SUPPLEMENTAL MATERIAL

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

Julia Driessen[1,2], Fer de Wit[1,2], Alex F. Herrera[3], Pier Luigi Zinzani[4,5], Ann S. LaCasce[6], Peter D. Cole[7], Craig H. Moskowitz[8], Ramón Garcia-Sanz[9], Michael Fuchs[10], Horst Müller[10], Peter Borchmann[10], Armando Santoro[11], Heiko Schöder[12], Josée M. Zijlstra[2,13], Barbara A. Hutten[14,15], Alison J. Moskowitz[16], and Marie José Kersten[1,2].

1) Department of Hematology, Amsterdam UMC, Location University of Amsterdam, and LYMMCARE Amsterdam, The Netherlands; 2) Cancer Center Amsterdam, Imaging and Biomarkers, Amsterdam, The Netherlands; 3) Department of Hematology and Hematopoietic Cell Transplantation, City of Hope National Medical Center, Duarte, CA, USA; 4) IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli", Italy; 5) Dipartimento di Scienze Mediche e Chirurgiche, Università di Bologna, Bologna, Italy; 6) Division of Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA, USA;
7) Rutgers University, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; 8) Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, Florida, USA; 9) Department of Hematology, Hospital Universitario de Salamanca (HUSA/IBSAL), CIBERONC, CIC-IBMCC (USAL-CSIC), Universidad Salamanca, Spain; 10) German Hodgkin Study Group (GHSG) and Department I of Internal Medicine, Center for Integrated Oncology Aachen Bonn Cologne Düsseldorf (CIO ABCD), University of Cologne, Germany; 11) Department of Biomedical Sciences, Humanitas University, IRCCS Humanitas Research Hospital- Humanitas Cancer Center, Milan, Italy; 12) Molecular Imaging and Therapy Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA; 13) Department of Hematology, Amsterdam UMC, Vrije Universiteit Amsterdam, Cancer Center Amsterdam, Amsterdam, The Netherlands; 14) Department of Epidemiology and Data Science, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands;
15) Amsterdam Cardiovascular Sciences, Diabetes & Metabolism, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; 16) Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA;

INDEX

EXTENDED METHODS

Part I: Literature search and inclusion of clinical trials

Inclusion criteria:

- Published after the year 2000
- Prospective design
- Included at least 10 patients
- Included only transplant eligible patients with Hodgkin' lymphoma
- Treatment with single agent or a combination of different chemotherapeutic agents followed by high-dose chemotherapy and autologous stem-cell transplantation
- Patients either relapsed after or were primary refractory on first-line chemotherapy treatment
- Biopsy proven relapse or refractory disease

Chemo-cohort

(((((((Hodgkin Disease[MeSH]) OR Hodgkin disease[tiab]) OR Hodgkin's disease[tiab]) OR ((Hodgkin lymphoma[tiab] NOT Non-Hodgkin lymphoma[tiab]))) OR ((Hodgkin's lymphoma[tiab] NOT Non-Hodgkin's lymphoma[tiab])))) AND ((Refractory[tiab]) OR Relapse*[tiab]))) AND ((((((((((Chemotherapy, adjuvant[MeSH]) OR Consolidation chemotherapy[MeSH]) OR Chemoradiotherapy[MeSH]) OR Induction chemotherapy[MeSH]) OR Maintenance chemotherapy[MeSH]) OR Antineoplastic protocols[MeSH]) OR Chemo*[tiab]) OR Salvage therapy[MeSH]) OR Salvage Therapy[tiab]) OR Salvage chemotherapy[tiab]) OR Salvage regiment[tiab])*

The above search string for PubMed was performed on 01-06-2019 and yielded 2677 results and was checked regularly after this date for new published studies. Studies published before 2000 (n=1107) were excluded from the search. N=7 were selected as

potentially includable (based on title/abstract screening and full text if inclusion was unsure) of which the authors were contacted. Three studies were assessed by the German Hodgkin Study Group (GHSG) and in contact with them we only included the most recent study from 2010 and therefore excluded the two older trials. Three studies were conducted by C. Moskowitz et al and as with the GHSG we decided to only include the most recent study from 2012 that also had PET data available. The third study of Santoro et al. was also included. This led to the inclusion of 3 prospective clinical trials of which the authors were contacted. All authors responded and were willing to collaborate.

BV-cohort

(((((((Hodgkin Disease[MeSH]) OR Hodgkin disease[tiab]) OR Hodgkin's disease[tiab]) OR ((Hodgkin lymphoma[tiab] NOT Non-Hodgkin lymphoma[tiab]))) OR ((Hodgkin's lymphoma[tiab] NOT Non-Hodgkin's lymphoma[tiab])))) AND ((Refractory[tiab]) OR Relapse*[tiab]))) AND ((((Brentuximab vedotin[MeSH]) OR Brentuximab vedotin[tiab]) OR SGN-35[tiab]) OR Adcetris[tiab])*

The above search string for PubMed was performed on 01-06-2019 and yielded 329 results and was checked regularly after this date for new published studies. N=4 were selected as potentially includable. Two other studies were identified through abstract screening and were published shortly after the search date. Additionally, the clinicaltrials.gov database was searched on the following terms: Hodgkin lymphoma, brentuximab, SGN-35 or adcetris and identified 160 trials of which five trials were selected as potentially includable that were not yet identified on PubMed, including our own trial (Kersten et al., Haematologica 2021). The investigators of the remaining studies were contacted but eventually did not lead to inclusion since three of these trials were still recruiting and results were not expected on time for our analysis and another trial also included patients

with multiple relapses and had less than 10 patients who were eligible according to our inclusion criteria. The authors of the six identified studies were contacted and were all willing to collaborate. Including our own study (Kersten et al., 2021) we included seven studies in the BV-cohort.

Part II: Matching of BV- and Chemo-cohorts

Matching was performed on a one-to-one base using propensity scores with the nearest neighbor method using the R package *MatchIt* (https://cran.r-project.org/web/packages/MatchIt/MatchIt.pdf) which has been validated for usage in relatively small cohorts.[1] As variables that are related to the outcome can influence outcomes of a propensity score analysis, the prognostic value of baseline characteristics on the whole dataset was determined using univariate cox regression and multivariate cox regression and variables that were independently related to the outcome were used as matching variables [**Extended methods Table 1** and **2**].[2] The following variables were independently associated with a significant higher risk of progressive disease: primary refractory disease, B symptoms, Ann Arbor stage IV disease, bulky disease, primary treatment with escBEACOPP, early relapse <1 year and progressive disease (PD) after primary treatment (i.e. no PR/SD). Extranodal disease was associated with a significant higher risk of progressive disease but was not dependent of stage IV disease. However, since one study missed Ann Arbor stage at relapse, but did have information about extranodal disease, we also used extranodal disease as matching variable. Early relapse and PD after primary treatment were not used as matching variable because of too many missing values, however after matching the distribution of these variables was checked between the cohorts. For each case in the BV-cohort exactly one case in the chemo-cohort will be matched. Because of an unequal number of patients with primary refractory disease in the BV- and chemo-cohorts (n=211 and n=78, respectively), we performed the matching separately for patients with relapsed disease or primary refractory disease. In addition, for some studies not all matching variables were known. For example, the study of LaCasce et al., did not have information about Ann Arbor stage at relapse and the study of Santoro et al. did not have information about bulky disease and B symptoms [**Extended methods**

Table 3]. Hence, we performed the matching in two steps: first, patients with all information available (Part 1) are matched separately from patients with a missing matching variable (Part 2) [**Extended methods Figure 1**]. In Part 1, patients are matched on all matching variables (i.e. primary refractory disease, bulky disease, extranodal disease, stage IV, presence of B-symptoms and primary treatment with escBEACOPP). In Part 2, patients are matched on primary refractory disease, extranodal disease and primary treatment with escBEACOPP. Second, patients with relapsed disease from the BV-cohort (*patient sample*) are matched one-to-one to a patient with relapsed disease from the chemo-cohort (*population sample*) while patients with primary refractory disease from the chemo-cohort (*patient sample*) are matched one-to-one to a patient with primary refractory disease from the BV-cohort (*population sample*). This is performed separately for Part 1 and 2. These two parts are merged afterwards and the spread of variables is checked in the final matched dataset [**Extended methods Figure 1**]. As sensitivity analysis, we also performed a one-stage matching in which patients with missing matching variables were excluded.

