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Brentuximab Vedotin and Chemotherapy in Relapsed/Refractory Hodgkin Lymphoma: a Propensity Score Matched Analysis

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Abstract:
Several single-arm studies have explored the inclusion of brentuximab vedotin (BV) in salvage chemotherapy followed by autologous stem-cell transplantation (ASCT) for relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL). However, no head-to-head comparisons with standard salvage chemotherapy have been performed. This study presents a propensity score-matched analysis encompassing individual patient data from ten clinical trials to evaluate the impact of BV in transplant-eligible R/R cHL patients. We included 768 patients, of whom 386 were treated with BV +/- chemotherapy (BV-cohort), while 382 received chemotherapy alone (chemo-cohort). Propensity score matching resulted in balanced cohorts of 240 patients each. No significant differences were observed in pre-ASCT complete metabolic response (CMR) rates (p=0.69) or progression free survival (PFS) (p=0.14) between the BV- and chemo-cohorts. However, patients with relapsed disease had a significantly better 3-year PFS of 80% versus 70% in the BV- versus chemo-cohort (p=0.02), while there was no difference for primary refractory patients (56% versus 62%, respectively; p=0.67). Patients with stage IV disease achieved a significantly better 3-year PFS in the BV-cohort (p=0.015). Post-ASCT PFS was comparable for patients achieving a CMR after BV monotherapy and those receiving BV followed by sequential chemotherapy (p=0.24). While 3-year overall survival was higher in the BV-cohort (92% versus 80%, p<0.001, respectively), this is likely attributed to the use of other novel therapies in later lines for patients experiencing progression, given that studies in the BV-cohort were conducted more recently. In conclusion, BV +/- salvage chemotherapy appears to enhance PFS in relapsed but not primary refractory cHL patients.

Conflict of interest: COI declared - see note

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Data sharing

Researchers may request access to certain de-identified data and related study documents by contacting the corresponding author.

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JD and MJK designed the study. All authors collected the data. FdW and JD performed the database harmonization. HS performed the PET revision. JD performed the statistical analysis

under supervision of BAH. JD and FdW drafted the manuscript with contributions from all authors. All authors interpreted the data, read, commented on, and approved the final version of the manuscript.

CONFLICT OF INTEREST

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ABSTRACT: (250 of max 250 words)

Several single-arm studies have explored the inclusion of brentuximab vedotin (BV) in salvage chemotherapy followed by autologous stem-cell transplantation (ASCT) for relapsed/refractory (R/R) classical Hodgkin lymphoma (cHL). However, no head-to-head comparisons with standard salvage chemotherapy have been performed. This study presents a propensity score-matched analysis encompassing individual patient data from ten clinical trials to evaluate the impact of BV in transplant-eligible R/R cHL patients. We included 768 patients, of whom 386 were treated with BV +/- chemotherapy (BV-cohort), while 382 received chemotherapy alone (chemo-cohort). Propensity score matching resulted in balanced cohorts of 240 patients each. No significant differences were observed in pre-ASCT complete metabolic response (CMR) rates (p=0.69) or progression free survival (PFS) (p=0.14) between the BV- and chemo-cohorts. However, patients with relapsed disease had a significantly better 3-year PFS of 80% *versus* 70%

in the BV- *versus* chemo-cohort (p=0.02), while there was no difference for primary refractory patients (56% *versus* 62%, respectively; p=0.67). Patients with stage IV disease achieved a significantly better 3-year PFS in the BV-cohort (p=0.015). Post-ASCT PFS was comparable for patients achieving a CMR after BV monotherapy and those receiving BV followed by sequential chemotherapy (p=0.24). While 3-year overall survival was higher in the BV-cohort (92% *versus* 80%, p<0.001, respectively), this is likely attributed to the use of other novel therapies in later lines for patients experiencing progression, given that studies in the BV-cohort were conducted more recently. In conclusion, BV +/- salvage chemotherapy appears to enhance PFS in relapsed but not primary refractory cHL patients.

KEY POINTS (max 140 characters)

- BV +/- chemotherapy does not increase CMR rates or PFS in R/R cHL, but seems to increase PFS in patients with relapsed or stage IV disease
- Sequential treatment with BV and chemotherapy is feasible and could spare salvage chemotherapy in a subset of fast responding patients

INTRODUCTION

For the past 30 years, standard treatment of patients with classical Hodgkin lymphoma (cHL) who are primary refractory or relapse (R/R) after first-line (primary) treatment, has been to test for chemosensitivity with salvage chemotherapy and, upon response, to treat with myeloablative high-dose chemotherapy (HDCT) followed by autologous stem-cell transplantation (ASCT).[1-3] With this strategy about 70-80% of patients respond to salvage chemotherapy of whom approximately 60% achieve a complete metabolic response (CMR) based on a negative ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scan prior to ASCT.[1,4-6] However, 30-40% of patients will relapse within 5 years after ASCT and subsequently have a poor prognosis.[1,7] Importantly, it has been shown that patients who achieve a CMR pre-ASCT have a better prognosis with long-term post-ASCT progression free survival (PFS) of approximately 70-80%.[1,4,8]

In the past decade, new targeted treatment options such as brentuximab vedotin (BV) and checkpoint inhibitors have become available for patients with R/R cHL.[9-11] BV is an antibody-drug conjugate composed of an anti-CD30 monoclonal antibody with a cytotoxic payload of

monomethyl auristatin E (MMAE).[12] In the first-line setting, BV in combination with adriamycin, vinblastine and dacarbazine (BV-AVD) has been shown to improve PFS and overall survival (OS) in advanced stage patients compared to standard adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).[13,14] In the R/R setting, several phase II single arm clinical trials have investigated BV in combination with concomitant or sequential chemotherapy followed by ASCT.[15-24] These trials showed a high CMR rate prior to ASCT, and PFS and OS appear to be higher when compared to historical controls.[25] However, no randomized controlled trials (RCT) investigating the addition of BV to salvage chemotherapy compared to chemotherapy alone in R/R cHL have been published to this date. An individual patient-data analysis could provide more power for assessing the effect of novel treatments, and can also detect interactions between outcome parameters and patient characteristics outcomes, compared to standard meta-analyses.

Therefore, we aimed to perform a large, individual patient data analysis to investigate the effect of BV addition to salvage chemotherapy versus chemotherapy alone on pre-ASCT PET response, PFS and OS in patients with transplant-eligible R/R cHL.

