overall population was 82% (95% confidence interval [C.I.], 0.91–0.65; Figure 2). With a median follow-up of 60 months (range: 6–132 months) from Bv + Bs_{21} administration, the 5-year OS rate was 90% (95%

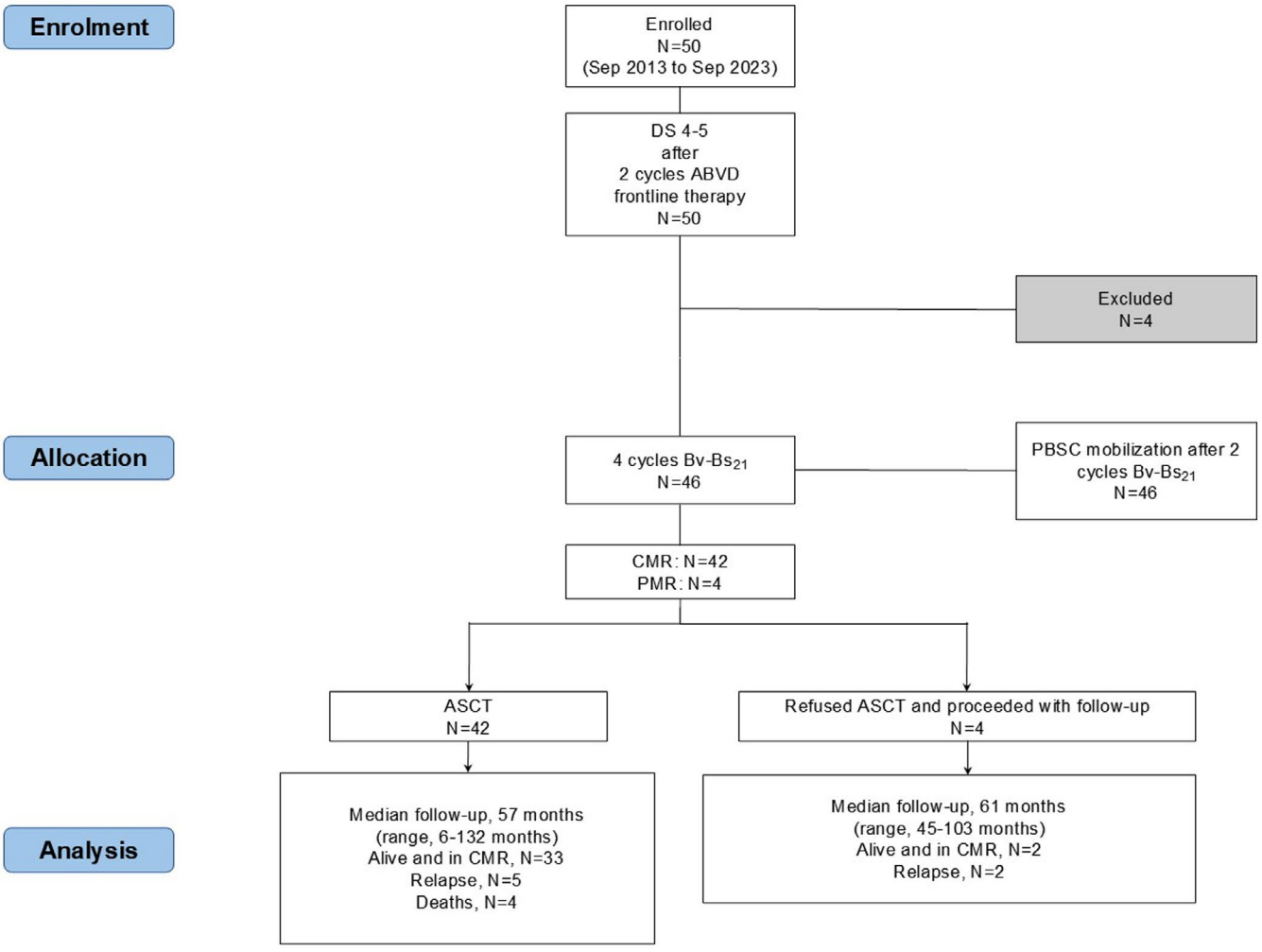


FIGURE 1 Flow chart of the participants throughout the study. ASCT, autologous stem cell transplant; Bs, bendamustin supercharge at 120 mg/m^2 i.v. on days 2 and 3 of the 3-week cycle; Bv, brentuximab vedotin at 1.8 mg/kg i.v. on day 1 of the 3-week cycle; CMR, complete metabolic response; DS, Deauville scale score of the FDG-PET at 30 days after ASCT, according to Lugano criteria; PBSC, peripheral blood stem cell; PMR, partial metabolic response. The 8% were excluded due to other salvage regimens (2 patients received IGEV and 1 patient received DHAP) and insufficient information (1 patient). [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Patients' characteristics at Bv + Bs_{21} start.