To reduce selection bias in the matched cohort, we performed an internal cross-validation by repeating the whole matching process 2000 times in which patients are randomly matched. For each matching iteration, we calculated the differences in progression free survival (PFS), event free survival (EFS) and overall survival (OS) for the BV- *versus* chemo-cohorts in the whole population and stratified for relapsed or primary refractory patients and took the iteration that produces the most median results as the final matched dataset [**Extended methods Table 4**].

EXTENDED METHODS TABLES & FIGURES

Extended Methods Table 1: Univariable and multivariable Cox regression on the association between baseline characteristics and PFS

	Univariable			*Multivariable, corrected for R/R status*		
Covariates	**HR**	**95% CI**	***P-value***	**HR**	**95% CI**	***P-value***
Sex (Male)	1.08	0.83 - 1.39	0.5698	1.11	0.86 - 1.43	0.4180
Age (per unit)	1.00	0.99 - 1.01	0.3975	1.01	1.00 - 1.02	0.2473
Primary treatment with BEACOPP (ref = ABVD/Other)	1.31	0.92 - 1.86	0.139	1.57	1.09 - 2.27	**0.0152**
Ann Arbor stage	(ref = I)					
II	1.41	0.76 - 2.62	0.2723	1.33	0.72 - 2.48	0.3616
II or III	2.31	0.97 - 5.47	**0.0581**	1.99	0.84 - 4.75	0.1199
III	1.87	0.96 - 3.61	**0.0644**	1.85	0.96 - 3.59	**0.0672**
IV	3.15	1.73 - 5.73	**0.0002**	3.01	1.66 - 5.48	**0.0003**
B symptoms	1.78	1.61 - 2.74	**0.0001**	1.85	1.39 - 2.45	**0.0000**
Extranodal disease	1.74	1.34 - 2.36	**0.0000**	1.76	1.36 - 2.27	**0.0000**
Bulky disease	1.65	1.34 - 2.24	**0.0004**	1.65	1.25 - 2.18	**0.0005**
Primary refractory (ref = relapse)	1.69	1.25 - 2.18	**0.0001**	-	-	-
Early relapse <1 year	1.98	1.45 - 2.70	**0.000**	1.75	1.26 - 2.44	**0.0010**
Response_Dx=PD	2.51	1.69 - 3.71	**0.000**	2.20	1.32 - 3.66	**0.0025**
WHO PS (ref=0)						
1	1.48	1.09 - 2.02	**0.011**	1.43	1.05 - 1.94	**0.0232**
2	1.81	1.06 - 3.09	**0.031**	1.64	0.96 - 2.83	**0.0718**

Univariable cox proportional hazard analysis was performed to assess the association between baseline patient characteristics and progression free survival. In multivariable analysis, the corresponding baseline characteristics were corrected for primary refractory *versus* relapsed disease (R/R status).

Abbreviations: HR, hazard ratio; CI, confidence interval; P, p-value; exp, exponential function; coef, coefficient; ref, reference group; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine; RR, relapsed/refractory; PD, progressive disease; PS, performance score.

Extended Methods Table 2: Multivariable Cox regression on the association between baseline characteristics and PFS

Covariates	HR	*Multivariable* 95% CI	*P*
Primary treatment with BEACOPP	1.47	0.99 - 2.19	**0.0559**
Ann Arbor stage			
III	1.31	0.84 - 2.05	0.2364
IV	1.92	1.22 - 3.01	**0.0045**
B symptoms	1.89	1.35 - 2.65	**0.0002**
Extranodal disease	1.19	0.78 - 1.82	0.4147
Bulky disease	1.40	1.02 - 1.91	**0.0364**
Primary refractory	1.45	1.03 - 2.04	**0.0331**
Early relapse <1 year	1.70	1.12 - 2.58	**0.0119**
WHO PS			
1	0.96	0.67 - 1.37	0.8157
2	1.17	0.66 - 2.06	0.5950

Multivariate cox proportional hazard analysis for progression free survival (PFS) on baseline characteristics that were significant in univariable analysis. *Abbreviations*: HR, hazard ratio; CI, confidence interval; P, p-value; exp, exponential function; coef, coefficient; ref, reference group; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; RR, relapsed/refractory; PS, performance score.

Extended Methods Table 3: Missing values of matching variables

Variable	Missing	Patients with missing values per study (n)
R/R status	0	-
Extranodal	9	Garcia-Sanz (2), Herrera (6), Josting (1)
B symptoms	60	Santoro (59), LaCasce (1), Herrera (1)
Stage IV	61	Josting (4), LaCasce (55), Garcia-Sanz (2), Herrera (6)
Stage III	85	Josting (4), LaCasce (55), Garcia-Sanz (2), Herrera (6), Santoro (24)
Bulky	100	Cole (39), Herrera (1), Josting (1), Santoro (59)
BEACOPP	0	-
Early relapse	48	AMoskowitz (30), Broccoli (12), Herrera (1), Josting (5)
Response_Dx = PD	135	AMoskowitz (34), Broccoli (1), CMoskowitz (41), Cole (27), Herrera (31), LaCasce (1)
WHO-PS	156	AMoskowitz (64), CMoskowitz (10), Cole (16), Josting (1), Kersten (3), LaCasce (55), Santoro (7)

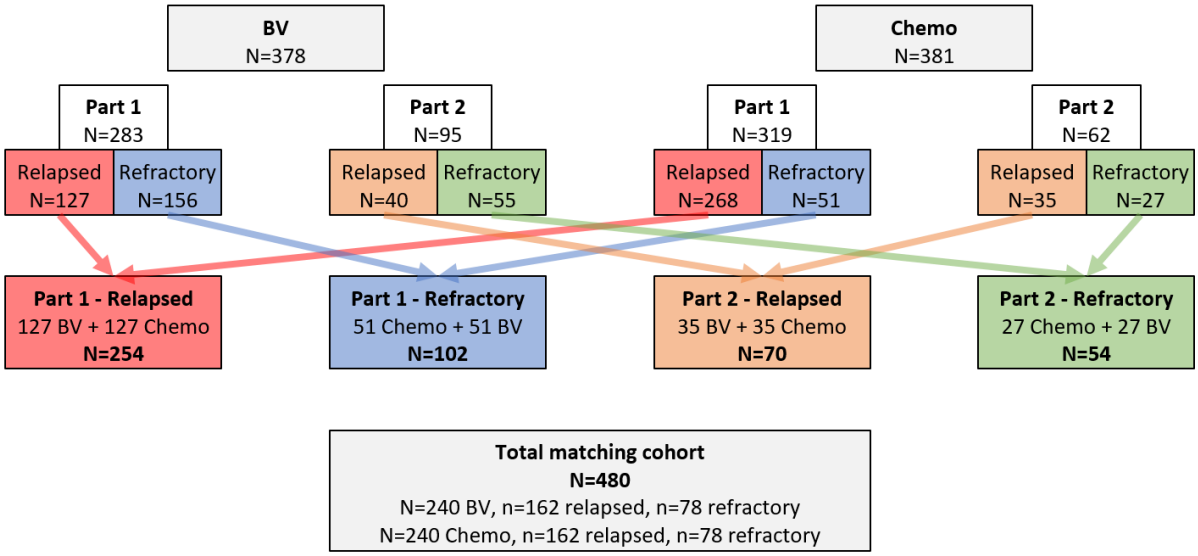
Number of patients per study with missing values in one or more matching variables.
Abbreviations: R/R, relapsed/refractory; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine and prednisone; PD, progressive disease; WHO-PS, world health organization performance score.