METHODS

Literature search and data collection

We performed a literature search on PubMed and clinicaltrials.gov to identify clinical trials investigating BV in combination with salvage chemotherapy (BV-cohort), or salvage chemotherapy alone (chemo-cohort) followed by ASCT in transplant-eligible cHL patients with a first relapse or primary refractory disease after first-line (primary) treatment [**Supplementary Extended Methods**]. Ten studies were identified that met our inclusion criteria, the investigators of all ten studies provided the individual-patient data for inclusion in the analysis. Seven studies, published between 2017 and 2021, were included in the BV-cohort and three studies, published between 2010 and 2016, were included in the chemo-cohort [**Supplemental Figure 1** and **Supplemental Table 1**]. We gathered pseudonymized individual patient-data from case record forms or study databases. For secondary use of data for this analysis, a waiver for informed consent was obtained from the Ethics Committee of all participating centers.

Endpoints and definitions

The primary endpoint was the 3-year PFS. A cutoff of 3 years was chosen because most relapses occur within 2-3 years, and limited follow-up for several studies.[7] Secondary endpoints included event free survival (EFS), OS, and pre-ASCT CMR rate. PFS was defined as time from enrollment in the clinical trial to progressive disease (PD) or death from any cause, whichever occurs first. To eliminate bias in PFS occurring due to differences in study protocols, patients with stable disease (SD) after salvage treatment who did not proceed to ASCT were censored at time of going off study. Patients who did not undergo ASCT but received BV monotherapy instead were censored at time of end of salvage chemotherapy. EFS was defined as time from enrollment to PD or death, or until end of salvage therapy if patients could not proceed to ASCT due to toxicity or insufficient response (SD/PD) after salvage therapy. Patients with SD who received additional therapy before ASCT were counted as event. OS was defined as time from enrollment to death from any cause.

CMR was defined as Deauville score (DS) 1-3 according to the 2014 Lugano criteria.[26] A partial metabolic response (PMR) was defined as DS 4-5 without progression or development of new lesions. In the ICE-GVD study of Moskowitz et al., the pre-ASCT PET-scans in the chemo-cohort were evaluated according to the international working group criteria, in which a positive scan was defined as uptake greater than the mediastinal or abdominal aortic blood pool (comparable to ≥DS3).[4,27] To harmonize response assessment, all positive PET-scans from the ICE-GVD study were re-assessed according to the Lugano criteria by a nuclear medicine physician (HS).[26]

The definition of primary refractory disease varied among studies, and not all collected relapse interval data. We defined primary refractory disease as 'not having achieved a complete response on first line treatment', encompassing partial response, SD or PD, irrespective of relapse interval. Bulky disease was defined as a tumor bulk ≥5 cm. Early relapse was defined as relapse interval <1 year. Stage was defined according to the Ann Arbor criteria. In the study of Santoro et al.[5] (n=59 patients), stage was not collected but information about the number of lymphatic and extralymphatic sites allowed to identify patients with stage I (one lymphatic site) or stage IV disease (≥1 lymphatic and ≥1 extralymphatic site, and the investigators confirmed that there were no patients with stage IE/IIE disease). However, stage II and III were combined for n=24 patients because the infra- or supradiaphragmatic distribution was unknown. Primary treatment was categorized into ABVD, escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone (escBEACOPP) or other therapies. Patients initially treated with ABVD and later escalated to escBEACOPP were categorized under escBEACOPP.

Statistical analysis

Pearson's chi-squared or Fisher's exact test were used to compare categorical variables, and Kruskal–Wallis rank-sum test for assessing continuous variables. Survival outcomes were analyzed using the Kaplan-Meier method and pairwise log-rank tests. Univariable and multivariable Cox regression analyses were performed to assess the association between baseline characteristics and survival outcomes. Logistic regression was used to assess the association between baseline characteristics and binary response outcomes. Patients with missing data were only excluded from analyses when the missing variable was required for the specific analysis.

A 1:1 propensity score matching analysis was performed to adjust for the effects of unbalanced covariates between the BV- and chemo-cohort.[28] We conducted matching based on baseline patient characteristics significantly associated with PFS. To ensure a robust distribution of patients within the matched dataset, we repeated the matching process 2000 times as part of internal cross-validation. More detailed information about the matching procedure is provided in the **Supplementary Extended Methods**.

Statistical analysis was performed using R software version 4.0.3. A P-value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Individual patient-data of ten clinical trials with a total of 832 transplant-eligible patients were collected.[4-6,15-21] Sixty-four patients were excluded (mainly because they had received >1 line of therapy). In total, 768 patients were included, with 386 in the BV-cohort (BV +/- salvage chemotherapy) and 382 in the chemo-cohort (salvage chemotherapy only) [**Figure 1** and **Table 1**]. There was an imbalance in primary refractory cases (55% versus 20% for the BV- and chemo-cohort, respectively) due to a substantial number of patients enrolled in the study of Josting et al.[6] (225 of 382; 59%) that specifically excluded primary refractory patients. Moreover, this study included more patients who were treated with escBEACOPP as primary treatment. An overview of study information including treatment regimens and summarized patient characteristics can be found in **Supplemental Table 1** and **2**.

Survival outcomes in the whole cohort

The median follow-up time was 38 months (interquartile range, IQR, 24-50) for the BV-cohort and 47 months (IQR 31-68) for the chemo-cohort. Of 242 patients with PD, only 17 (7%) progressed beyond three years, supporting the 3-year cutoff for survival analysis [**Supplemental Table 3**]. The 3-year PFS, without matching for baseline characteristics, was not significantly different between the BV- and chemo-cohort: 66.7% (95% confidence interval (CI): 62-72) versus 67.4% (95% CI: 63-72) (p=0.61), respectively, and EFS was comparable to PFS [**Supplementary Figure 2**]. In the BV cohort, 40 (10.4%) patients died, of whom 9 patients died without having PD (n=2 toxicity, n=3 infection, n=1 other cause, n=3 unknown). In the chemo-cohort, a total of 76 (19.9%) patients died, of whom 14 patients died without PD (n=7 toxicity, n=1 infection, n=3 other cause, n=3 unknown). Three-year OS was significantly higher for the BV-cohort compared to the chemo-cohort: 91.0% (95% CI: 88-94) versus 80.4% (95% CI: 76-85) (p=0.002) [**Supplementary Figure 2** and **3**].

