haematologica
Journal of The Ferrata Storti Foundation

# 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

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Haematologica 2020 [Epub ahead of print]

*Citation: Marie José Kersten, Julia Driessen, Josée M. Zijlstra, Wouter J. Plattel, Franck Morschhauser, Pieternella J. Lugtenburg, Pauline Brice, Martin Hutchings, Thomas Gastinne, Roberto Liu, Coreline N. Burggraaff, Marcel Nijland, Sanne H. Tonino, Anne I. J. Arens, Roelf Valkema, Harm van Tinteren, Marta Lopez-Yurda, Arjan Diepstra, Daphne De Jong, and Anton Hagenbeek. 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. 2020;105:xxx*
*doi:10.3324/haematol.2019.243238*

## Title

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

## Short title

BV-DHAP in relapsed or refractory Hodgkin lymphoma

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## Keywords

Hodgkin Lymphoma, Relapsed or Refractory, Brentuximab Vedotin, DHAP, BEAM, Autologous Stem Cell Transplant

**Regular article:**

Text word count: 3622/4000

Abstract word count: 228/250

Number of tables: 3

Number of figures: 3

Number of references: 42

## Abstract

Achieving a metabolic complete response (mCR) before high-dose chemotherapy (HDC) and autologous peripheral blood stem-cell transplant (auto-PBSCT) predicts progression free survival (PFS) in relapsed/refractory classical Hodgkin lymphoma (R/R cHL). We added brentuximab vedotin (BV) to DHAP to improve the mCR rate. In a Phase I dose-escalation part in 12 patients, we showed that BV-DHAP is feasible. This Phase II study included 55 R/R cHL patients (23 primary refractory). Treatment consisted of three 21-day cycles of BV 1.8 mg/kg on day 1, and DHAP (dexamethasone 40mg days 1-4, cisplatin 100mg/m² day 1 and cytarabine 2x2g/m² day 2). Patients with a metabolic partial response (mPR) or mCR proceeded to HDC/auto-PBSCT. Based on independent central FDG-PET-CT review, 42 of 52 evaluable patients (81% [95% CI: 67-90]) achieved an mCR before HDC/auto-PBSCT, five had an mPR and five had progressive disease (three were not evaluable). After HDC/auto-PBSCT, four patients with an mPR converted to an mCR. The 2-year PFS was 74% [95% CI: 63-86], and the overall survival 95% [95% CI: 90-100]. Toxicity was manageable and mainly consisted of grade 3/4 hematological toxicity, fever, nephrotoxicity, ototoxicity (grade 1/2) and transiently elevated liver enzymes during BV-DHAP. Eighteen patients developed new onset peripheral neuropathy (maximum grade 1/2) and all recovered. In conclusion, BV-DHAP is a very effective salvage regimen in R/R cHL patients, but patients should be monitored closely for toxicity. ClinicalTrials.gov identifier: NCT02280993.

## INTRODUCTION

Salvage chemotherapy followed by high-dose chemotherapy (HDC) and autologous peripheral blood stem-cell transplant (auto-PBSCT) has been the standard of care for patients with relapsed or refractory classical Hodgkin Lymphoma (R/R cHL) for decades.(1, 2) With this treatment, cure rates of 40% to 60% can be achieved. Patients failing this treatment and those relapsing after second line treatment generally have a very poor prognosis.(3-5)

Response to salvage treatment is one of the most important predictors of outcome after auto-PBSCT, with metabolic active residual disease, as assessed by [$^{18}$F]fluorodeoxyglucose (FDG) - positron emission tomography (PET) - computed tomography (CT) scan, before HDC/auto-PBSCT conferring an inferior prognosis.(6-8) Therefore, higher cure rates may be achieved by improving the metabolic complete response (mCR) rate before HDC/auto-PBSCT. Conventional salvage chemotherapy regimens result in mCR rates of about 50–60%.(6, 9-11) DHAP (dexamethasone, high-dose cytarabine, cisplatin) is one of the most commonly used salvage regimens for R/R cHL in Europe.(12)

Brentuximab vedotin (BV) is targeted high-dose intracellular chemotherapy, consisting of an anti-CD30 antibody conjugated to the potent antimicrotubule agent monomethyl auristatin-E.(13, 14) Several Phase II studies have shown promising clinical activity of BV in R/R cHL, both as monotherapy and combined with chemotherapy.(15-20) Toxicities of BV include infusion related reaction (IRR), myelosuppression and peripheral neuropathy, the latter being reversible in the majority of patients.(15, 16, 18, 20, 21)

In the current prospective, multicenter, international Phase I/II Transplant BRaVE study we investigated the efficacy and safety of BV-DHAP followed by HDC (BEAM) and auto-PBSCT in R/R cHL patients.

Results of the Phase I part of this study in 12 patients have been published previously and showed that the combination of BV-DHAP is feasible with acceptable toxicity.(22) The recommended dose level was established at full dose of all drugs with BV dosed at 1.8 mg/kg.(22). The primary endpoints for the Phase II single arm part were the fraction of patients achieving an mCR as judged by independent review of PET-CT scan after the third cycle of BV-DHAP, and the rate of grade 3/4 non-hematological adverse events (AEs), including neurotoxicity, during BV-DHAP.

## METHODS

### *Patients*

The study enrolled patients aged ≥18 years with histologically confirmed CD30 positive cHL by local pathology assessment, either having primary refractory disease or a first relapse after first-line chemotherapy. **Supplemental Table 1** shows the complete list of inclusion and exclusion criteria. Central pathology review was performed by two experienced hematopathologists (DDJ, AD).

All patients provided written informed consent. The study protocol was approved by the Ethical Review Committee (ERC) of all participating centers. The study was carried out in accordance with the principles of the Helsinki Declaration.

### *Study design and treatment*

Transplant BRaVE (ClinicalTrials.gov identifier, NCT02280993) is a prospective, open-label study conducted at eight centers in the Netherlands (n=5), France (n=3) and Denmark (n=1). An independent Data Safety Monitoring Board (DSMB) evaluated the general progress and safety aspects of the study at predefined intervals.