	n	%
Total population	46	100
Age, median (range)	37 (19–60)	
Male sex	24	52
Characteristics of disease		
Histological subtype		
Nodular sclerosis	40	87
Mixed cellularity	5	11
Lymphocyte-rich	1	2
Ann Arbor/Cotswold staging		
I–II	11	24
III–IV	35	76
≥3 nodal sites involved	18	39
Extranodal involvement	15	32
Mediastinal bulky	18	39
Bone marrow involvement	2	4
ESR >50	11	24
B symptoms	24	52
Early unfavourable disease	11	24
IPS score		
1–4	20	43
5–7	15	32
Front-line ABVD		
N cycles received = 2	46	100
FDG PET after two courses of front-line ABVD		
DS 4	12	26
DS 5	34	74

Note: Values are *n* (%) unless otherwise specified. FDG-PET results were reported according to the DS score and were assigned as follows: score 4, uptake moderately >liver (up to twice the maximal standardized uptake value [SUVmax] in a large region of normal liver); score 5, uptake markedly increased than liver (more than twice the SUVmax in a large region of normal liver) and/or new lesions. Ann Arbor staging: Stage I defined as involvement of a single lymph nodal site or a single extralymphatic organ or site; stage II: involvement of two or more lymph node sites on the same side of the diaphragm or localized involvement of an extralymphatic organ or site; stage III, defined as multiple lymph node sites on both sides of the diaphragm; stage IV, defined as multiple extra-nodal sites or lymph nodes and extra-nodal disease; B symptoms: fever, weight loss >10% in the last 6 months, nocturnal sweat; Mediastinal bulky: defined as lymph node mass with long axis >7.5 cm.

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; DS, Deauville score; ESR, erythrocyte sedimentation rate; IPS, International prognostic scoring system, stratifies patients with advanced stage classical Hodgkin lymphoma into six prognostic groups.

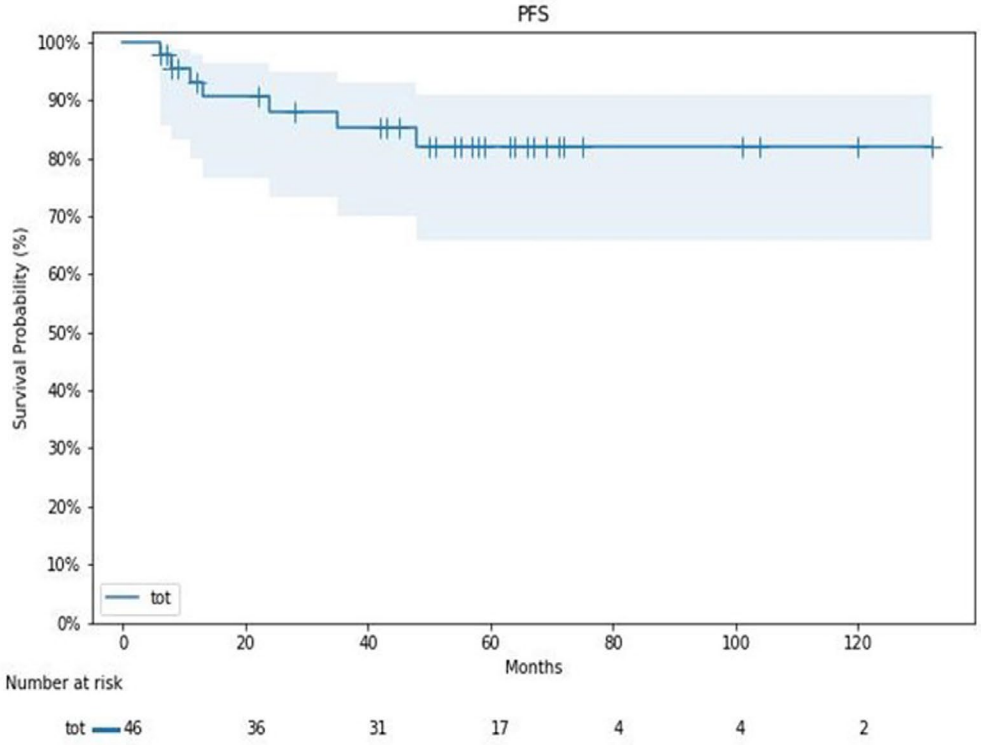
C.I, 0.96–0.76) for the entire population analysed (Figure 2). The survival analysis was stratified according to the FDG-PET DS pre-salvage treatment score results and the analysis findings are reported in Figures S2 and S3 and in the Data S1. PBSC collection, in terms of percentage of success and amount of PBSC, was evaluated for all patients ($n = 46$). All patients underwent PBSC mobilization after two courses of Bv + Bs_{21} (details in Table S1). Both mobilization and harvest were successful in all cases, with a median CD34+ cells/kg yield of 4.1×10^6 (range: $1.9–5.1 \times 10^6$).