Survival outcomes in the matched dataset

The following variables were significantly related to PFS and were used for propensity score matching: R/R status, bulky disease, extranodal disease, stage IV, B symptoms (at time of enrollment in the studies) and primary treatment with escBEACOPP [**Supplementary Extended methods Table 2**]. The matched dataset consists of a total of 480 patients with 240 patients each in the BV- and chemo-cohort in which the patient characteristics are now equally distributed, except for WHO performance status 2, but this was not significantly related to PFS (p=0.6) or OS (p=0.6) [**Table 2**, **Extended methods Table 2**].

In the matched dataset, 3-year PFS did not significantly differ between the BV- and chemo-cohort with a 3-year PFS of 72.2% (95% CI: 67-78) *versus* 67.1% (95% CI: 61-73) (p=0.14), respectively [**Figure 2A** and **Supplemental Table 4**]. The EFS was similar to PFS. However, there was a significant higher 3-year OS for patients treated within the BV-cohort of 91.9% (95% CI: 88-96) vs 79.5% (95% CI: 74-85) for the chemo-cohort, p=0.00043 [**Figure 2C**]. In patients with PD, significantly more patients died in the chemo-cohort (31/72; 43%) compared to the BV-cohort (19/65; 29%) (p=0.0011), while in patients without PD there was no significant difference in the number of deaths between the BV-cohort (5/175; 3%) versus the chemo-cohort (8/168; 5%) (p=0.4), suggesting that advances in later lines of therapy are most likely the cause of improved OS in the BV-cohort.

In patients with relapsed disease, the BV-cohort showed a significantly better 3-year PFS compared to the chemo-cohort of 79.9% (95% CI: 74-87) versus 69.7% (95% CI: 63-77), respectively (p=0.02) [**Figure 2D**]. The EFS and OS for relapsed patients were also significantly better in the BV-cohort (p=0.043 and p<0.0001, respectively). However, for patients with primary refractory disease, there were no significant differences in 3-year PFS (p=0.67), EFS (p=0.54) and OS (p=0.32) between the BV- and chemo-cohorts [**Figure 2G-I**].

In the BV-cohort, 216 (90%) patients underwent ASCT compared to 199 (83%) patients in the chemo-cohort (p=0.023) [**Table 3**]. Post-ASCT survival outcomes were comparable between the BV- and chemo-cohorts [**Supplementary Figure 4**]. In patients with relapsed disease who underwent ASCT, the 3-year PFS (p=0.32) and EFS (p=0.32) were not significantly different, but the OS was significantly better for the BV-cohort (p=0.0097). Again, for primary refractory patients there was no difference in PFS (p=0.18), EFS (p=0.22) and OS (p=0.48) [**Supplemental Table 5** and **Supplementary Figure 4**].

Subgroup analysis for survival between BV- and chemo-cohort

In the matched dataset, we tested differences in 3-year PFS between the BV- and chemo-cohort for specific subgroups using univariable Cox regression [**Figure 3**]. Patients with relapsed disease in the BV-cohort had a significantly lower risk of PD compared to the chemo-cohort (HR 0.59; 95% CI: 0.37-0.93; p=0.022). Similarly, patients with stage IV disease had significantly lower risk of PD in the BV-cohort (HR 0.53, 95% CI: 0.32-0.88; p=0.015). Patients with extranodal disease showed a trend for better PFS in the BV-cohort with a HR of 0.65 (95% CI: 0.41-1.03; p=0.067), but this was not significant. Exploratory multivariable subgroup analysis of R/R status and stage IV showed a trend for better PFS in the BV-cohort for patients who had both stage IV and relapsed disease (n=97) (HR 0.50; 0.25-1.02; p=0.058).

Pre-ASCT PET responses in the whole cohort

Nine out of ten studies had PET-CT data available. N=225 patients from the study of Josting et al. were excluded from the chemo-cohort because responses were assessed using conventional CT scan. Consequently, the chemo-cohort comprised 157 patients with available PET data. The CMR rate in the whole BV-cohort was 76% versus 80% in the chemo-cohort (p=0.30) [**Table 3**]. The ORR rates based on PET were not significantly different between the BV- and chemo cohorts. However, when including patients from the study of Josting et al. in which the ORR was based on conventional CT, the BV-cohort displayed a significantly higher ORR of 89%, compared to 79% in the chemo-cohort (p<0.001) [**Table 3**].

In subgroup analysis, patients with relapsed disease exhibited higher CMR rates compared to patients with primary refractory disease. However, no significant differences in

CMR or ORR rates were observed between the BV- and chemo cohorts within these subgroups [**Table 3**].

In the study of Moskowitz et al. within the chemo-cohort, patients with a PMR or SD after ifosfamide, carboplatin, and etoposide (ICE) treatment underwent sequential gemcitabine, vinorelbine, and docxorubicin (GVD). This sequential therapy resulted in a conversion from PMR/SD to a CMR in n=21 patients (of whom n=15 were included in the matched cohort). To ensure a comprehensive assessment, we recalculated the CMR rate after ICE-only, excluding these patients from the CMR count. This adjustment yielded a CMR rate of 67% for the total matched chemo-cohort. Upon comparing the CMR rate of 76% in the BV-cohort to the CMR rate of 67% after ICE-only in the chemo-cohort, a notable significance emerged in both univariable (p=0.025) and multivariable analysis (p=0.0017) [**Table 3**]. This distinction was particularly pronounced among patients with relapsed disease, as in this subgroup the CMR rate was significantly higher in the BV-cohort compared to the chemo-cohort. Conversely, in primary refractory patients, no significant differences in CMR rates were observed between the two cohorts [**Table 3**].

Slightly more patients underwent ASCT in the BV-cohort (335/386; 87%) versus the chemo-cohort (324/382; 85%), but this was not significant in univariable (p=0.38) or multivariable analysis adjusted for baseline characteristics (p=0.06). For relapsed patients, a significant higher percentage of patients underwent ASCT in the BV-cohort compared to the chemo-cohort (90% versus 86%; p=0.012 multivariate) [**Table 3**]. Among patients who underwent ASCT, those achieving a CMR (n=398) pre-ASCT had a 3-year PFS of 78.3% (95% CI: 74-83), which was significantly higher than those transplanted after a PMR (n=57) with a 3-year PFS of 64.2% (95% CI: 53%-78%) (p=0.01), or SD (n=8) with a 3-year PFS of 37.5% (95%

CI: 15-92; p=0.0004) [**Figure 4A**]. In all patients who were transplanted while having obtained a CMR, there was no difference in 3-year PFS between the BV- and chemo-cohorts (p = 0.92; data not shown). Notably, post-ASCT there was a significantly lower OS for patients with SD compared to a CMR (p=0.0042), while no OS difference was observed for patients with a PMR versus CMR (p=0.286 [**Figure 4B**].