Baseline assessment included a lymph node and bone marrow biopsy, and a PET-CT scan. Patients filled in a neurotoxicity questionnaire at study entry, prior to each cycle and at three months after auto-PBSCT.

Patients were treated with three 21-day cycles of BV (1.8 mg/kg, i.v., day 1), dexamethasone (40 mg orally or i.v., days 1-4), cisplatin (100 mg/m$^2$, continuous i.v. (24hr), day 1) and cytarabine (2x2 g/m$^2$ q12hr, 3hr for each infusion, day 2). After cycle 2, stem cells were mobilized and harvested using granulocyte colony-stimulating factor (G-CSF). A PET-CT scan was performed after cycle 3. Patients with progressive disease (PD) went off study, whereas patients with a partial response (mPR) or mCR proceeded to BEAM (carmustine, 300 mg/m$^2$, day -7, etoposide, 100 mg/m$^2$ and cytarabine, 100

mg/m$^2$, 2x/day, days -6, -5, -4 and -3, and melphalan, 140 mg/m$^2$, day -2), followed by auto-PBSCT (on day 0). Six weeks after auto-PBSCT, response evaluation was performed by PET-CT. G-CSF was recommended to prevent long-lasting neutropenia.

### *Endpoints*

All endpoints and their definitions are described in **Supplemental Table 2**. Responses were determined according to the 2014 Lugano criteria.(23) All PET-CT scans were centrally reviewed by two independent nuclear medicine physicians (AA, RV) and a third adjudicator (OH) in case of discrepancies. Visual assessment was performed using the Deauville score (DS), assessing DS1-3 as mCR. Toxicity was reported according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

### *Statistical analysis*

Details about the study design and statistical analysis are provided in **Appendix 1**. Efficacy analysis was performed among all evaluable patients. Primary safety analysis was performed among all patients who received at least one dose of study medication. Response rates and their corresponding 95% two-sided exact confidence intervals (CI) were calculated. AEs were analyzed descriptively. The Kaplan-Meier method was used for time-to-event analysis. An exploratory analysis with a Cox proportional hazards regression was performed on all Phase II patients, and 6 patients from the Phase I part of the study who were treated at the recommended dose level. The Kaplan-Meier method and log-rank test were used to analyze univariable associations with progression free survival (PFS). All statistical analyses were performed using R software version 3.6.1 and SAS software version 9.4.

## RESULTS

### *Patients and treatment*

Between May 2014 and July 2017, a total of 67 patients with R/R cHL were enrolled for the entire Transplant BRaVE Phase I/II study (n=12 in Phase I and n=55 in Phase II). Due to withdrawal of consent of two patients after one cycle of BV-DHAP and three patients not completing all BV-DHAP cycles, five more patients were enrolled in Phase II than planned according to the sample size calculations (n=50), to allow for sufficient evaluable patients in the primary analysis.

Patient characteristics for the Phase II patients are summarized in **Table 1**. The median age was 29 years, and 27 patients were female (49%). Twenty-three patients (43%) had primary refractory disease, and 16 patients (29%) had relapsed within one year of first-line treatment. Among the first 20 patients of Phase II (stage 1), enough responses were observed (16 mCR) with acceptable toxicity (seven patients experienced significant toxicity), which led to a positive advice of the DSMB to proceed to stage 2.

Of the 55 enrolled patients, 49 (89%) completed all three cycles of BV-DHAP, and 47 (85%) underwent BEAM and auto-PBSCT [**Figure 1**]. Two patients withdrew consent after cycle 1 due to psychological issues, and two patients had PD after cycle 2. In cycle 3, two patients did not receive BV due to toxicity. One of these patients received VIM (ifosfamide, mitoxantrone and etoposide) in cycle 3 because of hepatotoxicity and was not evaluable for response. However, this patient still proceeded successfully to BEAM and auto-PBSCT. The other patient received DHAP without BV because of an anaphylactic shock following BV infusion in cycle 2. This patient went off study thereafter because of toxicity and a mixed response by local PET-CT assessment (which was eventually considered mCR by central PET-CT review) and proceeded to auto-PBSCT after additional treatment with miniBEAM.

Besides the two patients who did not receive BV in cycle 3, dose reductions or delays included 3 delays of cycle 2 due to infection (n=1), venous thrombosis (n=1), or neutropenia (n=1), and 3 delays of BV infusion due to IRR (grade 1/2). Cycle 3 was delayed in 2 patients (malaise and neutropenia), and there were 2 delays of BV infusion (IRR: one grade 2 and one grade 3). Furthermore, eight patients switched from cisplatin to carboplatin due to ototoxicity (n=7; grade 1/2) or nephrotoxicity (n=1; grade 3, recovered completely), and one patient received no cisplatin and cytarabine in cycle 3 due to electrolyte disorder and sepsis.

### *Efficacy and stem cell harvest*

Three patients were not evaluable for response after three cycles of BV-DHAP: two patients withdrew consent after cycle 1, and one patient did not have a PET-CT scan after cycle 3. By independent central PET-CT review, 42 of 52 evaluable patients achieved an mCR (81% [95% CI: 67 – 90]) and five patients an mPR (10%), resulting in an overall response rate of 90% [95% CI: 79 – 97]. A total of five patients had PD (10%) and did not proceed to BEAM. Two of those patients showed PD on a CT scan after cycle 2 and three had PD on the PET-CT scan after cycle 3 [**Figure 1**]. After auto-PBSCT, four out of five patients with mPR converted to mCR. One patient had a persisting mPR and received additional radiotherapy according to the local physician's decision, and is still in mCR thereafter.

Baseline characteristics (i.e. age, time to relapse and first-line treatment) did not differ significantly between patients with mCR or mPR. The mCR rate was lower for patients with primary refractory disease compared to patients with a later relapse, but this was not statistically significant (mCR rate 73% [95% CI: 69 – 96] versus 86% [95% CI: 50 – 89]; p=0.29, respectively).

Stem cell harvest after cycle 2 was successful using G-CSF in all patients, with one apheresis session in 43 patients and two apheresis sessions in 9 patients, of whom two patients received plerixafor (three patients went off study before apheresis). The median yield was $5.3x10^6$ CD34+/kg (range 1.8 – 22.7).