Extended Methods Table 4: Progression free survival in the matched cohort for cross-validated matching repeats

	Two-stage matching (n=480)		One-stage matching (n=356)		Final matched dataset (n=480)	
Cohort	**Median 3-year PFS of 2000 repeats (95% CI)**	***P***	**Median 3-year PFS of 2000 repeats (95% CI)**	***P***	**PFS (95% CI)**	***P***
N per cohort *(refractory; %)*	N=240 *(n=78; 32%)*		N=178 *(n=51; 29%)*		N=240 *(n=78; 32%)*	
All patients						
BV	72.2% (66.5% - 78.4%)	0.1329	73.7% (67.2% - 80.7%)	0.1925	72.2% (66.5% - 78.3%)	0.1373
Chemo	66.9% (61.1% - 73.2%)		68.8% (62.3% - 76.1%)		67.1% (61.3% - 73.4%)	
HR	1.3 (0.9 - 1.8)	0.1326	1.3 (0.9 - 1.9)	0.1922	1.3 (0.9 - 1.8)	0.1370
Relapsed						
BV	79.7% (73.4% - 86.6%)	**0.0196**	80.6% (73.7% - 88.2%)	**0.0335**	79.9% (73.6% - 86.7%)	**0.0203**
Chemo	69.4% (62.5% - 77.0%)		70.7% (63.1% - 79.3%)		69.7% (62.8% - 77.2%)	
HR	1.7 (1.1 - 2.7)	**0.0192**	1.7 (1.0 - 2.9)	**0.0331**	1.7 (1.1 - 2.7)	**0.0199**
Refractory						
BV	56.9% (46.6% - 69.3%)	0.6388	56.3% (44.2% - 72.1%)	0.4580	56.6% (46.4% - 69.1%)	0.6716
Chemo	61.7% (51.7% - 73.8%)		64.4% (52.5% - 79.1%)		61.7% (51.7% - 73.8%)	
HR	0.9 (0.5 - 1.5)	0.6387	0.8 (0.4 - 1.5)	0.4578	0.9 (0.6 - 1.5)	0.6722

Matching was repeated 2000 times and for each iteration a log-rank comparison of 3-year PFS for the BV- vs chemo-cohort was performed on the whole dataset and stratified for relapsed and primary refractory status. Median results for all 2000 iterations are shown for the two-stage matching and for a one-stage matching sensitivity analysis in which patients with missing matching variables were excluded. *P*-values represent the median *P*-value for all iterations. The final matched dataset represents the iteration that approximates the median results the most and results for this single dataset are presented in the last column. *P*-values represent log-rank comparisons and hazard ratios of univariable cox regression between the BV- and chemo-cohort.
Abbreviations: BV, brentuximab vedotin; Chemo, chemotherapy; n, number; PFS, progression free survival; I, iteration; x, times; CI, confidence interval, HR; hazard ratio.

Extended methods Figure 1: Matching process of BV- and chemo-cohorts



Matching of BV- and chemo-cohorts in two steps. Part 1 includes patients with all information of matching variables available, Part 2 includes patients who have a missing variable in B-symptoms, Ann Arbor stage IV or bulky disease. The colored arrows indicate to which group patients are being matched.

Abbreviations: BV, brentuximab vedotin; Chemo, chemotherapy; n, number.

Supplemental Table 1: Salvage regimen and BV dose per study

Study	Therapy	Salvage therapy schedule and dose
Moskowitz, Blood 2012.[3]	ICE-GVD	Two treatment arms: 1. One cycle of etoposide (100mg/m^2) IV on day 1 and 3, carboplatin (5 AUC), and ifosfamide (5000mg/m^2) with equal dose MESNA. Followed by one cycle of ifosfamide (5000mg/m^2) mixed with equal dose MESNA IVCI 2 times starting on day 1, carboplatin (5 AUC) on day 3, etoposide (200mg/m^2) every 12 hours at 3 doses starting day 1. Second cycle was administered 14-21 days after cycle 1 dependent on platelet recovery. 2. Two cycles of ifosfamide (5000mg/m^2) mixed with equal dose mesna IVCI 2 times starting on day 1, carboplatin (5 AUC) on day 3, etoposide (200mg/m^2) every 12 hours at 3 doses starting day 1. Regimen was administered on a 17-21 day schedule. PET-positive patients after two cycles of (aug)ICE received two cycles of gemcitabine (1000mg/m^2), vinorelbine (20mg/m^2) and liposomal doxorubicin (15mg/m^2) every two weeks.
Josting, JCO 2010.[4]	DHAP	Two cycles of dexamethasone (40 mg) IV on days 1 to 4, 2x cytarabine (2000 mg/m^2) over 3 hours on day 2, cisplatinum (100mg/m^2) IVCI for 24 hours on day 1. Second cycle was administered after platelet and white blood cell count recovery.
Santoro, Blood 2016.[5]	BeGEV	Four cycles of gemcitabine (800mg/m^2) on days 1 to 4, vinorelbine (20mg/m^2) on day 1, bendamustine (90mg/m^2) on days 2 and 3, and prednisolone (100mg) on days 1 to 4. Regimen was administered every 21 days.
Herrera, Ann Oncol 2018.[6]	BV-ICE (seq)	Two treatment arms: 1. A maximum of four 21-day cycles of BV (1.8mg/kg). Patients achieving CR or PR could proceed to ASCT after two cycles. 2. BV (1.8 mg/kg) every 21 days for a maximum of four cycles. Patients in PR or SD after two cycles received escalated BV (2.4 mg/kg) for two cycles. Patients with PR were given the option to receive salvage chemotherapy. Patients with PD or SD were required to undergo salvage chemotherapy. Therapy choice was at physicians discretion.
Moskowitz, Lancet Oncol 2015.[7]	BV-ICE (seq)	Two cycles of BV (1.2 mg/kg) on day 1, 8 and 15 of 28 day cycles. Patients with a Deauville score > 3 received two cycles of ifosfamide (5000 mg/m^2) combined with equal dose MESNA IVCI over 24 hours on days 1 and 2, 3x etoposide (200mg/m^2) IVCI over 60 min every 12 hours beginning on day 1, and carboplatin (5AUC) on day 3
LaCasce, Blood 2018.[8]	BV-benda	Two to six cycles of BV (1.8 mg/kg) on day 1 and bendamustine (90mg/m^2) on days 1 and 2 of a 21 day cycle. Patients in CR may go off study to proceed to ASCT after at least two cycles. Patients who underwent ASCT are reregistered and may receive BV monotherapy until a total of 16 cycles has been reached (including pre-ASCT BV).
Cole, Lancet Oncol 2018.[9]	BV-gem	BV (1.8 mg/kg) on day 1 and gemcitabine (1000 mg/m^2) over 100 min on days 1 and 8 for a median of four cycles.
Broccoli, Blood Cancer J 2019.[10]	BV-benda	Up to six cycles of BV (1.8 mg/kg) on day 1 and bendamustine (90 mg/m^2) on days 1 and 2 of each 21 day cycle. Patients in response after two cycles were allowed to proceed to ASCT.
Garcia-Sanz, Ann Oncol 2019.[11]	BV-ESHAP	Three 21-day cycles of BV (1.8 mg/kg) on day 1, etoposide (40 mg/m^2) on days 1 to 4, methylprednisolone (250mg/day) on days 1 to 4, cisplatin (25 mg/m^2) as 24h IVCI on days 1 to 4 and cytarabine (2g/m^2) on day 5. A fourth BV dose was given 21 days after the third dose.
Kersten, Haematologica 2021.[12]	BV-DHAP	Three 21-day cycles of BV (1.8 mg/kg) on day 1, dexamethasone (40 mg) on days 1 to 4, cisplatin (100mg/m^2) as 24h IVCI on day 1 and cytarabine (2x 2 g/m^2) over a 3 hour infusion on day 2.