Influence of BV dose and salvage chemotherapy schedule

Within the whole BV-cohort (unmatched dataset, BV-cohort n=386), subgroup analysis shows a non-significant trend for a higher PFS (HR 0.72; 95% CI: 0.50 – 1.04; p=0.079) in studies that used BV with a combination of chemotherapeutic agents, e.g. dexamethasone, high-dose cytarabine, and cisplatin (DHAP), ICE, or etoposide, methylprednisolone, cisplatin and cytarabine (ESHAP), versus a single agent, e.g. bendamustine or gemcitabine [**Supplemental Table 6**].[16,17,21,24] The use of a sequential schedule (i.e. BV monotherapy followed by chemotherapy), the number of BV cycles and the cumulative BV dose did not have an impact on 3-year PFS or pre-ASCT CMR rate between studies in the BV-cohort. This suggests that more cycles of BV does not improve CMR rates or PFS. Two studies applied BV maintenance after ASCT (11% of total number of patients).[17,19] However, not all patients received BV maintenance and many patients received less than the intended number of maintenance cycles due to toxicity or other reasons, which limits an analysis to assess the effect of BV maintenance [**Supplemental Table 2**].[17,19]

Outcomes of sequential treatment

Three studies followed a sequential approach: two studies in the BV-cohort used 2-4 cycles of BV monotherapy, allowing patients with a CMR to proceed directly to ASCT while PET-positive patients received additional ICE salvage chemotherapy before ASCT, and one study in the chemo-cohort used two cycles of ICE and patients without CMR received additional GVD chemotherapy before ASCT.[4,21,24] Subgroup analysis showed no significant differences in 3-year PFS between patients achieving CMR with one line of therapy (BV monotherapy or ICE only) and those requiring two lines (BV-ICE or ICE-GVD) to achieve a CMR (p=0.24) [**Figure 4C** and **4D**]. OS also showed no significant differences between these groups (p=0.62) [**Supplemental Table 7**].

We gathered pseudonymized individual patient-data from case record forms or study databases from clinical trials through the corresponding authors / investigators from the studies. For secondary use of data for this analysis, a waiver for informed consent was obtained from the Ethics Committee of all participating centers.

DISCUSSION

In this matched analysis of individual patient-data from prospective single-arm clinical trials, we investigated the effect of BV addition to salvage chemotherapy followed by ASCT in transplant-eligible R/R cHL patients. We found no statistically significant differences in PFS, EFS and pre-

ASCT CMR rate for patients treated with BV +/- chemotherapy compared to patients treated with salvage chemotherapy only. However, relapsed patients and patients with stage IV disease had a significantly better PFS and EFS when adding BV to the salvage treatment. While OS was significantly better in the BV-cohort, this may be influenced by the time in which the BV studies were conducted (2015-2021) compared to chemo-cohort studies (2010-2016). A recent retrospective study in R/R cHL patients who underwent ASCT showed an OS improvement over time, corresponding to the increased usage of immune-checkpoint inhibitors and BV.[29] Therefore, the observed OS difference in the BV cohort is probably driven by the availability of checkpoint inhibitors for patients who fail salvage therapy or relapse after ASCT.[9-11,30]

The disparity in survival outcomes between primary refractory and relapsed patients could potentially be explained by the antitumor mechanism of action of BV. BV elicits its antitumor effect through the cytotoxic warhead MMAE, a substrate for the multidrug resistance pump P-glycoprotein (PGP).[31] It has been shown that BV-resistant cell lines have elevated PGP, which is known to also occur after exposure to other cytotoxic agents such as doxorubicin.[32,33] Thus, tumor cells that are able to resist first-line chemotherapy might employ the same mechanism to convey resistance to BV. Because patients with primary refractory disease are more likely to be resistant to chemotherapy, this might explain that they could also be resistant to BV. Therefore, in patients with primary refractory disease there is still an unmet need to improve outcomes, and other non-chemotherapeutic therapies such as immune checkpoint inhibitors should be considered.[34-36]

Patients with stage IV disease had improved PFS in the BV-cohort versus the chemo-cohort. This may be attributed to a larger total tumor volume, necessitating intensified treatment which could be achieved by augmenting standard chemotherapy with BV. In subgroup analyses

of the Echelon-1 trial, stage IV was also associated with better PFS in patients treated with BV-AVD compared to ABVD, suggesting a similar effect in the R/R setting.[13,14]

We showed that patients who were treated with a sequential approach who achieved a PMR after BV or ICE only, yet converting to a CMR following salvage chemotherapy with ICE (after BV) or GVD (after ICE), exhibited comparable survival outcomes to those directly achieving CMR. This highlights the feasibility of a sequential approach, potentially sparing chemotherapy in rapid responders. Emphasizing the significance of attaining CMR pre-ASCT, our study suggests that improving survival in PMR patients could be accomplished by inducing CMR through additional salvage chemo- or immunotherapy before ASCT.[4,21,24]

Our analysis is limited by missing variables in certain studies, partially mitigated by our matching method. Consequently, not all patients could be included in specific (multivariable) analyses. While our analysis approach addresses inherent differences in trial populations and design as much as possible, it is essential to emphasize several significant distinctions in design: a large portion of patients in the chemo-cohort lacked response assessment using PET, restricting the comparison of pre-ASCT CMR rates between the BV- and chemo-cohorts. Unfortunately, we could not evaluate the impact of BV maintenance in our analysis as only a limited number of patients received BV maintenance in our cohort, and the number of BV maintenance cycles differed widely across patients due to various reasons, limiting a proper analysis. Additionally, assessing the impact of radiotherapy was hindered by varying protocols among the studies. While some universally applied pre-ASCT radiotherapy to patients with extranodal and bulky disease, others selectively used it on residual lesions either before or after ASCT.[4,16,24]

Generally, the PFS, OS and CMR rates in the chemo-cohort appear favorable compared to real-world data.[7,37] However, the studies in our analysis only included transplant-eligible

patients, known for better outcomes compared to elderly or unfit patients. Furthermore, the study of Josting et al. specifically excluded primary refractory patients. While our analysis minimizes bias through matching and inclusion of prospective trials, caution is warranted in generalizing to real-world scenarios. Therefore, the observed results of our analysis should be interpreted with caution and cannot replace an RCT. Nonetheless, at the moment this is the largest matched analysis based on individual patient-data in R/R cHL, incorporating recent clinical trial data. Therefore, it serves as a benchmark for future (single-arm) studies exploring novel therapies or regimens that aim to replace HDCT/ASCT with novel drugs.