### *Safety*

During BV-DHAP treatment, 20 patients (36%) experienced one or more AEs that met the dose limiting toxicity criteria (considered significant toxicity).

Grade 3/4 neutropenia and thrombocytopenia were common [**Supplemental Table 3**]. After BEAM/auto-PBSCT, the median recovery time to an absolute neutrophil count (ANC) $\geq 0.5x10^9$/L was 12 days [range: 8 – 29], and the median recovery time to platelets $\geq 20x10^9$/L was 15 days [range: 6 – 46] [**Supplemental Table 3**].

During BV-DHAP, febrile neutropenia (n=14) was the most common non-hematological grade 3/4 toxicity, followed by elevated liver enzymes (n=10) and electrolyte disorders (n=6) [**Table 2**]. After BEAM/auto-PBSCT, one patient developed veno-occlusive disease (VOD) that was fatal. This patient had elevated levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and gamma-glutamyl transferase (GGT) already during BV-DHAP and very high levels of AST (2400 Units/Liter (U/L)), ALT (970 U/L), lactate dehydrogenase (LDH; 1400 U/L), GGT (900 U/L) and direct bilirubin (660 µmol/L) during the VOD after BEAM/auto-PBSCT.

Peripheral neuropathy grade 1/2 was present before study entry in 11 patients (one grade 2) but did not worsen during BV-DHAP treatment. During BV-DHAP treatment, 15 (27%) and 3 (5%) patients developed novel onset grade 1 and 2 peripheral neuropathy, respectively, but all recovered. Of all patients, regardless of the presence of peripheral neuropathy at baseline, 12 patients reported transient muscle weakness (grade

1/2) in the neurotoxicity questionnaire, of whom 11 recovered without sequelae. No grade 3/4 neuropathy has occurred [**Supplemental table 4**].

In total, 7 patients experienced ototoxicity (three grade 1, four grade 2) and switched from cisplatin to carboplatin in cycle 2 or 3. Three patients recovered without sequelae, and three patients had continuing ototoxicity (hearing loss or tinnitus) 6 months after auto-PBSCT (one patient unknown).

Serious AEs (SAE)s grade 3/4 following BV-DHAP treatment are described in **Table 3**. In total, 18 (33%) patients experienced one or more SAEs during BV-DHAP. SAEs that occurred in more than one patient were febrile neutropenia (n=9), infections (n=2) and renal function disorder (n=2). Most SAEs recovered, except for the two renal function disorders which recovered with sequelae (persisting grade 1 or 2 nephrotoxicity, e.g. decreased glomerular filtration rate or persisting high levels of creatinine). One additional nephrotoxicity grade 3 was not considered an SAE because of rapid recovery without hospitalization.

### *Survival*

After a median follow-up of 27 months, the 2-year PFS by intention-to-treat for all 55 patients was 73.5% [95% CI: 62.6 – 86.4]; (events=14/55), and the 2-year overall survival (OS) was 94.9% [95% CI: 89.5 – 100.0]; events=3/55), [**Figure 2A+B**].

Three patients died during the study period: one patient died of encephalitis (exact cause remained unknown despite a brain autopsy, the patient did not recover from seizures; brain autopsy did not show cerebral localization of lymphoma or infection), and one patient died due to VOD. Both occurred within four months after BEAM/auto-PBSCT. The third patient died of an unrelated head trauma, nine months after BEAM/auto-PBSCT while in mCR. One patient who withdrew consent after cycle 1 went off study and later died from PD and was censored at the time of withdrawal of consent.

Patients with progression after treatment in this study received salvage treatment according to the treating physician's choice. Four patients received BV monotherapy, two of whom had a complete response, but all progressed again and needed a third salvage regimen.

### *Exploratory analysis of survival*

For an exploratory analysis of PFS, 6 patients from Phase I who were treated at the recommended dose level were added to the analysis to a total of 61 patients.(22)

Patients with mPR after 3 cycles showed a significantly lower PFS compared to patients with mCR. Two year PFS rates of patients with mPR (n=5) versus patients with mCR (n=48) were 40% (95% CI: 14 – 100) versus 87% (95% CI: 78 – 97), log-rank $p$=0.004, hazard ratio (HR): 6.02 (95% CI: 1.50 – 24.2; $p$=0.011), respectively [**Figure 3A** and **Supplemental Table 5**]. A multivariable Cox analysis showed that patients with an mPR had a significantly increased risk of progression, independently of primary refractory status. [**Supplemental table 5**]. Patients with relapsed disease (n=37) had a lower risk of progression compared to patients with primary refractory disease (n=24), with two year PFS rates of 86% (95% CI: 75 – 98) versus 63% (95% CI: 46 – 85), log-rank $p$=0.036, HR: 0.33 (95% CI: 0.11 – 0.98; $p$=0.046), respectively. [**Figure 3B** and **Supplemental Table 5**]. Univariable analysis did not show significant associations for other baseline risk factors (i.e. B-symptoms, age, stage and first line treatment regimen) [**Supplemental table 5**].

### *Central pathology review*

Based on morphology, immunophenotype, and molecular clonality analysis if needed, central pathology review confirmed cHL (according to the WHO classification 2016(24)) in 59 of all 67 patients (88%) of the complete Phase I (cHL confirmed in 10 of 12

patients in total) and Phase II (cHL confirmed in 49 of 55 patients in total) part of the study. In all cases with equivocal morphological and/or immunohistochemical features, including cases with high numbers of EBER positive atypical large cells and/or small lymphocytes (n=16), extensive immunohistochemical and molecular T-cell receptor and immunoglobulin heavy and light chain gene rearrangement assays (BIOMED) were performed [**Supplemental table 6**]. In eight patients, cHL could not be confirmed. Of these, five patients were diagnosed with peripheral T-cell lymphoma (PTCL), not otherwise specified (NOS), one patient with angioimmunoblastic T-cell lymphoma (AITL) and one patient with immunodeficiency-associated B-lymphoproliferative disorder (IA-B-LPD).(25) In one patient a classifying diagnosis could not be made due to lack of representative material in the biopsy sample. Additionally, in one patient, a composite lymphoma of cHL and lymphoplasmacytic lymphoma (LPL) was diagnosed. In all cases high CD30 expression was present. Of the seven patients with PTCL, AITL or IA-B-LPD, six had an mCR after three cycles of BV-DHAP. One patient with PTCL had PD after cycle 2, one with AITL had PD after auto-PBSCT, and one patient with PTCL died due to unrelated head-trauma. When excluding the patient with unrelated death, the PFS was not significantly different for patients with confirmed cHL versus patients with another diagnosis (2-year PFS 81% versus 67%, log-rank $p$=0.36).

