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

We read with great interest the Comment by Giordano and Picardi which discussed with insight our findings in the light of the current state-of-the-art 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] the results from which were published during the early stages of our manuscript preparation. This regimen's rationale derives from *in vitro* data suggesting that the high bendamustine dosage may enhance Bv activity, and B+Bs21 did, indeed, produce very high rates of complete response (CR: 91%) and sustained progression-free survival (PFS: 82% at 5 years) in patients with positive interim positron emission tomography (iPET$^+$) after 2 cycles of front-line ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine). 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 minimal impact on stem cell collection.

While these results are certainly of interest, any direct comparison between the B+Bs21 cohort and our own (or that of others) should be made with caution. The B+Bs21 regimen was administered in early or advanced stage patients who had not achieved complete metabolic response (CMR) after 2 cycles of front-line ABVD, i.e., patients with Deauville score 4 or 5 (DS4/5). Such patients may already experience satisfactory survival with conventional practices. The 3 year-PFS of patients not achieving CMR at iPET following front-line ABVD treatment reached approximately 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. Notably, the HD 0607 trial showed that the outcomes of these iPET$^+$ patients largely depend on DS; DS4 and DS5 is associated with 3 year-PFS of 73% and 35%, respectively, the DS5 group being more likely enriched in *bona fide* refractory cases. Outcomes of patients with early stage iPET$^+$ disease are even better, with 5 year-PFS in the H10 trial reaching 77.4-90.6%.[9] These data clearly indicate that the purpose of any strategy aiming to escalate patients not reaching CMR at interim evaluation after front-line ABVD is to enhance a cure rate which may already be significant.

On the other hand, our cohort focused on R/R HL in need of salvage therapy, most of whom presented with high-risk clinical features. Among the 150 patients deemed eligible for transplantation, 56 (37%) were in third-line or more, 37 (24.6%) were in first relapse, and 57 (38%) were considered refractory to their first-line treatment. This last group were considered refractory either due to stable or progressive disease after completion of front-line therapy (which was the case for half of them) or due to iPET results that were considered to be too poor for BEACOPP escalation or continuation as per the RATHL or the AHL2011[10] protocols (which was the case for the other half). (It should be remembered that BEACOPP escalation or continuation is standard practice in France for this patient population.) Our cohort is, therefore, a mixture of various patterns of R/R diseases and not merely of patients who did not respond sufficiently to the short ABVD exposure. The potential superiority of B+Bs21 over the conventional Bv-Bendamustine (B2) regimen warrants assessment in the context of homogeneous disease characteristics and through a rigorous methodological framework. Ideally, this would undergo subsequent prospective validation.

We also found it worthy of note that Giordano and Picardi pointed out that no stem cell collection failure was observed after the 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 in LYSA centers, which was reported in our study, was to harvest stem cells before starting B2. This is because a significant rate of failure had been observed in the small subset of patients in which harvesting was attempted after treatment (4 out of 18 patients). We acknowledge that this high rate of failure may have been another consequence of enrichment in heavily treated patients in our cohort, and possible sampling fluctuation. As a matter of fact, these 4 patients received high doses 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. We believe that stem cell collection strategy should be considered on a case-by-case basis, particularly in patients exposed to a high cumulative dose of cytotoxic agents for whom the possibility of mobilization prior to bendamustine treatment may be considered.

Our data, together with those of Giordano *et al.* and others, contribute to refining the understanding of B2 efficacy and toxicity patterns in R/R HL. Academic efforts to address the

question of the best dosing and scheduling of the Bv-based regimen in those patients failing modern checkpoint inhibitor-based front-line therapy should now be actively pursued.

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Contributions

All authors wrote the manuscript and are accountable for all aspects of the work.

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