Preliminary results of an ongoing phase IIb RCT, comparing BV-ESHAP to ESHAP alone in a cohort of 150 patients, indicate a higher CMR rate in the BV-ESHAP group.[38] However, the limited sample size of the study may impede subgroup analyses for risk factors. In addition, this study evaluates the substitution of ASCT by BV maintenance therapy in patients with a CMR after salvage treatment. While this investigation could provide valuable insights into the potential replacement of ASCT with maintenance therapy, it may complicate the direct comparison of long-term outcomes between the BV-ESHAP and ESHAP arms.

Emerging novel therapies, including immune-checkpoint inhibitors, are gaining attention in the relapsed/refractory setting. In a phase III head-to-head comparison, single-agent pembrolizumab demonstrated superior median PFS and lower toxicity to BV.[40] Checkpoint inhibition, either alone or in combination with BV or chemotherapy, has proven effective in single-arm studies.[34-36] Exploring a similar individual patient-data analysis for studies combining chemotherapy with checkpoint inhibitors versus BV-chemo or chemotherapy alone could offer valuable insights. The evolving landscape, where BV is increasingly used in newly diagnosed patients, raises questions about its retreatment efficacy in the salvage setting.[13] However,

retreatment with BV in patients with multiple relapses showed persistent efficacy.[41] Preliminary findings from an extensive ongoing RCT comparing nivolumab-AVD to BV-AVD demonstrated favorable outcomes for the nivolumab-AVD arm.[42] This outcome might potentially prompt a shift toward integrating checkpoint inhibitors as a first-line treatment, thereby reinstating the use of BV in the salvage setting. Consequently, our results remain pertinent for future treatment contexts. As novel therapeutic options shift to earlier lines of therapy, such as the use of checkpoint inhibitors in the first or second line, studying the sequencing effects of these agents becomes increasingly crucial, ideally through prospective clinical trials. However, it is essential to acknowledge the lack of universal global access to these novel (and often expensive) agents, a consideration that should also be addressed in guidelines outlining the optimal treatment for patients with R/R cHL.

In summary, our study indicates that the addition of BV to chemotherapy did not enhance CMR rates or PFS in the overall population of R/R cHL patients compared to standard salvage chemotherapy. However, notable PFS improvements were observed in patients with relapsed or stage IV disease undergoing salvage treatment that includes BV. Moreover, a sequential approach involving BV monotherapy followed by salvage chemotherapy is both viable and has the potential to reduce the need for salvage chemotherapy in certain patients. In the absence of RCTs, this propensity score matched analysis on individual patient-data, offers valuable insights in the treatment landscape for patients with R/R cHL. .e

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AUTHORSHIP CONTRIBUTIONS

JD and MJK designed the study. All authors collected the data. FdW and JD performed the database harmonization. HS performed the PET revision. JD performed the statistical analysis under supervision of BAH. JD and FdW drafted the manuscript with contributions from all authors. All authors interpreted the data, read, commented on, and approved the final version of the manuscript.

FIGURE LEGENDS

Figure 1: Consort diagram. *Abbreviations: BV, Brentuximab vedotin; Chemo, chemotherapy; n, number of patients.*

Figure 2: Kaplan-Meier survival analyses on the matched cohort. Kaplan-Meier curves showing the progression free survival (PFS), event free survival (EFS) and overall survival (OS) in the brentuximab vedotin (BV) and chemotherapy (chemo)-cohort in the matched dataset (**A, B, C**), and corresponding analyses stratified for patients with relapsed (**D, E, F**) or primary refractory disease (**G, H, I**).
Abbreviations: ICE, ifosfamide, carboplatin and etoposide; GVD, gemcitabine, vinorelbine and doxorubicin; CMR, complete metabolic response; PR, partial response.

Figure 3: Forest plot of the association between baseline characteristics and differences in progression free survival between the BV- and chemo-cohorts. Hazard ratios are shown for univariable Cox regression on subgroup analyses of baseline characteristics for progression free survival (PFS) comparing the brentuximab vedotin (BV)- and chemo-cohorts. A hazard ratio lower than 1 corresponds to a higher PFS in the BV-cohort compared to the chemo-cohort.
Abbreviations: BV, *Brentuximab vedotin; Chemo, chemotherapy; CI, confidence interval; yr, year; R/R status, relapsed or primary refractory disease status; ABVD, Adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.*

Figure 4: Kaplan-Meier subgroup survival analyses on the whole dataset. A) Progression free survival (PFS) and **B)** overall survival (OS) in patients who underwent ASCT stratified for pre-ASCT PET response in the whole dataset. **C-D)** PFS for patients who were treated in studies with a sequential approach and achieved a complete metabolic response (CMR) after one line of salvage treatment (BV or ICE only) *versus* patients who initially had no CMR but converted to a CMR after two lines of sequential treatment with additional chemotherapy (BV-ICE or ICE-GVD).

Abbreviations: BV, brentuximab vedotin; ICE, ifosfamide, carboplatin and etoposide; GVD, gemcitabine, vinorelbine and doxorubicin; PFS, progression free survival; OS, overall survival.