## DISCUSSION

In this international, prospective Phase II study we investigated the efficacy and safety of BV-DHAP as first salvage treatment for patients with R/R cHL. This study is the first to investigate this combination. Treatment with BV-DHAP resulted in a high proportion of patients with an mCR prior to HDC/auto-PBSCT, and toxicity was mostly reversible.

Data on FDG-PET-CT results following treatment with DHAP are scarce, but generally only about 25% of patients achieved a CR as assessed by CT scan.(4, 26). Other trials have recently investigated BV in combination with other salvage chemotherapy combinations, such as bendamustine, ICE (ifosfamide, carboplatin, etoposide) or ESHAP (etoposide, methylprednisolone, high-dose cytarabine and cisplatin) and have shown mCR rates up to 76% prior to HDC/auto-PBSCT.(15-18, 27) The administration schedule of BV differed among these studies, and most studies used more than 3 administrations of BV in total.(15-18, 27) In the current study, three cycles of BV-DHAP resulted in a high mCR rate with only 3 administrations of BV. This makes it a less 'financially toxic' therapy than using BV in first line for all patients or to use it as consolidation therapy after auto-PBSCT.

In R/R cHL patients treated with salvage chemotherapy followed by HDC and auto-PBSCT, historical studies demonstrate a 5-years PFS of approximately 50%.(1-4, 26, 28, 29) In 97 patients treated with ICE the 2-year event free survival was 70%.(6) Another regimen consisting of bendamustine, gemcitabine and vinorelbine (in 59 patients) resulted in a 2-year PFS of 63%.(30) With the present treatment protocol, we have been able to achieve a high 2-year PFS rate of 74%. A total of 14 events occurred (including 3 deaths), and at the present median follow up of 27 months, no relapses have occurred beyond 18 months from enrollment. Longer follow-up is needed to confirm that the majority of patients in remission after 2 years are indeed cured.(3, 28, 31)

The unprecedented high response rate and prolonged PFS of this treatment regimen were achieved at the cost of higher toxicity in comparison to other salvage regimens. However, most of the observed toxicities, including neutropenia, thrombocytopenia, fever, nausea/vomiting, ototoxicity and nephrotoxicity are toxicities of specific concern during treatment with DHAP.(4, 26, 32, 33). Other regimens of BV with bendamustine, nivolumab, ICE or ESHAP seem to induce less AEs, with most toxicities consisting of hematological toxicity.(15, 16, 18, 19, 34) While the occurrence of grade 3/4 non-hematological toxicity was low with BV-bendamustine, a substantial part of the patients (25%) did not undergo auto-PBSCT, resulting in a lower 2-years PFS of 62.6%.(16) Another recent study with BV-bendamustine in 40 patients had a 3-years PFS of 67.3% and 82.5% of patients underwent auto-PBSCT.(19) The combination of BV with nivolumab resulted in an mCR rate of 61% with almost all patients experiencing grade 1/2 toxicity and 31% having grade 3/4 toxicity, however these AEs were also manageable.(34)

A sequential approach of BV monotherapy followed by chemotherapy in PET-positive patients is interesting, since some patients could be spared the toxicity of salvage chemotherapy without losing efficacy. However, only a minority of patients achieved a PET-negative response after BV monotherapy.(15) The ESHAP regimen is similar to DHAP, except for containing methylprednisolone instead of dexamethasone, and cisplatin being given over four days of 25 mg/m$^2$/day compared to 100 mg/m$^2$ in one day with the DHAP regimen.(18) Hematological AEs were comparable between BV-ESHAP and BV-DHAP with about 50% of patients experiencing grade 3/4 thrombocytopenia and neutropenia. For BV-ESHAP, grade 3 fever and mucositis were the most frequent non-hematological grade 3/4 toxicities whereas DHAP was also associated with fever, but not with mucositis. In contrast, only grade 1/2 renal dysfunction occurred with BV-ESHAP, and no cases of elevated liver enzymes or ototoxicity are described.(18)

In 10 patients, a transient grade 3/4 increase in liver enzymes was observed during BV-DHAP treatment (one grade 4), which was reversible in all patients. One patient developed a fatal VOD after BEAM/auto-PBSCT. Additionally, one patient treated in the Phase I part of this study also developed a grade 3 VOD, which however recovered without sequelae. Both patients already had elevated liver enzymes during BV-DHAP treatment. This complication has previously been described in patients receiving high-dose alkylating agents such as melphalan or cyclophosphamide.(35)

BV as consolidation therapy has been shown to prolong PFS in high-risk R/R cHL patients who have undergone HDC/auto-PBSCT.(36) Whether BV before auto-PBSCT in combination with chemotherapy, or as consolidation after auto-PBSCT will be more effective is unknown. Of note, with BV consolidation, peripheral neuropathy occurred in 67% of patients, including 13% (n=22) grade 3 peripheral neuropathy. With BV-DHAP, the incidence of peripheral neuropathy was lower, mostly reversible and no grade 3/4 occurred, probably because only three administrations of BV were given.

In depth pathology workup and reclassification was performed to exclude lymphomas that are known as cHL mimickers such as AITL and PTCL (with follicular helper T-cell immunophenotype with secondary cHL-like blasts), as well as IA-B-LPD.(37-39) In retrospect, seven cases were identified as cHL-mimickers with central pathology review. Awareness for cHL-mimickers is important because patients with T-cell lymphoma generally have a worse prognosis.(40) In this cohort of patients no significant differences in response rates or PFS were observed between patients with confirmed or unconfirmed cHL, although the number of patients is too small to validate this finding.