Regarding treatment toxicity, the most common haematological adverse event reported was febrile neutropenia involving five patients (11%); CMV reactivation with viraemia was recorded in five patients successfully treated with valganciclovir pre-emptive therapy. Notably, due to the specific premedication (Figure S1) against acute toxicity during the iv administration of Bv + Bs_{21}, serious infusion-related reactions were reported only for three patients (6%) during the first cycle of administration (Table S2). Overall, a total of five patients (11%) temporarily discontinued therapy due to treatment-related adverse events. In particular, at least one Bv and/or Bs dose modification in terms of delays ($n = 3$) or reductions ($n = 2$) was recorded.

To the best of our knowledge, this is the first study to present long-term data of the clinical effectiveness of Bv + Bs_{21} combination as a very early first salvage regimen in a selected population of relatively young and fit patients with high-risk HL (primary refractory to ABVD), considering as the primary end-point the 5-year PFS. In comparison with the standard scheme,[3–5] we have employed the increased B dose (120 mg/m^2) adjusting the timing of administration (after Bv), as already reported.[9,12] The regimen was promptly employed in these patients with *i*-FDG-PET positive scans after only two cycles of ABVD characterized by very poor prognostic factors for primary refractory disease which strongly correlates with the response to salvage therapy and survival.[15] Conventional salvage chemotherapy shows no significant differences regarding the outcome in the same subset of high-risk patients: PFS—40%–50% and OS—60%–70% at 5 years following ASCT.[16–18]

Our survival results compare favourably with data reported from studies with similar treatment schemes in primary refractory/relapsed patients: 3-year OS and PFS of 92% and 60.3%, respectively, for La Casce et al.[7] and 3-year OS and PFS of 88.1% and 67%, respectively, for Broccoli et al.[19] (both studies with relatively short median follow-up). In our study, Bv + Bs_{21} proved highly effective, resulting in significant rates of overall and complete response (100% ORR with CMR of 91%) and an overall 5-year PFS of 82% and OS of 90% with a median follow-up of 60 months was reported. Moreover, a substantial percentage of patients (91%) received ASCT after the Bv + Bs_{21} regimen. This encouraging data were largely due to the sustained response and lack of disease progression during the pre-transplantation period. Thus, this salvage regimen has a twofold advantage: initially reducing tumour burden and subsequently prolonging the duration of metabolic response. Indeed, the regimen's safety profile was notable, but a comprehensive approach to primary prophylaxis with broad-spectrum supportive care and close clinical and laboratory monitoring, especially for CMV-DNA, is crucial.[9] Bone marrow toxicity that could potentially compromise subsequent stem cell mobilization was minimal, and this was corroborated by successful mobilization and harvest procedures in all patients.

Our study has limitations that must be pointed out: the small sample size and retrospective design that limit the power in assessing adverse events, and lack of data regarding