Tables

Table 1: Baseline patient characteristics in the whole dataset

Patient characteristics (N; %)	BV-cohort (N=386)	Chemo-cohort (N=382)	*P-value*
Female sex	202 (52%)	168 (44%)	0.021
Age, median (range)	31 (5 - 68)	34 (18 - 72)	0.031
WHO PS			< 0.001
0	158 (64%)	256 (70%)	0.1030
1	85 (34%)	79 (22%)	0.0008
2	5 (2%)	29 (8%)	0.0029
Unknown	138	18	
Ann Arbor stage			< 0.001
I	29 (9%)	43 (11%)	0.3589
II	132 (41%)	135 (36%)	0.1861
III	53 (16%)	59 (16%)	0.8534
II or III[1]	0 (0%)	24 (6%)	*NA*
IV	109 (34%)	117 (31%)	0.4791
Unknown	63	4	
B symptoms	107 (28%)	74 (23%)	0.133
Unknown	2	59	
Extranodal disease	142 (38%)	134 (35%)	0.493
Unknown	8	1	
Bulky disease[2]	128 (37%)	101 (31%)	0.126
Unknown	40	60	
Primary refractory[3]	213 (55%)	78 (20%)	< 0.001
Relapse interval in days, median (range)	147 (0 - 4883)	250 (0 - 5258)	0.123
Unknown	*212*	*6*	
Early relapse <1 year	259 (76%)	230 (61%)	< 0.001
Unknown	43	5	
Response to primary treatment			< 0.001
Complete response	173 (59%)	304 (89%)	< 0.001
Partial response	55 (19%)	21 (6%)	< 0.001
Stable disease	18 (6%)	2 (1%)	< 0.001
Progressive disease	46 (16%)	14 (4%)	< 0.001
Unknown	94	41	
Primary treatment			< 0.001
ABVD	254 (90%)	259 (71%)	< 0.001
BEACOPP	16 (6%)	79 (22%)	< 0.001
Other	11 (4%)	25 (7%)	0.1455
Unknown	105	19	
BV maintenance post-ASCT	87 (24%)	*NA*	*NA*

Patient characteristics are measured at time of enrollment in the studies, i.e. at time of relapse or primary refractory disease, unless indicated otherwise.

[1]For 24 patients in the chemo-cohort from the trial by Santoro et al, stage at relapse was not recorded but stage I and IV were deducted from the amount of involved lymph node sites,

extranodal sites and bone marrow involvement. It was not possible to distinguish between stage II and III disease because no data was available on the spatial distribution of nodal sites (i.e. infra- and/or supradiaphragmatic location). *Abbreviations:* BV, Brentuximab vedotin; Chemo, chemotherapy; PS, performance status; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone.

Table 2: Patient characteristics in the matched dataset

	BV-cohort (N=240)	Chemo-cohort (N=240)	*P-value*
Female sex	132 (55%)	130 (54%)	0.855
Age, median (range)	30 (11 - 66)	33 (18 - 72)	0.118
Primary refractory	78 (32%)	78 (32%)	1.000
B symptoms at relapse	70 (29%)	42 (23%)	0.163
Unknown	*1*	*59*	
Stage at relapse[1]			
I	16 (8%)	23 (10%)	0.627
II	77 (38%)	84 (35%)	0.631
II or III	0 (0%)	24 (10%)	*NA*
III	37 (18%)	27 (11%)	0.112
IV	72 (36%)	79 (33%)	0.612
Unknown	*38*	*3*	
Extranodal disease at relapse	102 (42%)	94 (39%)	0.458
Bulky disease at relapse[2]	89 (41%)	71 (39%)	0.689
Unknown	*24*	*59*	
Primary treatment with escBEACOPP	14 (8%)	17 (7%)	0.985
Early relapse <1year	129 (65%)	162 (68%)	0.480
Unknown	42	3	
WHO PS			
0	98 (66%)	158 (70%)	0.505
1	49 (33%)	48 (21%)	1.000
2	2 (1%)	21 (9%)	0.0036
Unknown	91	13	
Response to primary treatment = PD	14 (7%)	14 (7%)	0.414
Unknown	*38*	*41*	

[1]For 24 patients in the chemo-cohort from the trial by Santoro et al, stage at relapse was not recorded but stage I and IV were deducted from the amount of involved lymph node sites, extranodal sites and bone marrow involvement. It was not possible to distinguish between stage II and III disease because no data was available on the spatial distribution of nodal sites (i.e. infra- and/or supradiaphragmatic). *Abbreviations:* BV, Brentuximab vedotin; Chemo, chemotherapy; escBEACOPP, escalated bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; PS, performance score; PD, progressive disease; BV, brentuximab vedotin; N, number.

Table 3: Pre-ASCT response rates and patients who underwent ASCT

Outcome	Dataset	BV-cohort			Chemo-cohort			P	P
		N	Total	%	N	Total	%	chisq[1]	multivar[2]
Underwent ASCT	Whole	335	386	87%	324	382	85%	0.38	**0.064**
Underwent ASCT	PET	335	386	87%	130	157	83%	0.20	0.23
Underwent ASCT	Matched	216	240	90%	199	240	83%	**0.023**	**0.020**
Underwent ASCT	Whole - Relapsed	156	173	90%	262	304	86%	0.20	**0.012**
Underwent ASCT	Whole - Refractory	179	213	84%	62	78	79%	0.32	0.40
Underwent ASCT	Whole - Stage IV	92	109	84%	91	117	78%	0.15	0.29
CMR	PET	292	386	76%	126	157	80%	0.30	0.23
CMR	Matched[4]	193	240	80%	108	137	79%	0.69	0.28
CMR	PET - Relapsed	148	173	86%	78	90	87%	0.72	0.75
CMR	PET - Refractory	144	213	68%	48	67	72%	0.67	0.11
CMR	PET - Stage IV	74	109	68%	46	60	77%	0.22	0.42
ORR (PET)	PET	343	386	89%	136	157	87%	0.46	0.51
ORR (PET)	PET - Relapsed	164	173	95%	81	90	90%	0.14	0.11
ORR (PET)	PET - Refractory	179	213	84%	55	67	82%	0.71	0.43
ORR (PET)	PET - Stage IV	90	109	83%	50	60	83%	0.90	0.97
ORR (CT)	Whole	343	386	89%	300	382	79%	**<0.001**	**<0.001**
ORR (CT)	Whole - Relapsed	164	173	95%	238	304	78%	**<0.001**	**<0.001**
ORR (CT)	Whole - Refractory	179	213	84%	62	78	79%	0.36	0.84
ORR (CT)	Whole - Stage IV	90	109	83%	88	117	75%	0.18	**0.020**
CMR ICE/BeGEV[5]	PET	292	386	76%	105	157	67%	**0.025**	**0.0017**
CMR ICE/BeGEV	Matched[4]	193	240	80%	93	137	68%	**0.005**	**0.0040**
CMR ICE/BeGEV	PET - Relapsed	148	173	86%	67	90	74%	**0.030**	**0.007**
CMR ICE/BeGEV	PET - Refractory	144	213	68%	38	67	57%	**0.067**	0.15
CMR ICE/BeGEV	PET - Stage IV	74	109	68%	39	60	65%	0.69	0.11

[1]P values from chi-square comparison of BV- versus Chemo-cohort

[2]P values from multivariable logistic regression comparing BV- versus Chemo-cohort corrected for baseline characteristics: R/R status, stage, B symptoms, extranodal disease, bulky disease and primary treatment with escBEACOPP.