An exploratory analysis on PFS showed that patients with an mPR prior to BEAM/auto-PBSCT have a higher risk of relapse, despite conversion to an mCR after auto-PBSCT. This finding is in line with other trials investigating risk factors for relapse

after auto-PBSCT.(5-7) PET-adapted therapy could probably further improve outcome by intensifying treatment for high-risk patients with new agents, such as checkpoint inhibitors in addition to BV. Moreover, a group of patients at low-risk for relapse, might possibly be cured with a combination of new drugs only, without the toxic consequences of HDC and auto-PBSCT. Risk stratification based on the PET-CT scan at relapse could also be further improved by quantitative analysis and the assessment of metabolic tumor volume.(41, 42)

The addition of BV to salvage treatment has not yet been investigated in a randomized Phase III trial. However, several Phase II studies have now shown that BV in combination with chemotherapy results in high mCR rates prior to HDC/auto-PBSCT. A combined pooled analysis of all of these studies is planned to give more insight into the effect of BV on response rates and toxicity in this setting.

In conclusion, in R/R cHL, three cycles of BV-DHAP is a highly effective salvage regimen resulting in an mCR rate of 81% prior to HDC/auto-PBSCT as shown by independent central PET-CT review. Patients should be monitored closely for toxicity, especially hematological toxicity, nephrotoxicity and liver toxicity.

## ACKNOWLEDGEMENTS

The authors would like to thank all patients who participated in the trial, the Transplant BRaVE-trial team of the Trial Office of the Amsterdam UMC, location AMC for their efforts in trial management and central data management and the members of the Data Safety and Monitoring Board. The authors thank Marjolein Spiering, Edith van Dijkman, the data managers, trial nurses, lab- and pharmacy personnel for their essential assistance with collecting and managing the study data. The authors thank prof. dr. Otto S. Hoekstra and drs. Gerben J.C. Zwezerijnen for reviewing discrepancies of the central FDG-PET-CT review and ing. Nathalie Hijmering, HOVON Pathology Facility and Biobank for biopsy collection and support of central pathology review.

This work was supported by research funding from Takeda.

## AUTHORSHIP CONTRIBUTIONS

MJK and AH designed the study; all authors collected the data; JD, MLY and HvT analyzed the data; JD and MJK wrote the manuscript with contributions from all authors, who also interpreted the data, read, commented on, and approved the final version of the manuscript; DdJ and AD performed the central pathology review; JZ, CB, AA and RV organized and performed the central FDG-PET-CT review; MJK and AH supervised the study.

## CONFLICT OF INTEREST DISCLOSURES

The study drug (BV) was provided for the study and the study was funded by Takeda. Takeda did not have any influence on the analysis of the data or the interpretation of the results.

**Hagenbeek:** Millennium/Takeda: Consultancy, Honoraria, Research Funding.

**Kersten:** Millennium/Takeda: Honoraria, Research Funding; Celgene: Honoraria, Research Funding; Roche: Honoraria, Research Funding; Gilead: Honoraria; Kite Pharma: Honoraria; Novartis: Honoraria.

**Morschhauser:** Janssen: Scientific Lectures; BMS: Membership on an entity's Board of Directors or advisory committees; Epizyme: Consultancy; Gilead: Consultancy, Membership on an entity's Board of Directors or advisory committees; Roche: Membership on an entity's Board of Directors or advisory committees; Celgene: Consultancy, Membership on an entity's Board of Directors or advisory committees.

**Lugtenburg:** Millennium/Takeda: Consultancy, Research Funding; Servier: Consultancy, Research Funding; Roche: Consultancy; BMS: Consultancy; Sandoz: Consultancy; Genmab: Consultancy.

**Diepstra:** Millennium/Takeda: Consultancy, Honoraria, Research Funding.

**Brice**: Millennium/Takeda: Honoraria, Research Funding, Scientific Advisory Board; Roche: Honoraria; BMS: Honoraria, Scientific Advisory Board; MSD: Honoraria, Scientific Advisory Board; Jansen: Honoraria.

**Hutchings:** Consultant/advisor: Roche, Takeda, Celgene, Genmab; Research support: Roche, Takeda, Celgene, Genmab, Novartis, Janssen, Incyte, Genentech

**Gastinne**: Millennium/Takeda: Honoraria, Gilead, Roche, MSD.

**Zijlstra:** Consultant/advisor: Gilead, Roche, Takeda; Honoraria: Gilead, Roche, Takeda, Janssen.

**De Jong:** Consultant/advisor: Takeda.

All remaining authors have declared no conflicts of interest.

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## Tables

Table 1: Patient Characteristics

| Number of patients [n; (%)] | Phase II patients (n=55) |
|---|---|
| **Age (years)** | |
| Median [range] | 29 [19 – 71] |
| **Female** | 27 (49) |
| **Ann Arbor stage at baseline** | |
| I | 8 (15) |
| II | 16 (29) |
| III | 10 (18) |
| IV | 20 (36) |
| Unknown | 1 (2) |
| **ECOG PS at baseline** | |
| 0 | 35 (64) |
| 1 | 17 (31) |
| Unknown | 3 (5) |
| **Baseline B-symptoms** | 20 (36) |
| **Bone marrow involvement** | 2 (4) |
| **First line treatment** | |
| ABVD | 40 (73) |
| BEACOPP baseline | 2 (4) |
| Escalated BEACOPP | 8 (15) |
| Other | 5 (9) |
| **Prior radiotherapy** | 9 (16) |
| **Response to first line treatment** | |
| CR | 32 (58) |
| PR | 10 (18) |
| SD | 2 (4) |
| PD | 11 (20) |
| **Time from response to first line treatment to relapse** | |
| Primary refractory disease* | 23 (42) |
| Relapse within 1 year | 16 (29) |
| Relapse after 1 year | 16 (29) |
| Median time (months; [range]) | 5 [0 – 160] |

