haematologica
Journal of the Ferrata Storti Foundation

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Received: July 1, 2026.
Accepted: July 1, 2026.

Citation: Jean Galtier, Gaetan Basile and Krimo Bouabdallah. Response to comment on: "Brentuximab-vedotin and bendamustine for relapsed or refractory Hodgkin lymphoma: the LYSA real-world experience".
Haematologica. 2026 July 9. doi: 10.3324/haematol.2026.301477 [Epub ahead of print]

Response to comment on: "Brentuximab-vedotin and bendamustine for relapsed or refractory Hodgkin lymphoma: the LYSA real-world experience"

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Author contributions: JG, GB and KB wrote the manuscript and are accountable for all aspects of the work.

Disclosures: JG reports honoraria and travel expenses from Takeda. KB reports honoraria, travel expenses and consultancy from Takeda. GB reports no disclosure.

The study commented here received no funding.

To the editor,

We read with great interest the Comment by C. Giordano and M. Picardi which insightfully discussed our findings in light of the current state of the art in the management of relapsed or refractory Hodgkin lymphoma (R/R HL)[1]. Giordano and Picardi notably highlighted the extremely good outcome associated with Bv + Bendamustine "supercharge" (B+Bs21) in a real-life cohort of 46 consecutive patients treated over a 10-year period in Italy[2] and published during the early steps of our manuscript preparation. This regimen's rationale derives from *in vitro* data suggesting that bendamustine high dosage may enhance Bv activity, and B+Bs21 indeed produced very high rate of complete response (CR, 91%) and sustained progression-free survival (PFS, 82% at 5 years) in patients with positive interim PET (iPET+) after 2 cycles of frontline ABVD. These results compare favorably not only with our own real-life data[3], but also with those of the pivotal phase II studies from LaCasce et al[4] and Broccoli et al[5]. and other smaller retrospective studies. Moreover, the toxicity pattern of B+Bs21 was favorable with a minimal impact on stem cells collection.

While these results are certainly of interest, direct comparison between B+Bs21 cohort and our cohort or others should be made with caution. The B+Bs21 regimen was administered in early or advanced stage patients not achieving complete metabolic response after 2 cycles of first line ABVD, i.e patients with Deauville score 4 or 5 (DS4/5). Such patients may already experience satisfactory survival with conventional practices. The 3y-PFS of patients not achieving CMR at iPET following frontline ABVD treatment reached ≈ 60 – 65% after BEACOPP escalation in the SWOG S0816[6], HD 0607[7] and RATHL[8] trials, and the superiority of this strategy over ABVD continuation has not been prospectively demonstrated in advanced diseases. HD 0607 notably showed that the outcomes of these iPET+ patients largely depend on DS, DS4 and DS5 being associated with 3y-PFS of 73% and 35%, respectively – the latter group being more likely enriched in *bona fide* refractory cases. Outcomes of patients with early stage iPET+ disease is even better, with 5y PFS reaching 77.4 – 90.6% in the H10 trial[9]. These data clearly indicate that any strategy aiming to escalate patients not reaching CMR at interim

evaluation after frontline ABVD has the purpose to enhance a cure rate which may already be significant.

On another hand our cohort focused on R/R HL in need for salvage therapy, most of them presenting with high-risk clinical features. Among the 150 patients deemed eligible for transplantation, 56 (37%) were in 3rd line or more, 37 (24.6%) were in first relapse, and 57 (38%) were considered refractory to their first line, either due to stable or progressive disease after completion of frontline therapy for half of them, either due to iPET results deemed too poor for BEACOPP escalation or continuation as per RATHL or AHL2011[10] strategies (that were standard practice in France) in the other half of them. Our cohort is therefore a mixture of various patterns of R/R diseases and not merely of insufficient responders after short ABVD exposure. The potential superiority of B+Bs21 over conventional Bv-Bendamustine (B2) regimen warrants to be assessed in a homogeneous disease context and through a rigorous methodological framework and would ideally require prospective validation.

We also found it noteworthy that Giordano and Picardi pointed out the absence of stem cells collection failure observed after B+Bs21 regimen. While the rate of collection failure was also very low (0- 5%) in the aforementioned pivotal phase II studies, the main practice within LYSA centers reported in our study was to harvest stem cell before starting B2 – for a significant rate of failure has been observed in the small subset of patients in which harvest was attempted after treatment (4 out of 18 patients). We acknowledge that this high rate of failure may have been another consequence of the enrichment in heavily treated patients in our cohort, as well as the subject of a sampling fluctuation. As a matter of fact, these 4 patients received high dose of alkylating agent (through prior BEACOPP exposure and/or more than one prior line of treatment) that likely contributed to the collection failure. While data from Giordano et al. are reassuring, their observation after short ABVD exposure may not be generalizable to more heavily treated patients, and we believe that cautions must be taken in a case-per-case basis – notably in patients exposed to high cumulative dose of cytotoxic agents for whom mobilization prior to bendamustine treatment may be considered if possible.

Altogether with those of Giordano et al. and others, our data contribute to refine the understanding of B2 efficacy and toxicity patterns in R/R HL. Academic effort aiming to address the best dosing and scheduling of Bv-based regimen in patients failing to modern checkpoint inhibitor-based frontline therapy should now be pursued.

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