Abbreviations: IVCI, intravenous continuous infusion; IV, intravenous; AUC, area under the curve; PET, positron emission tomography; seq, sequential; BV, brentuximab vedotin; CR, complete response; PR, partial response; PD, progressive disease; SD, stable disease; ASCT, autologous stem cell transplantation;

Supplemental Table 2: Study characteristics

Study	Year of publication	N	Salvage therapy	Primary refractory	Underwent ASCT	Received BV maintenance	Event PFS	Event EFS	Event OS	**Median follow-up time** (months) Median [Q1-Q3] (range)
AMoskowitz	2015	64	BV-ICE (seq)	34 (53%)	62 (97%)	0 (0%)	13 (20%)	14 (22%)	3 (5%)	58 [40.8 - 66.8] (2 - 82.6)
Broccoli	2019	40	BV-benda	28 (70%)	32 (80%)	0 (0%)	13 (32%)	14 (35%)	2 (5%)	24.7 [21.1 - 29.5] (4.8 - 34)
Cole	2018	39	BV-gem	27 (69%)	32 (82%)	0 (0%)	16 (41%)	18 (46%)	7 (18%)	50.4 [39.1 - 54.6] (19.7 - 63.9)
GarciaSanz	2019	66	BV-ESHAP	40 (61%)	60 (91%)	56 (85%)	19 (29%)	20 (30%)	6 (9%)	22.1 [19.6 - 28.1] (3.1 - 34.5)
Herrera	2018	57	BV-ICE (seq)	31 (54%)	47 (84%)	0 (0%)	27 (47%)	28 (49%)	6 (11%)	61.4 [49.2 - 65.8] (17.4 - 89.5)
Kersten	2021	65	BV-DHAP	25 (38%)	60 (92%)	0 (0%)	15 (23%)	15 (23%)	3 (5%)	39.4 [38.4 - 40.7] (22.7 - 45.7)
LaCasce	2018	55	BV-benda	28 (51%)	42 (76%)	31 (56%)	19 (35%)	22 (40%)	4 (7%)	26.5 [12.4 - 38.8] (1.9 - 48)
CMoskowitz	2012	98	ICE-GVD (seq)	41 (42%)	86 (88%)	0 (0%)	29 (30%)	29 (30%)	18 (18%)	75.6 [59.7 - 100] (9.8 - 146.5)
Josting	2010	225	DHAP	11 (5%)	194 (86%)	0 (0%)	69 (31%)	75 (33%)	35 (16%)	42 [27.3 - 60.7] (0.1 - 93.5)
Santoro	2016	59	BeGEV	26 (44%)	44 (75%)	0 (0%)	22 (37%)	22 (37%)	12 (20%)	36 [29.7 - 47.2] (3 - 59.4)
Total		**768**		**291 (38%)**	**659 (86%)**	**87 (11%)**	**242 (32%)**	**257 (33%)**	**96 (12%)**	**39.8 [27.1 - 59.8] (0.1 - 146.5)**

Overview of number of included patients, salvage regimens used in each study, number of patients receiving post-ASCT BV maintenance therapy, summarized patient characteristics and outcome parameters, and median follow-up time in patients without PFS event in months including interquartile ranges and min-max ranges.

Abbreviations: ASCT, autologous stem cell transplantation; PFS, progression free survival; EFS, event free survival; OS, overall survival; seq, sequential; BV, brentuximab vedotin; ICE, ifosfamide, cytarabine and etoposide; benda, bendamustine; gem, gemcitabine; ESHAP, etoposide, methylprednisolone, cisplatin and cytarabine; DHAP, dexamethasone, high dose cytarabine and cisplatin; GVD, gemcitabine, vinorelbine and doxorubicin; BeGEV, bendamustin, gemcitabine, and vinorelbine; AMoskowitz, study of A. Moskowitz et al., Lancet Oncol 2015[7]; Broccoli, study of Broccoli et al., Blood Cancer J 2019[10]; Cole, study of Cole et al., Lancet Oncol 2018[9]; GarciaSanz, study of Garcia-Sanz et al., Ann Oncol 2019[11]; Herrera, study of Herrera et al., Ann Oncol 2018[6]; Kersten, study of Kersten et al., Haematologica 2021[12]; LaCasce, study of LaCasce et al., Blood 2018[8]; CMoskowitz, study of C. Moskowitz et al., Blood 2012[3]; Josting, study of Josting et al., JCO 2010[4]; Santoro, study of Santoro et al., JCO 2016[5].

Supplemental Table 3A: PFS per 6 months on the whole dataset before matching

	BV-cohort				Chemo-cohort			
Time (months)	**N at risk**	**N events**	**N censor**	**PFS (95% CI)**	**N at risk**	**N events**	**N censor**	**PFS (95% CI)**
0	386	0	0	100%	382	0	0	100%
6	333	44	9	88% (85% - 92%)	322	52	8	86% (83% - 90%)
12	281	46	6	76% (72% - 81%)	276	39	7	76% (71% - 80%)
18	247	24	10	70% (65% - 74%)	254	16	6	71% (67% - 76%)
24	200	4	43	68% (64% - 73%)	230	9	15	69% (64% - 74%)
30	164	1	35	68% (63% - 73%)	203	4	23	67% (63% - 72%)
36	144	3	17	67% (62% - 72%)	179	0	24	67% (63% - 72%)
42	88	1	56	66% (61% - 71%)	152	2	25	67% (62% - 72%)
48	75	1	11	65% (60% - 71%)	127	2	23	66% (61% - 71%)
60	43	2	30	63% (57% - 69%)	91	2	34	65% (60% - 70%)

Progression free survival (PFS) results per 6 months up to 10 years from enrollment. Number of patients at risk at given time point, number of events (i.e. progressive disease or death), number of patients censored and cumulative PFS at given time point, stratified for the BV and chemo-cohorts.

Abbreviations: BV, brentuximab vedotin; chemo, chemotherapy; N, number; PFS, progression free survival; CI, confidence interval.

Supplemental Table 3B: Survival analysis on the whole dataset before matching

Group	**N**	**3-year PFS (95% CI)**	***P***	**3-year EFS (95% CI)**	***P***	**3-year OS (95% CI)**	***P***
Whole dataset							
BV	386	66.7% (62.0-71.8)	0.64	64.8% (60.1-69.9)	0.47	91.0% (88.0-94.1)	0.002
Chemo	382	67.4% (62.8-72.4)		66.0% (61.4-71.1)		80.4% (76.2-84.9)	
Relapsed							
BV	173	79.2% (73.0-85.9)	0.063	77.3% (71.1-84.1)	0.087	97.0% (94.5-99.6)	***<0.0001***
Chemo	304	68.9% (63.8-74.5)		67.1% (62.0-72.8)		82.1% (77.6-87.0)	
Refractory							
BV	213	56.9% (50.4-64.2)	0.53	54.9% (48.4-62.2)	0.33	85.9% (80.9-91.2)	0.19
Chemo	78	61.7% (51.7-73.8)		61.7% (51.7-73.8)		74.2% (64.4-85.4)	
BV cohort per study							
AMoskowitz (BV-ICE_1)	64	78.6% (69.0-89.6)		77.4% (67.6-88.6)		95.0% (89.6-100.0)	
Broccoli (BV-benda_1)	40	66.2% (52.7-83.1)		64.2% (50.7-81.3)		96.8% (90.8-100.0)	
Cole (BV-gem)	39	59.0% (45.4-76.6)		53.8% (40.3-72.0)		80.6% (68.6-94.6)	
GarciaSanz (BV-ESHAP)	66	70.5% (60.2-82.6)		69.4% (59.1-81.6)		90.9% (84.2-98.1)	
Herrera (BV-ICE_2)	57	52.4% (40.8-67.2)		50.6% (39.1-65.5)		89.2% (81.4-97.8)	
Kersten (BV-DHAP)	65	76.7% (67.0-87.8)		76.7% (67.0-87.8)		95.4% (90.4-100.0)	
LaCasce (BV-benda_2)	55	57.3% (43.9-74.8)		54.1% (41.1-71.1)		92.3% (85.3-99.9)	
Chemo cohort per study							
CMoskowitz (ICE-GVD)	98	70.2% (61.7-79.9)		70.2% (61.7-79.9)		80.9% (73.4-89.3)	
Josting (DHAP)	225	67.9% (61.9-74.5)		65.5% (59.4-72.2)		81.0% (75.4-87.0)	
Santoro (BeGEV)	59	60.7% (49.1-75.0)		60.8% (49.2-75.1)		78.8% (68.9-90.2)	

Log-rank comparison for 3-year PFS, EFS and OS of BV- versus chemo-cohorts in the whole dataset before matching and stratified for patients with relapsed or primary refractory disease. Survival outcomes for each BV and chemo study are provided.