***** Primary refractory disease is defined as failure to obtain a complete response with front-line therapy.

Abbreviations: N, number; ECOG PS, Eastern Cooperative Oncology Group Performance Score; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 2: Adverse Events grade ≥ 3 during BV-DHAP

| Adverse Event | Cycle 1 (n=55) | | Cycle 2 (n=53) | | Cycle 3 (n=51) | | Total* (n=55) | |
|---|---|---|---|---|---|---|---|---|
| **CTCAE grade (n)** | **3** | **4** | **3** | **4** | **3** | **4** | **3** | **4** |
| Febrile neutropenia | 7 | 1 | 2 | 0 | 3 | 1 | 12 (22%) | 2 (4%) |
| Elevated liver enzymes | 3 | 0 | 5 | 1 | 1 | 0 | 9 (16%) | 1 (2%) |
| Electrolyte disorders | 2 | 1 | 0 | 1 | 2 | 0 | 4 (7%) | 2 (4%) |
| Nausea/vomiting | 1 | 0 | 3 | 0 | 2 | 0 | 4 (7%) | 0 (0%) |
| Fever | 0 | 0 | 1 | 0 | 2 | 0 | 3 (5%) | 0 (0%) |
| Renal function disorder | 1 | 0 | 0 | 0 | 2 | 0 | 3 (5%) | 0 (0%) |
| Sepsis | 0 | 0 | 1 | 1 | 1 | 0 | 2 (4%) | 1 (2%) |
| Bone pain | 2 | 0 | 0 | 0 | 0 | 0 | 2 (4%) | 0 (0%) |
| Diarrhea | 1 | 0 | 1 | 0 | 0 | 0 | 2 (4%) | 0 (0%) |
| Epistaxis | 0 | 0 | 1 | 0 | 1 | 0 | 2 (4%) | 0 (0%) |
| Infection | 0 | 0 | 1 | 0 | 1 | 0 | 2 (4%) | 0 (0%) |
| Infusion related reaction | 0 | 0 | 2 | 0 | 0 | 0 | 2 (4%) | 0 (0%) |
| Malaise | 1 | 0 | 1 | 0 | 0 | 0 | 1 (2%) | 0 (0%) |
| Abdominal pain | 1 | 0 | 0 | 0 | 0 | 0 | 1 (2%) | 0 (0%) |
| Back pain | 0 | 0 | 0 | 0 | 1 | 0 | 1 (2%) | 0 (0%) |
| Constipation | 0 | 0 | 0 | 0 | 1 | 0 | 1 (2%) | 0 (0%) |
| Headache | 1 | 0 | 0 | 0 | 0 | 0 | 1 (2%) | 0 (0%) |
| Myalgia shoulder | 1 | 0 | 0 | 0 | 0 | 0 | 1 (2%) | 0 (0%) |
| Periodic paralysis (hypokalemia) | 1 | 0 | 0 | 0 | 0 | 0 | 1 (2%) | 0 (0%) |
| Syncope | 0 | 0 | 0 | 0 | 1 | 0 | 1 (2%) | 0 (0%) |
| **Total** | **22** | **2** | **18** | **3** | **18** | **1** | **55** | **6** |
| *Individual patients* † | *17* | *2* | *14* | *2* | *11* | *1* | *29* | *5* |
| *Individual patients total* ‡ | *18 (33%)* | | *15 (28%)* | | *11 (22%)* | | *30 (55%)* | |

* Patients with a specific toxicity in more than one cycle were only counted once in the column representing the total toxicity.

† Total of patients that experienced one or more grade 3 or 4 toxicity during the concerning cycle.

‡ Total of patients that experienced one or more grade 3 or 4 toxicity during the concerning cycle. Patients who experienced both a grade 3 and grade 4 toxicity were only counted once.

Abbreviations: N, number; CTCAE, Common Terminology Criteria for Adverse Events.

Table 3: Serious adverse events grade ≥ 3 during BV-DHAP

| **Serious Adverse Event** | **Cycle 1** (n=55) | | **Cycle 2** (n=53) | | **Cycle 3** (n=51) | | **Total**** (n=55) | | **Recovered** |
|---|---|---|---|---|---|---|---|---|---|
| **CTCAE grade (n)** | **3** | **4** | **3** | **4** | **3** | **4** | **3** | **4** | |
| Febrile neutropenia | 5 | 1 | 0 | 0 | 3 | 0 | 8 | 1 | All |
| Infection | 0 | 0 | 1 | 0 | 1 | 0 | 2 | 0 | All |
| Renal function disorder | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | With sequela* |
| Sepsis | 0 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | All |
| Epistaxis | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | All |
| Fever | 0 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | All |
| Elevated liver enzymes | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 1 | All |
| Infusion related reaction | 0 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | All |
| Malaise | 1 | 0 | 1 | 0 | 0 | 0 | 1 | 0 | All |
| Nausea/vomiting | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | All |
| Periodic paralysis (hypokalemia) | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | All |
| **Total** | **8** | **1** | **4** | **2** | **9** | **0** | **19** | **3** | |
| *Individual patients†* | *7* | *1* | *4* | *2* | *7* | *0* | *15* | *3* | |
| *Individual patients total‡* | *8 (15%)* | | *6 (11%)* | | *7 (14%)* | | *18 (33%)* | | |

* persisting grade 1 or 2 nephrotoxicity (e.g. decreased glomerular filtration rate or persisting high levels of creatinine)

** Patients with a specific toxicity in more than one cycle were only counted once in the column representing the total toxicity.

Abbreviations: N, number; CTCAE, Common Terminology Criteria for Adverse Events.

## Figure legends

**Figure 1. Consort diagram:** number of patients in the full analysis set going through the protocol treatment including reasons for exclusion.