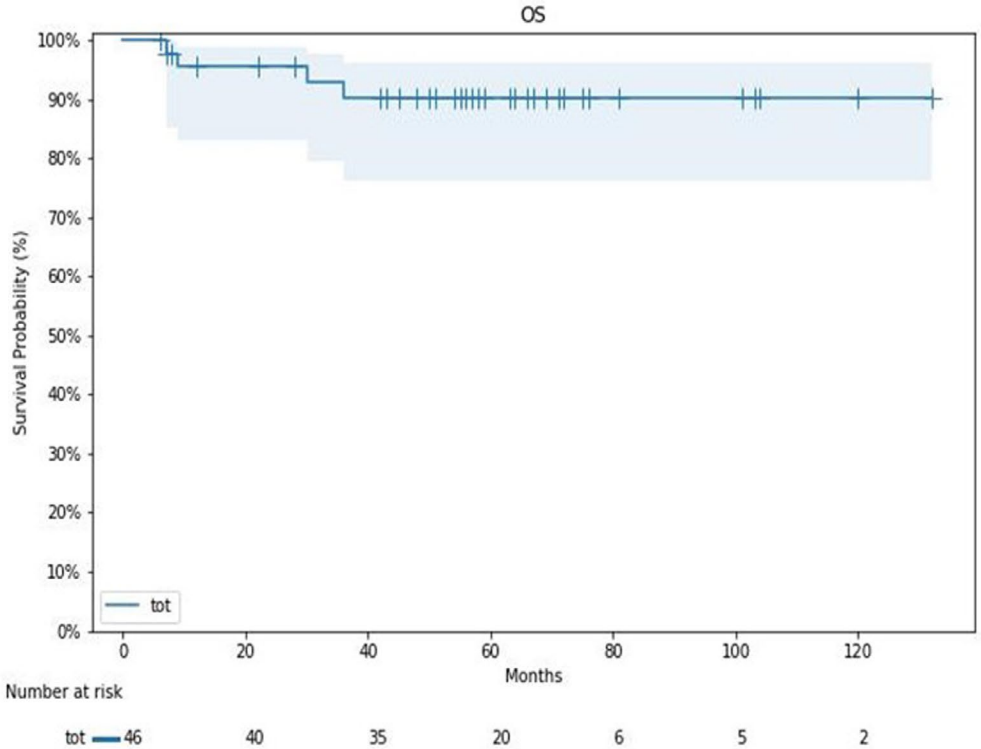


FIGURE 2 Survival curves: Progression-free survival and overall survival of the entire cohort. [Colour figure can be viewed at wileyonlinelibrary.com]

tissue biopsy repetition for patients with DS5 at *i*-FDG-PET. In addition, both Bv and B were used as off-label due to their very early employment (after only 2 ABVD cycles) in contrast with AIFA (Italian Agency of the drug) and EMA (European Medicine Agency) regulations.[20] Finally, other studies are needed to demonstrate leverage from therapy with $Bv + Bs_{21}$ in patients with R/R cHL and aged >60 years.

The potential benefits of $Bv + Bs_{21}$ followed by HDT and ASCT strategy, contrasting with the convention of delaying salvage therapy until disease progression/resistance to the full induction therapy, include improved long-term outcomes due to reduced resistance to salvage therapy and a potentially lower incidence of both early and late adverse events. In conclusion, this is a proof-of-concept study that needs further validation from large prospective phase II studies.

FUNDING INFORMATION
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KEYWORDS
autologous haematopoietic stem cell transplantation, bendamustine supercharge, brentuximab vedotin, refractory Hodgkin lymphoma

AUTHOR CONTRIBUTIONS
C. Giordano and M. Picardi designed the research; C. Giordano performed the research and wrote the paper; A. Vincenzi, L. De Fazio, M. Lamagna, R. Reina, A. Scarpa, A. Lombardi, E. Vigliar, G. Troncone, M. Mascolo, C. Mainolfi, V. Damiano, R. Bianco, F. Trastulli, F. Ronconi, and A. Salemme collected data; C. Giordano and N. Pugliese analysed data; F. Pane and M. Picardi performed the final revision of the manuscript.

CONFLICT OF INTEREST STATEMENT
Authors have no relevant financial conflicts of interest to declare.

ETHICS STATEMENT
All necessary approvals were obtained from our ethics committee, and the study was undertaken in accordance with the Declaration of Helsinki.

CLINICAL TRIAL REGISTRATION
All necessary approvals were obtained from our ethics committee (approval protocol number: 92/2024) and ClinicalTrials.gov (number, NCT06295211).

PATIENT CONSENT STATEMENT
All patients provided written informed consent for personal data analysis for research purposes.

DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES
1. Mariotti J, Ricci F, Giordano L, Taurino D, Sarina B, De Philippis C, et al. Outcome of high-dose chemotherapy followed by autologous stem cell transplantation in relapsed/refractory Hodgkin lymphoma after different numbers of salvage regimens. Cells. 2024;13(2):118. https://doi.org/10.3390/cells13020118
2. Moskowitz AJ, Perales MA, Kewalramani T, Yahalom J, Castro-Malaspina H, Zhang Z, et al. Outcomes for patients who fail high dose chemoradiotherapy and autologous stem cell rescue for relapsed and primary refractory Hodgkin lymphoma. Br J Haematol. 2009;146(2):158–63. https://doi.org/10.1111/j.1365-2141.2009.07727.x
3. O'Connor OA, Lue JK, Sawas A, Amengual JE, Deng C, Kalac M, et al. Brentuximab vedotin plus bendamustine in relapsed or refractory