Abbreviations: PFS, progression free survival; EFS, event free survival; OS, overall survival; seq, sequential; BV, brentuximab vedotin; ICE, ifosfamide, cytarabine and etoposide; benda, bendamustine; gem, gemcitabine; ESHAP, etoposide, methylprednisolone, cisplatin and cytarabine; DHAP, dexamethasone, high dose cytarabine and cisplatin; GVD, gemcitabine, vinorelbine and doxorubicin; BeGEV, bendamustin, gemcitabine, and vinorelbine; AMoskowitz, study of A. Moskowitz et al., Lancet Oncol 2015[7]; Broccoli, study of Broccoli et al., Blood Cancer J 2019[10]; Cole, study of Cole et al., Lancet Oncol 2018[9]; GarciaSanz, study of Garcia-Sanz et al., Ann Oncol 2019[11]; Herrera, study of Herrera et al., Ann Oncol 2018[6]; Kersten, study of Kersten et al., Haematologica 2021[12]; LaCasce, study of LaCasce et al., Blood 2018[8]; CMoskowitz, study of C. Moskowitz et al., Blood 2012[3]; Josting, study of Josting et al., JCO 2010[4]; Santoro, study of Santoro et al., JCO 2016[5].

Supplemental Table 4: Survival analysis on the matched dataset

Group	N	3-year PFS (95% CI)	*P*	3-year EFS (95% CI)	*P*	3-year OS (95% CI)	*P*
Matched dataset							
BV	240	72.2% (66.5-78.3)	0.140	70.8% (65.1-77.0)	0.240	91.9% (88.3-95.6)	0.00043
Chemo	240	67.1% (61.3-73.4)		66.5% (60.7-72.9)		79.5% (74.2-85.1)	
[HR; 95% CI]		1.287 (0.92-1.80)	0.137	1.214 (0.88-1.68)	0.244	2.583 (1.49-4.47)	<0.0001
Relapsed							
BV	162	79.9% (73.6-86.7)	0.020	78.4% (72.0-85.3)	0.043	96.9% (94.2-99.6)	<0.0001
Chemo	162	69.7% (62.8-77.2)		68.9% (62.0-76.5)		82.1% (76.0-88.6)	
[HR; 95% CI]		1.705 (1.08-2.69)	0.020	1.57 (1.01-2.44)	0.043	5.53 (2.12-14.39)	<0.0001
Refractory							
BV	78	56.6% (46.4-69.1)	0.670	55.3% (45.1-67.8)	0.540	81.7% (73.1-91.4)	0.320
Chemo	78	61.7% (51.7-73.8)		61.7% (51.7-73.8)		74.2% (64.4-85.4)	
[HR; 95% CI]		0.898 (0.55-1.48)	0.672	0.858 (0.52-1.41)	0.545	1.435 (0.7-2.93)	0.318

Log-rank comparison for 3-year PFS, EFS and OS of BV- versus chemo-cohorts in the matched dataset and stratified for patients with relapsed or primary refractory disease. Hazard ratios of cox proportional hazard regression are provided for each survival comparison.

Abbreviations: PFS, progression free survival; EFS, event free survival; OS, overall survival; BV, brentuximab vedotin; HR, hazard ratio.

Supplemental Table 5: Survival analysis in patients who underwent ASCT

Group	N	3-year PFS (95% CI)	*P*	3-year EFS (95% CI)	*P*	3-year OS (95% CI)	*P*
Matched dataset							
BV	216	77.6% (72.0-83.6)	0.920	72.2% (65.6-79.4)	0.930	93.6% (90.3-97.1)	0.018
Chemo	199	78.5% (72.9-84.5)		76.3% (70.1-82.9)		85.6% (80.6-90.9)	
[HR; 95% CI]		0.979 (0.64-1.49)	0.921	1.214 (0.88-1.68)	0.244	2.188 (1.12-4.26)	0.017
Relapsed							
BV	147	83.9% (77.9-90.4)	0.320	81.0% (74.1-88.6)	0.320	96.6% (93.7-99.6)	0.0097
Chemo	137	79.8% (73.3-86.9)		77.8% (70.6-85.6)		87.3% (81.7-93.4)	
[HR; 95% CI]		1.333 (0.76-2.34)	0.316	1.57 (1.01-2.44)	0.043	3.467 (1.27-9.47)	0.0083
Refractory							
BV	69	64.0% (53.4-76.8)	0.180	53.4% (41.3-69.0)	0.220	87.3% (79.4-96.0)	0.480
Chemo	62	75.5% (65.4-87.1)		72.8% (61.7-85.8)		81.5% (71.7-92.7)	
[HR; 95% CI]		0.647 (0.34-1.23)	0.181	0.858 (0.52-1.41)	0.545	1.40 (0.55-3.55)	0.476

Log-rank comparison for 3-year PFS, EFS and OS in patients who underwent ASCT of BV- versus chemo-cohorts in the matched dataset and stratified for patients with relapsed or primary refractory disease. Hazard ratios of cox proportional hazard regression are provided for each survival comparison. Survival was measured from baseline because the date of stem-cell reinfusion was not known for all patients.

Abbreviations: PFS, progression free survival; EFS, event free survival; OS, overall survival; BV, brentuximab vedotin; CI, confidence interval; HR, hazard ratio.

Supplemental Table 6: Influence of salvage regimen and BV dose

Summary of salvage therapy schedule and BV dose for each study in the BV-cohort							
Study	**N**	**Regimen**	**Chemo[1]**	**Sequential[2]**	**BV cycles[3]**	**BV dose[4]**	**Cumulative dose[5]**
AMoskowitz	64	BV-ICE	Multiple	Sequential	6	1.2mg/kg	7.2 mg
Herrera	57	BV-ICE	Multiple	Sequential	4	1.8mg/kg	7.2 mg
GarciaSanz	66	BV-ESHAP	Multiple	Concomitant	4	1.8mg/kg	7.2 mg
Kersten	65	BV-DHAP	Multiple	Concomitant	3	1.8mg/kg	5.4 mg
LaCasce	55	BV-benda	Mono	Concomitant	2-6 + 16	1.8mg/kg	36 mg
Broccoli	40	BV-benda	Mono	Concomitant	4-6	1.8mg/kg	10.8 mg
Cole	39	BV-gem	Mono	Concomitant	8	1.8mg/kg	14.4

Cox proportional hazard analysis of salvage therapy and BV schedule for 3-years PFS									
	Univariable			***Corrected for R/R status***			***Multivariable***		
Covariate	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Multiple chemo agents[1]	0.72	0.50 - 1.04	0.079	0.81	0.56 - 1.17	0.258	0.69	0.37 - 1.30	0.252
Sequential vs concomitant[2]	1.01	0.69 - 1.48	0.954	1.07	0.73 - 1.56	0.740	1.07	0.68 - 1.68	0.780
BV cycles[3]	1.02	0.99 - 1.05	0.285	1.01	0.98 - 1.05	0.372	0.99	0.82 - 1.19	0.922
Cumulative BV dose[5]	1.01	1.00 - 1.03	0.167	1.01	0.99 - 1.03	0.229	1.12	0.98 - 1.30	0.106

Cox proportional hazard analysis was done for each covariate in a univariate analysis, in a multivariate analysis corrected for R/R status (only results of the covariate shown) and in a multivariate analysis corrected for R/R status, B symptoms, stage IV disease, extranodal disease, primary treatment with escBEACOPP and bulky disease (only results of the covariate shown). A hazard ratio of >1 corresponds to a higher chance of having progressive disease within 3-years.