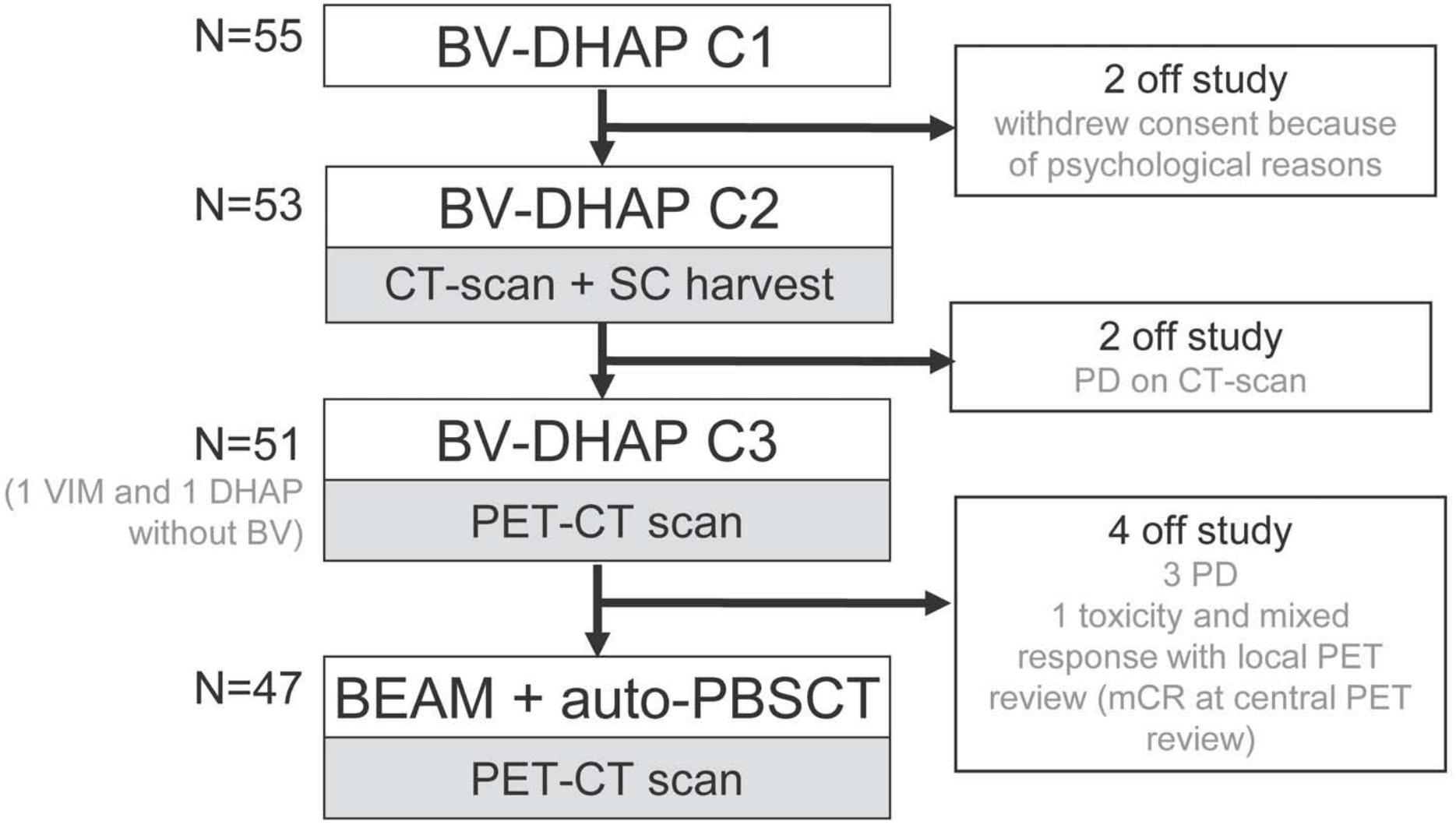
Abbreviations: BV, brentuximab vedotin; DHAP, dexamethasone, high-dose cytarabine, cisplatin; C, cycle; N, number; CT, computed tomography; SC, stem cell; PD, progressive disease; VIM, ifosfamide, mitoxantrone, etoposide; PET, positron emission tomography; mCR, metabolic complete response; BEAM, carmustine, etoposide, cytarabine, melphalan; auto-PBSCT, autologous peripheral blood stem-cell transplant.

**Figure 2. Kaplan-Meier survival analysis** for all 55 Phase II patients by intention-to-treat, including the number of patients at risk at 1, 2 and 3 years with regard to (**A**) progression free survival and (**B**) overall survival, measured from enrollment.

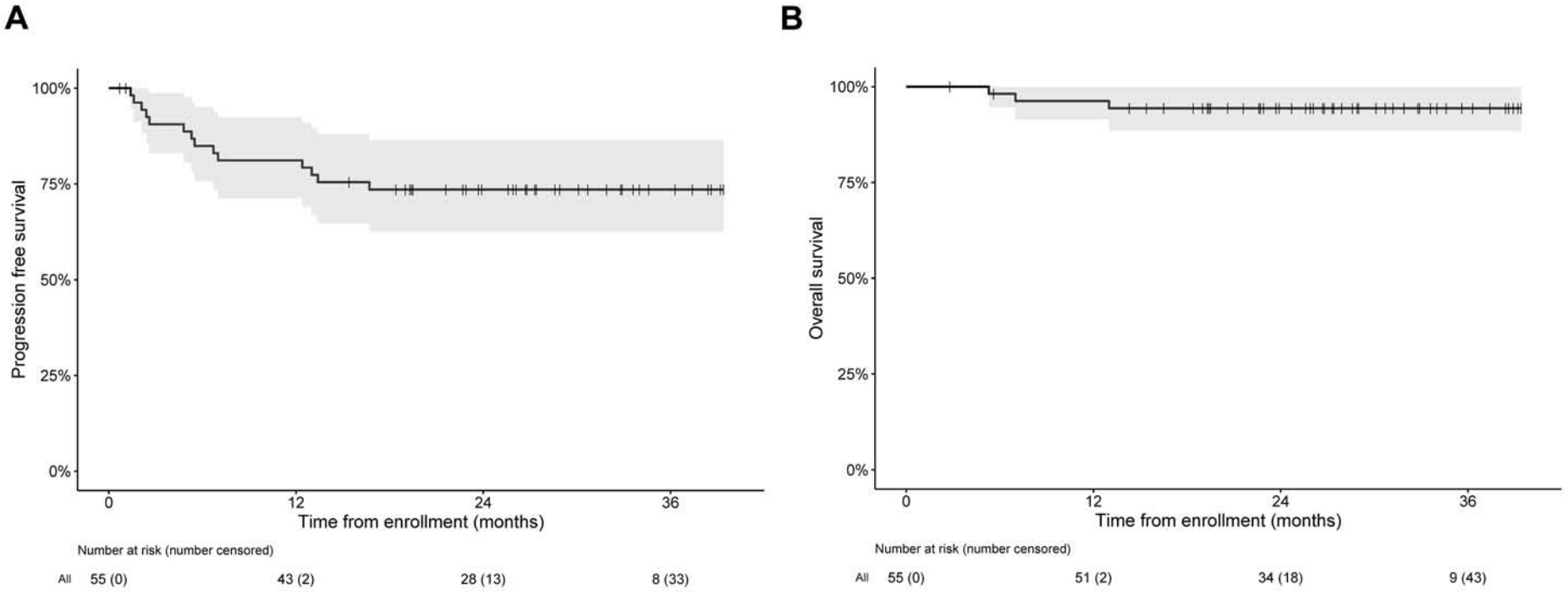
**Figure 3. Kaplan-Meier exploratory analysis** for all 55 Phase II patients and 6 patients from Phase I who were treated at the same dose level, including the number of patients at risk at 1, 2 and 3 years with regard to (**A**) progression free survival stratified for patients with a metabolic complete response (mCR; n=48) or partial response (mPR; n=5) on the PET-CT scan after 3 cycles of BV-DHAP, measured from the time of that PET-CT scan, and (**B**) progression free survival stratified for relapsed patients (n=37; defined as recurrent disease after having reached a complete response on first line treatment) versus patients with primary refractory disease (n=24; no complete response on first line treatment), measured from enrollment.