Hodgkin's lymphoma: an international, multicentre, single-arm, phase 1-2 trial. Lancet Oncol. 2018;19(2):257–66.
4. Kalac M, Lue JK, Lichtenstein E, Turenne I, Rojas C, Amengual JE, et al. Brentuximab vedotin and bendamustine produce high complete response rates in patients with chemotherapy refractory Hodgkin lymphoma. Br J Haematol. 2018;180(5):757–60.
5. LaCasce AS, Bociek RG, Sawas A, Caimi P, Agura E, Matous J, et al. Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood. 2018;132(1):40–8. https://doi.org/10.1182/blood-2017-11-815183
6. Sutherland MS, Sanderson RJ, Gordon KA, Andreyka J, Cerveny CG, Yu C, et al. Lysosomal trafficking and cysteine protease metabolism confer target-specific cytotoxicity by peptide-linked anti-CD30-auristatin conjugates. J Biol Chem. 2006;281(15):10540–47. https://doi.org/10.1074/jbc.M510026200
7. De Filippi R, Cillo M, Crisci S, Mele S, Zanotta S, De Monaco A, et al. Continuous exposure to bendamustine (BDM) results in stable up-regulation of CD30 and increased sensitivity to brentuximab vedotin (BV) in tumor cells of Hodgkin lymphoma (HL) [abstract]. Blood. 2015;126(23):2479.
8. Beeharry N, Rattner JB, Bellacosa A, Smith MR, Yen TJ. Dose dependent effects on cell cycle checkpoints and DNA repair by bendamustine. PLoS One. 2012;7(6):e40342.
9. Picardi M, Della Pepa R, Giordano C, Pugliese N, Mortaruolo C, Trastulli F, et al. Brentuximab vedotin followed by bendamustine supercharge for refractory or relapsed Hodgkin lymphoma. Blood Adv. 2019;3(9):1546–52. https://doi.org/10.1182/bloodadvances.2019000123
10. Corazzelli G, Angrilli F, D'Arco A, Ferrara F, Musto P, Guarini A, et al. Efficacy and safety of bendamustine for the treatment of patients with recurring Hodgkin lymphoma. Br J Haematol. 2013;160(2):207–15. https://doi.org/10.1111/bjh.12120
11. Moskowitz AJ, Hamlin PA Jr, Perales MA, Gerecitano J, Horwitz SM, Matasar MJ, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol. 2013;31(4):456. https://doi.org/10.1200/JCO.2012.45.3308
12. Picardi M, Giordano C. Comment on "combining brentuximab vedotin with dexamethasone, high-dose cytarabine and cisplatin as salvage treatment in relapsed or refractory Hodgkin lymphoma: the phase II HOVON/LLPC transplant BRaVE study". Haematologica. 2021;106(4):1226–7.
13. Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059–68.
14. Common Terminology Criteria for Adverse Events (CTCAE) Version 5. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.
15. Moskowitz AJ, Schöder H, Gavane S, Thoren KL, Fleisher M, Yahalom J, et al. Prognostic significance of baseline metabolic tumor volume in relapsed and refractory Hodgkin lymphoma. Blood. 2017;130(20):2196–203.
16. Josting A, Müller H, Borchmann P, Baars JW, Metzner B, Döhner H, et al. Dose intensity of chemotherapy in patients with relapsed Hodgkin's lymphoma. J Clin Oncol. 2010;28(34):5074–80. https://doi.org/10.1200/JCO.2010.30.5771
17. Labrador J, Cabrero-Calvo M, Pérez-López E, Mateos MV, Vázquez L, Caballero MD, et al. ESHAP as salvage therapy for relapsed or refractory Hodgkin's lymphoma. Ann Hematol. 2014;93(10):1745–53. https://doi.org/10.1007/s00277-014-2114-0
18. Santoro A, Mazza R, Pulsoni A, Re A, Bonfichi M, Zilioli VR, et al. Five-year results of the BEGEV salvage regimen in relapsed/refractory classical Hodgkin lymphoma. Blood Adv. 2020;4(1):136–40. https://doi.org/10.1182/bloodadvances.2019000984
19. Broccoli A, Argnani L, Botto B, Corradini P, Pinto A, Re A, et al. First salvage treatment with bendamustine and brentuximab vedotin in Hodgkin lymphoma: a phase 2 study of the Fondazione Italiana Linfomi. Blood Cancer J. 2019;9(12):100. https://doi.org/10.1038/s41408-019-0265-x
20. Gravanis I, Tzogani K, van Hennik P, de Graeff P, Schmitt P, Mueller-Berghaus J, et al. The European medicines agency review of brentuximab Vedotin (Adcetris) for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma or systemic anaplastic large cell lymphoma: summary of the scientific assessment of the Committee for Medicinal Products for human use. Oncologist. 2016;21(1):102–9. https://doi.org/10.1634/theoncologist.2015-0276

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