Cox proportional hazard analysis of salvage therapy and BV schedule for achieving a CMR									
	Univariable			***Corrected for R/R status***			***Multivariable***		
Covariate	**Est.**	**SE**	***P***	**Est.**	**SE**	***P***	**Est.**	**SE**	***P***
Multiple chemo agents[1]	-0.20	0.26	0.436	-0.33	0.27	0.217	-0.15	0.43	0.732
Sequential vs concomitant[2]	-0.26	0.26	0.302	-0.30	0.26	0.254	-0.13	0.31	0.668
BV cycles[3]	-0.03	0.08	0.722	0.02	0.08	0.837	0.07	0.13	0.572
Cumulative BV dose[6]	-0.04	0.04	0.319	-0.02	0.05	0.679	-0.04	0.10	0.659

Logistic regression was done for each covariate in a univariate analysis, in a multivariate analysis corrected for R/R status (only results of the covariate shown) and in a multivariate analysis corrected for R/R status, B symptoms, stage IV disease, extranodal disease, primary treatment with escBEACOPP and bulky disease (only results of the covariate shown). A positive estimate corresponds to a higher chance of achieving a CMR on the pre-ASCT PET-scan.

[1]Multiple chemotherapeutic agents versus a single chemotherapeutic agent. [2]Sequential treatment with BV monotherapy followed by salvage chemotherapy or concomitant BV plus salvage chemotherapy. [3]Total number of planned BV cycles including consolidation treatment, if a study provides an optional number of cycles the highest total number of cycles was used (for example in the study of LaCasce et al., patients could proceed to ASCT after 2-6 cycles of BV salvage treatment depending on the response and the local physicians discretion and patients could receive up to 16 cycles of BV consolidation monotherapy, the maximum number of cycles in 24 and was used in the analysis, despite not all patients having received the full number of cycles. [4]BV dose per cycle. [5]Cumulative dose of all BV cycles. [6]Cumulative dose of BV given during salvage treatment before ASCT.

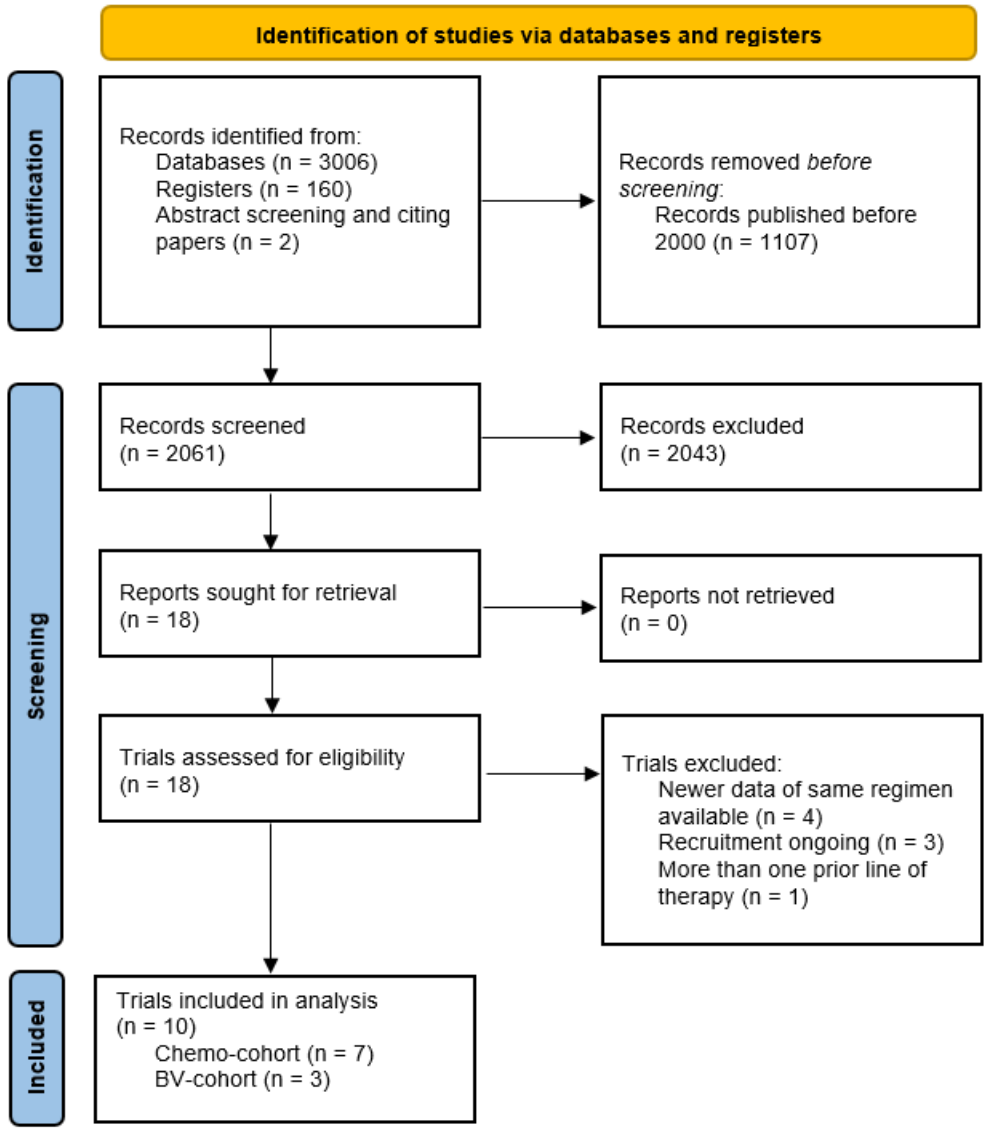
Abbreviations: BV, brentuximab vedotin; ICE, ifosfamide, cytarabine and etoposide; benda, bendamustine; gem, gemcitabine; ESHAP, etoposide, methylprednisolone, cisplatin and cytarabine; DHAP, dexamethasone, high dose cytarabine and cisplatin; PFS, progression free survival; R/R, relapsed/refractory; HR, hazard ratio; CI, confidence interval; CMR, complete metabolic response; Est, estimate; SE, standard error; AMoskowitz, study of A. Moskowitz et al., Lancet Oncol 2015[7]; Broccoli, study of Broccoli et al., Blood Cancer J 2019[10]; Cole, study of Cole et al., Lancet Oncol 2018[9]; GarciaSanz, study of Garcia-Sanz et al., Ann Oncol 2019[11]; Herrera, study of Herrera et al., Ann Oncol 2018[6]; Kersten, study of Kersten et al., Haematologica 2021[12]; LaCasce, study of LaCasce et al., Blood 2018[8].

Supplemental Table 7: Subgroup survival analyses on the whole dataset

Subgroup	N	3-year survival	95% CI	*P*
Sequential salvage regimen in patients who underwent ASCT while in CMR		**PFS**		
CMR after BV-ICE (sequential)	47	71.0%	58.9%-85.8%	0.67
CMR after BV only	41	80.4%	69.1%-93.6%	
CMR after ICE-GVD (sequential)	21	76.2%	60.0%-96.8%	
CMR after ICE only	61	81.6%	72.4%-92.1%	
Sequential salvage regimen in patients who underwent ASCT while in CMR		**PFS**		
CMR after BV or ICE only	102	81.1%	73.8%-89.2%	0.24
CMR after BV-ICE or ICE-GVD	68	72.8%	62.8%-84.4%	
Sequential salvage regimen in patients who underwent ASCT while in CMR		**OS**		
CMR after BV or ICE only	102	92.8%	87.7%-98.1%	0.62
CMR after BV-ICE or ICE-GVD	68	90.8%	84.1%-98.1%	
Patients who underwent ASCT		**PFS**		
CMR pre-ASCT	398	78.3%	74.2%-82.5%	
PMR pre-ASCT	57	64.2%	52.8%-78.1%	0.0106
SD pre-ASCT	8	37.5%	15.3%-91.7%	0.00043
Patients who underwent ASCT		**OS**		
CMR pre-ASCT	398	92.5%	89.8%-95.3%	
PMR pre-ASCT	57	88.4%	80.0%-97.7%	0.286
SD pre-ASCT	8	62.5%	36.5%-100.0%	0.0042

Abbreviations: CI, confidence interval; ASCT, autologous stem cell transplantation; CMR, complete metabolic response; PFS, progression free survival; BV, brentuximab vedotin; ICE, ifosfamide, cytarabine and etoposide; GVD, gemcitabine, vinorelbine and doxorubicin; OS, overall survival; PMR, partial metabolic response; SD, stable disease;