[3]The PET dataset is the whole dataset excluding patients from the study of Josting et al., in which response-assessment was done by conventional CT scan only.

[4]For CMR calculations in the matched dataset, patients from the study of Josting et al. have been removed from the chemo-cohort, resulting in a smaller chemo-cohort of n=137 patients instead of n=240.

[5]Comparison of pre-ASCT CMR rates measured after first sequential chemotherapy only. In the study of Moskowitz et al. patients received sequential ICE and GVD chemotherapy in case of no CMR. In this comparison the response after ICE only is used in the chemo cohort.

Abbreviations: PET, positron emission tomography; ASCT, autologous stem-cell transplant; CMR, complete metabolic response rate; ICE, ifosfamide, carboplatin, etoposide; BeGEV, bendamustine, gemcitabine, etoposide, vinorelbine; GVD, gemcitabine, vinorelbine, doxorubicin; BV, brentuximab vedotin; Chemo, chemotherapy; chisq, chi-square test; multivar, multivariable logistic regression analysis;

Figure 1

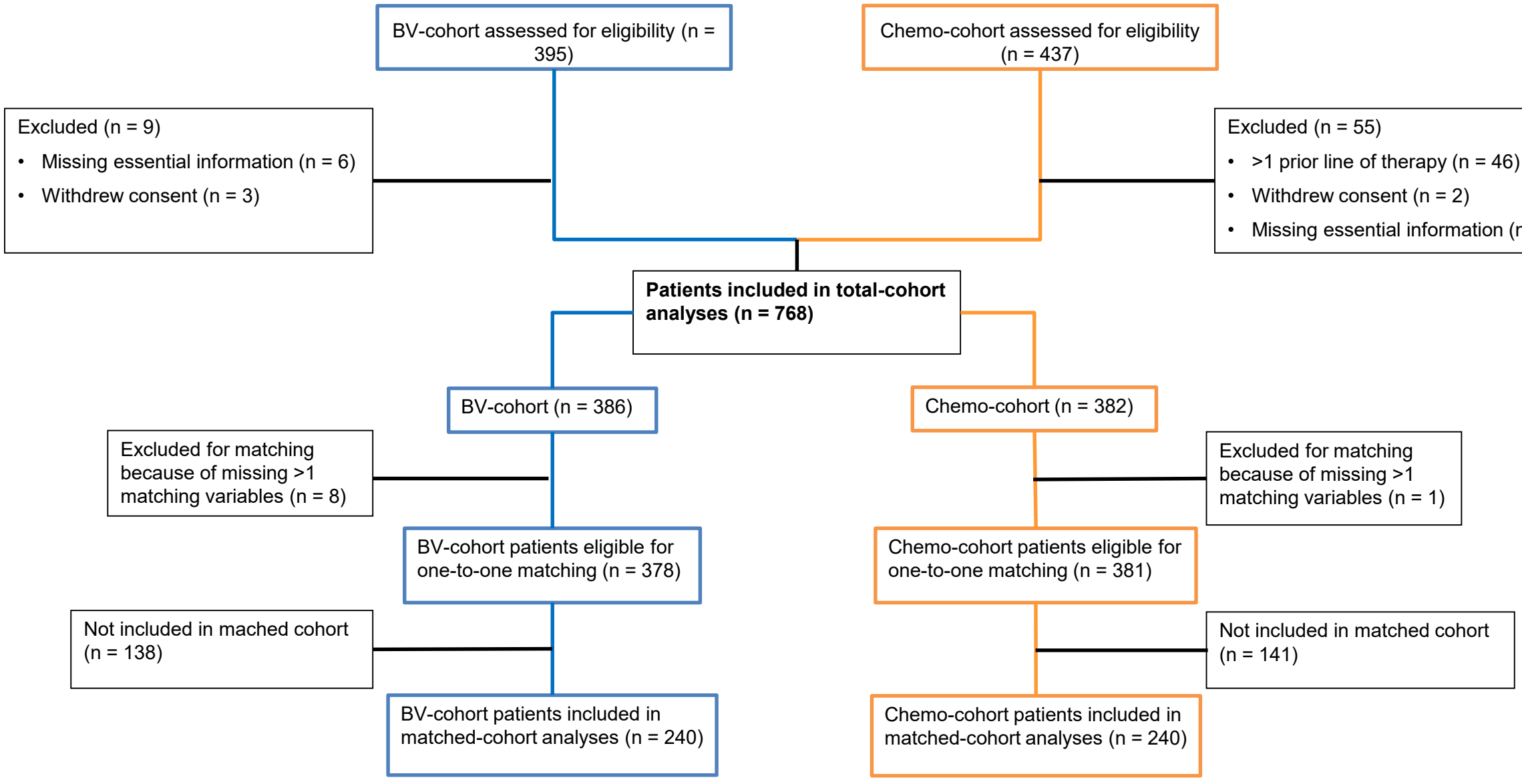

Figure 2

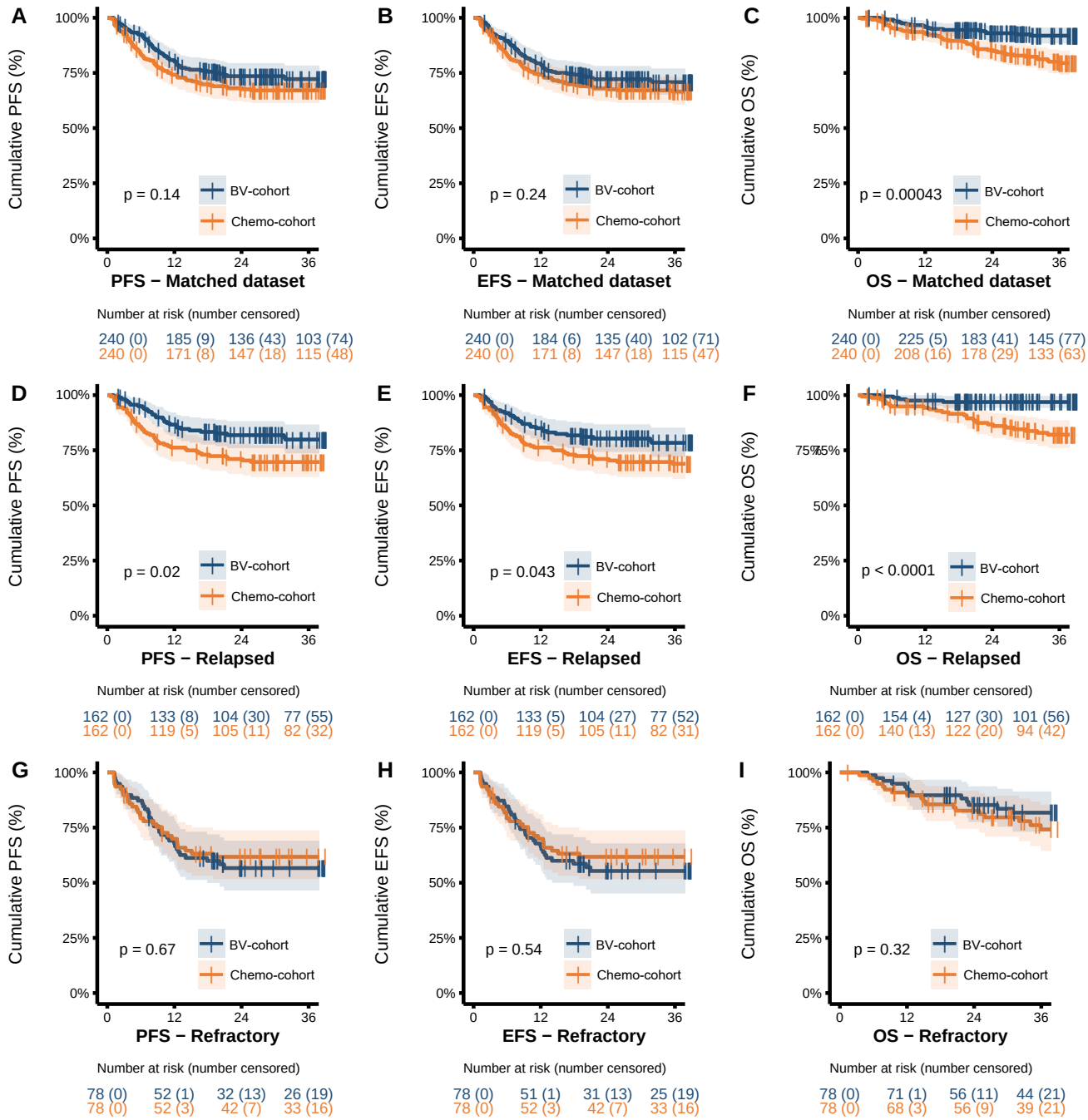

Figure 3

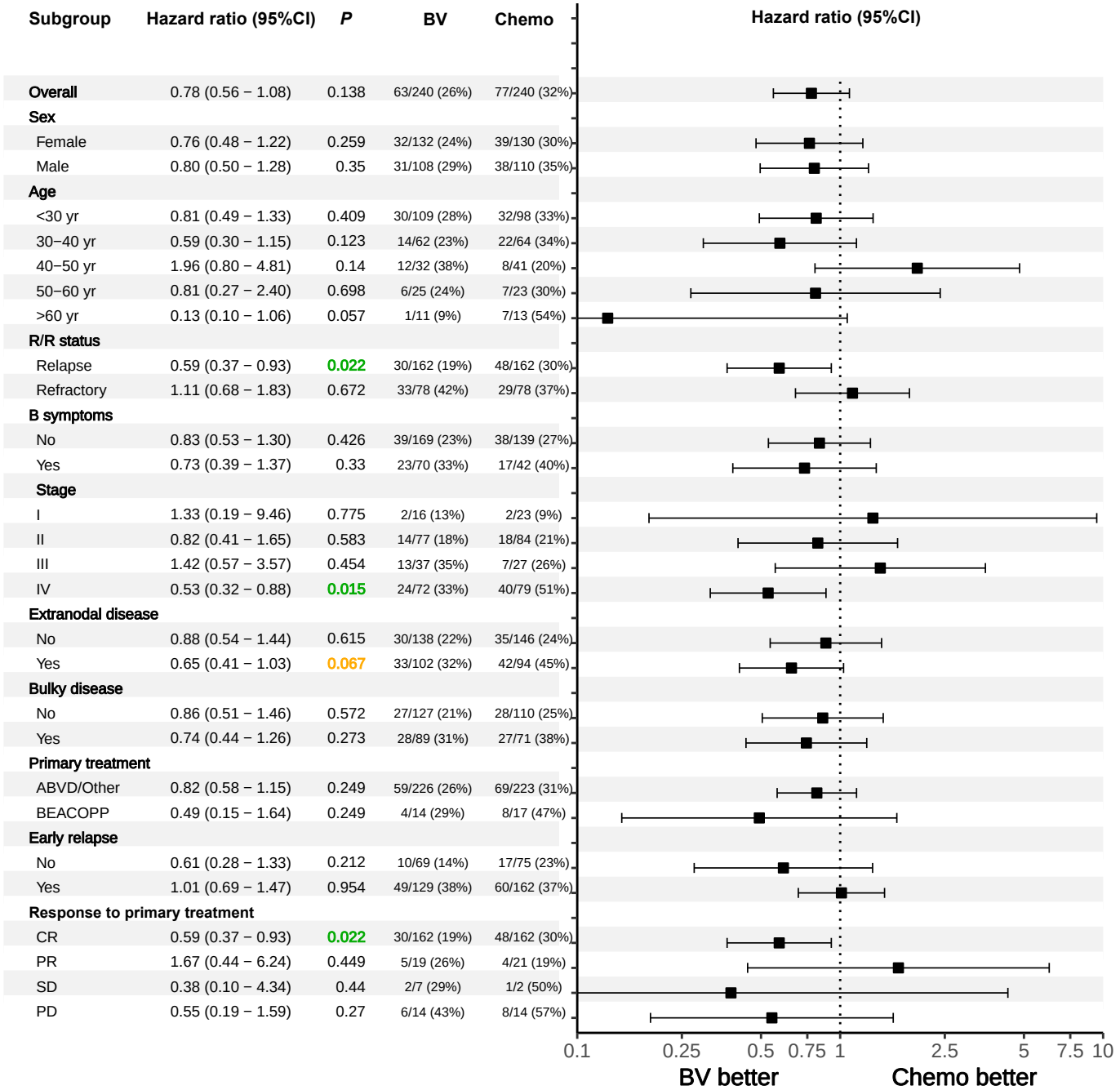

Figure 4