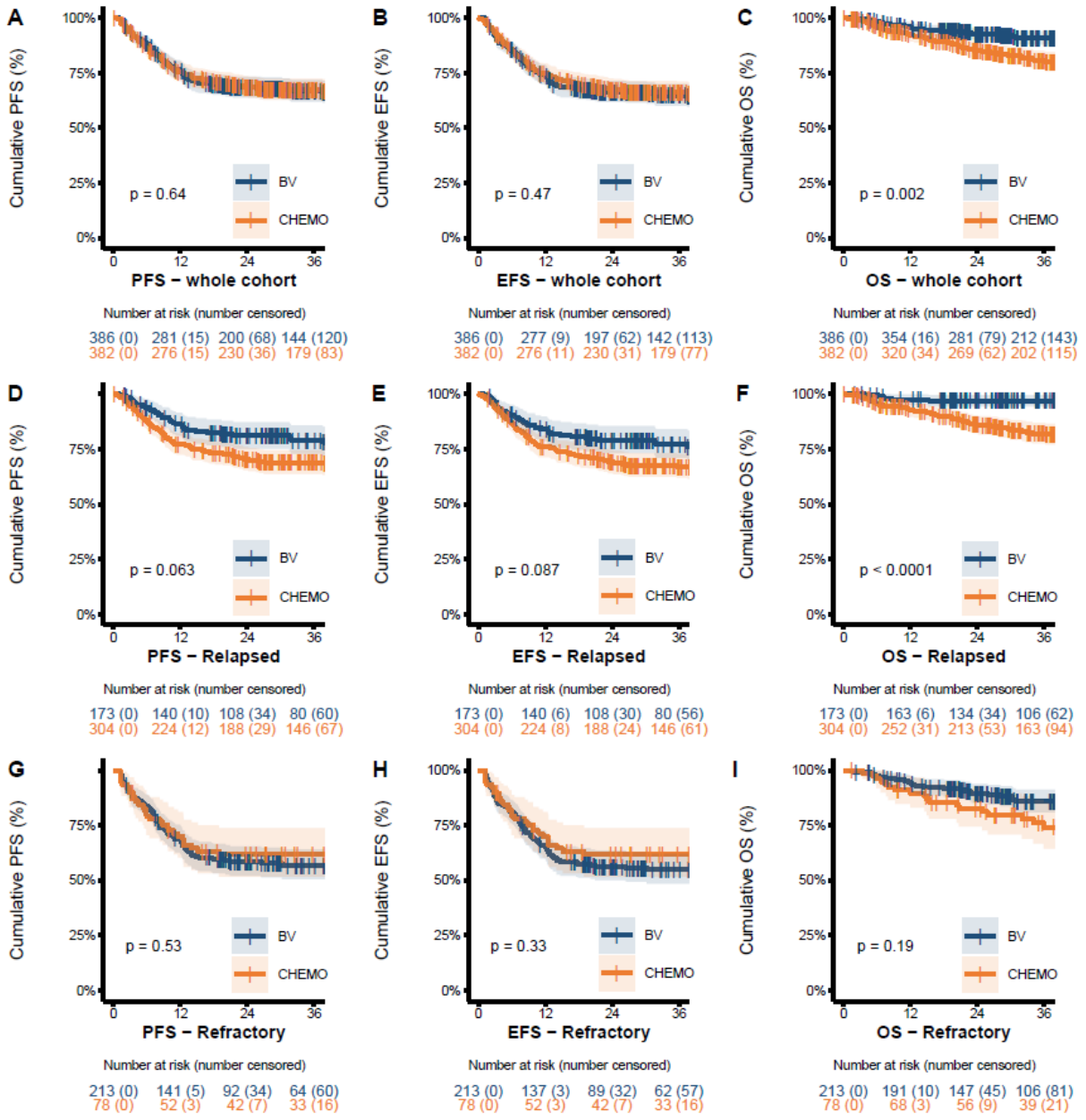
Supplemental Figure 1: PRISMA flowchart of included studies



PRISMA flowchart of included studies. Included articles were identified through the PubMed database and clinicaltrials.gov register.

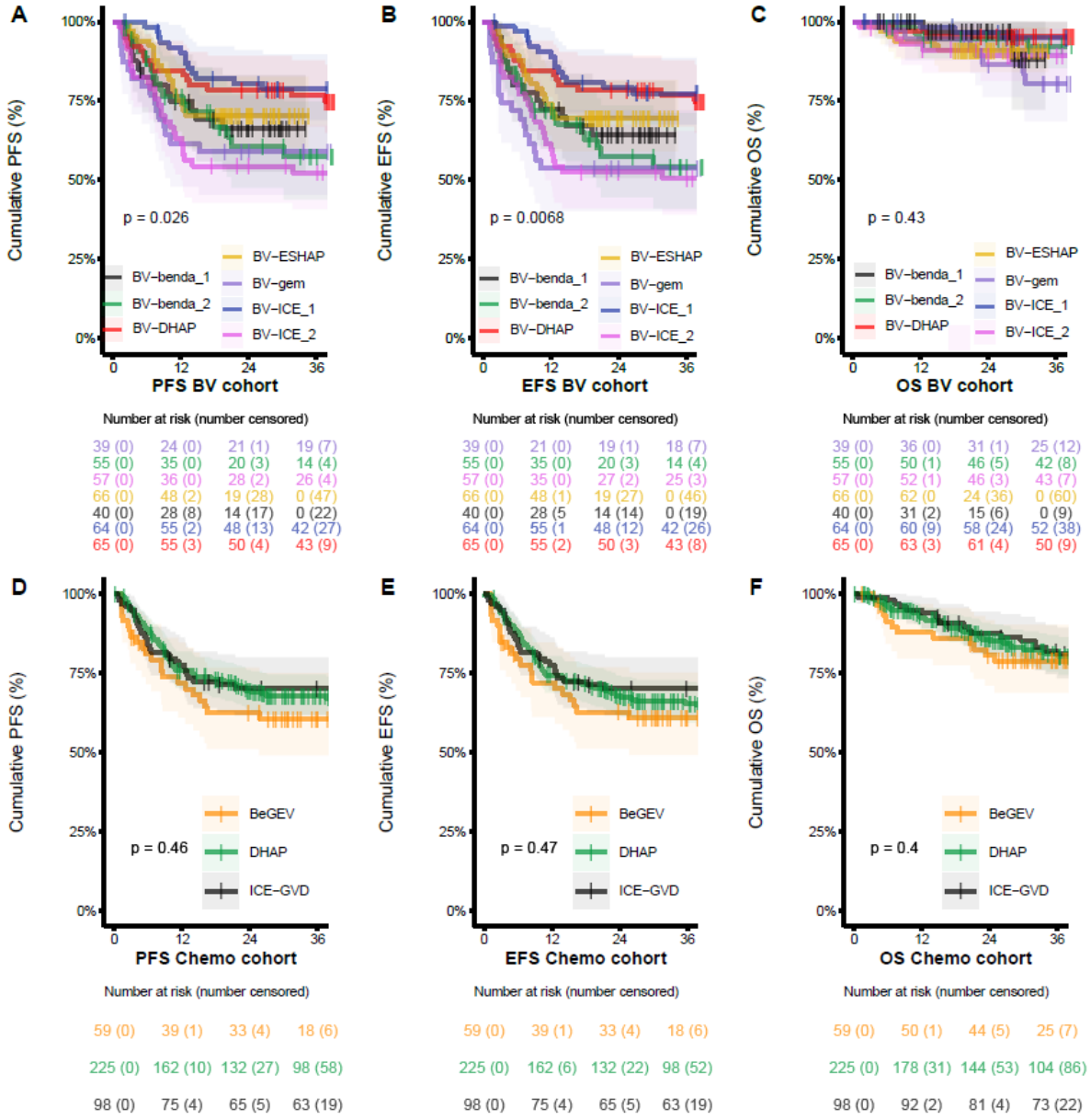
Abbreviations: BV, brentuximab vedotin; n, number; Chemo, chemotherapy.

Supplemental Figure 2: Kaplan-Meier survival analysis on the whole dataset



Kaplan-Meier survival curves in the whole, unmatched dataset comparing the chemo- and brentuximab vedotin (BV) cohorts. **(A-C)** progression free survival (PFS), event free survival (EFS) and overall survival (OS) in the whole cohort. **(D-F)** PFS, EFS and OS in all relapsed patients**. (G-I)** PFS, EFS and OS in all primary refractory patients.

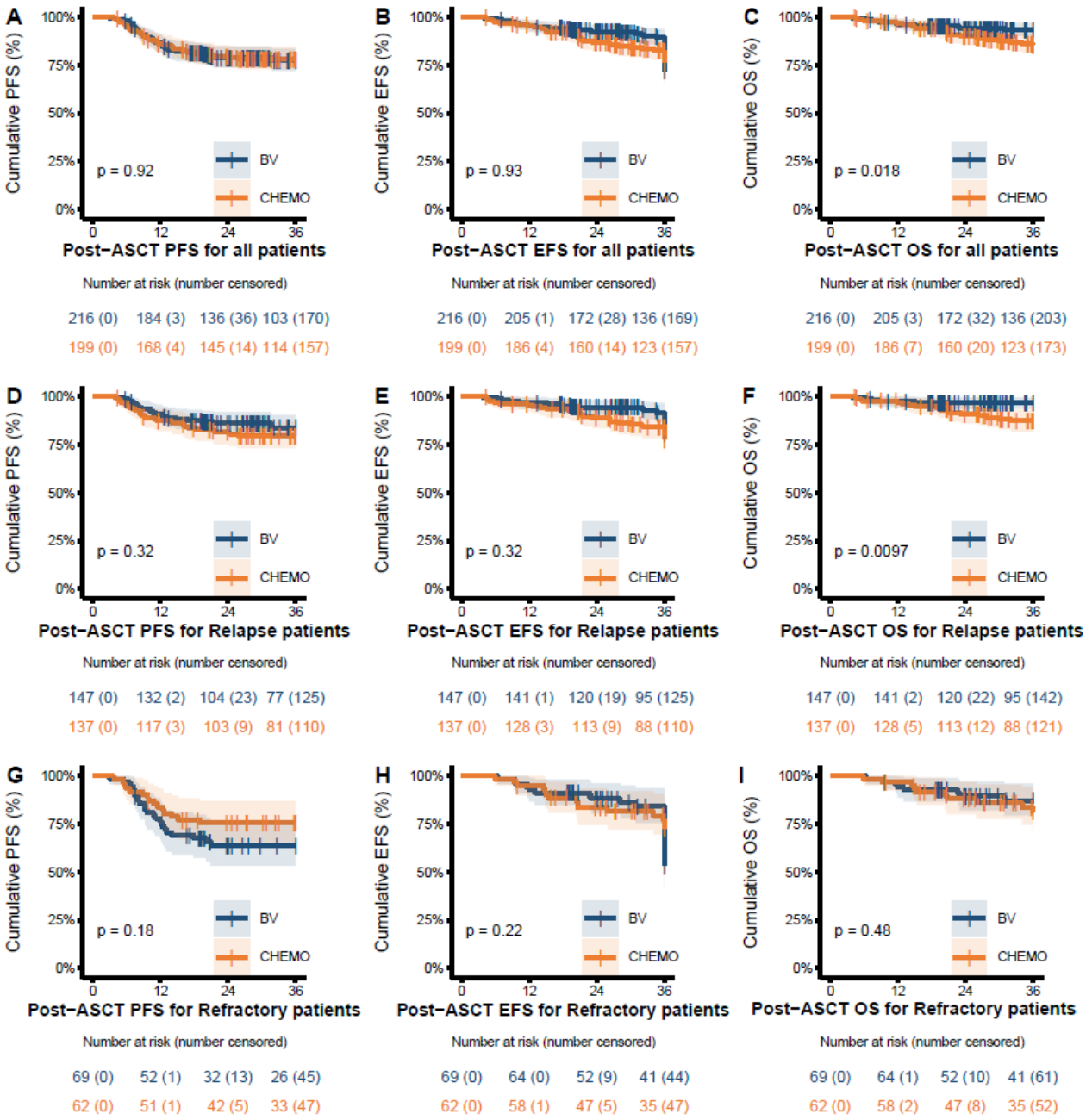
Supplemental Figure 3: Kaplan-Meier survival analysis per study



Kaplan-Meier survival analyses in all patients per study. **(A-C)** Progression free survival (PFS), event free survival (EFS) and overall survival (OS) per included study in the brentuximab vedotin (BV) cohort. BV-benda_1 is the study by Broccoli et al, BV-benda_2 by LaCasce et al, BV-ICE_1 by AMoskowitz et al and BV-ICE_2 by Herrera et al. **(D-F)** PFS, EFS and OS per included study in the chemo-cohort.

Abbreviations: ICE, ifosfamide, cytarabine and etoposide; benda, bendamustine; gem, gemcitabine; ESHAP, etoposide, methylprednisolone, cisplatin and cytarabine; DHAP, dexamethasone, high dose cytarabine and cisplatin; GVD, gemcitabine, vinorelbine and doxorubicin; BeGEV, bendamustin, gemcitabine, and vinorelbine

Supplemental Figure 4: Kaplan-Meier survival analysis in patients who underwent ASCT in the matched dataset



Kaplain-Meier analyses on all patients in the matched dataset who proceeded to autologous stem cell transplantation (ASCT). **(A-C)** Post-ASCT progression free survival (PFS), event free survival (EFS) and overall survival (OS) for all matched patients who underwent ASCT. **(D-F)** Post-ASCT PFS, EFS and OS in all matched relapsed patients who underwent ASCT. **(G-I)** Post-ASCT PFS, EFS and OS in all matched refractory patients who underwent ASCT.

Abbreviations: BV, brentuximab vedotin.

References:

1. Cenzer I, Boscardin WJ, Berger K: Performance of matching methods in studies of rare diseases: a simulation study. Intractable Rare Dis Res 9:79-88, 2020
2. Brookhart MA, Schneeweiss S, Rothman KJ, et al: Variable selection for propensity score models. Am J Epidemiol 163:1149-56, 2006
3. Moskowitz CH, Matasar MJ, Zelenetz AD, et al: Normalization of pre-ASCT, FDG-PET imaging with second-line, non-cross-resistant, chemotherapy programs improves event-free survival in patients with Hodgkin lymphoma. Blood 119:1665-70, 2012
4. Josting A, Muller H, Borchmann P, et al: Dose intensity of chemotherapy in patients with relapsed Hodgkin's lymphoma. J Clin Oncol 28:5074-80, 2010
5. Santoro A, Mazza R, Pulsoni A, et al: Bendamustine in Combination With Gemcitabine and Vinorelbine Is an Effective Regimen As Induction Chemotherapy Before Autologous Stem-Cell Transplantation for Relapsed or Refractory Hodgkin Lymphoma: Final Results of a Multicenter Phase II Study. J Clin Oncol 34:3293-9, 2016
6. Herrera AF, Palmer J, Martin P, et al: Autologous stem-cell transplantation after second-line brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. Ann Oncol 29:724-730, 2018
7. Moskowitz AJ, Schöder H, Yahalom J, et al: PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study. The Lancet Oncology 16:284-292, 2015
8. LaCasce AS, Bociek RG, Sawas A, et al: Brentuximab vedotin plus bendamustine: a highly active first salvage regimen for relapsed or refractory Hodgkin lymphoma. Blood 132:40-48, 2018
9. Cole PD, McCarten KM, Pei Q, et al: Brentuximab vedotin with gemcitabine for paediatric and young adult patients with relapsed or refractory Hodgkin's lymphoma (AHOD1221): a Children's Oncology Group, multicentre single-arm, phase 1–2 trial. The Lancet Oncology 19:1229-1238, 2018
10. Broccoli A, Argnani L, Botto B, 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 9:100, 2019
11. Garcia-Sanz R, Sureda A, de la Cruz F, et al: Brentuximab vedotin and ESHAP is highly effective as second-line therapy for Hodgkin lymphoma patients (long-term results of a trial by the Spanish GELTAMO Group). Ann Oncol 30:612-620, 2019
12. Kersten MJ, Driessen J, Zijlstra JM, et al: 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 106:1129-1137, 2021