Abbreviations: mCR, metabolic complete response; mPR, metabolic partial response; PET, positron emission tomography; BV, brentuximab vedotin; DHAP, dexamethasone, high-dose cytarabine, cisplatin.

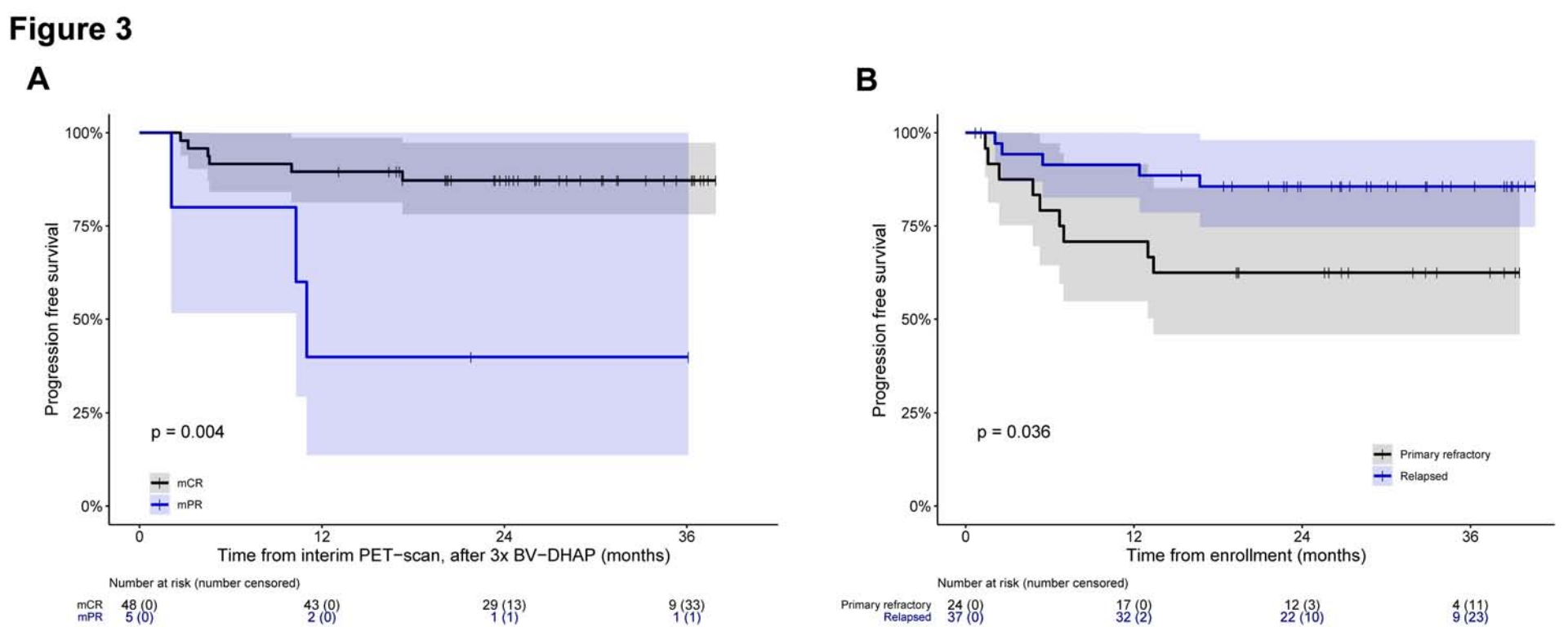
**Figure 1**


N=55
BV-DHAP C1
2 off study
withdrew consent because of psychological reasons
N=53
BV-DHAP C2
CT-scan + SC harvest
2 off study
PD on CT-scan
N=51
(1 VIM and 1 DHAP without BV)
BV-DHAP C3
PET-CT scan
4 off study
3 PD
1 toxicity and mixed response with local PET review (mCR at central PET review)
N=47
BEAM + auto-PBSCT
PET-CT scan

# Figure 2


A
100%
75%
50%
25%
0%
Progression free survival
0
12
24
36
Time from enrollment (months)
Number at risk (number censored)
All 55 (0) 43 (2) 28 (13) 8 (33)
B
100%
75%
50%
25%
0%
Overall survival
0
12
24
36
Time from enrollment (months)
Number at risk (number censored)
All 55 (0) 51 (2) 34 (18) 9 (43)

# Figure 3


A
100%
75%
50%
25%
0%
Progression free survival
p = 0.004
mCR
mPR
0
12
24
36
Time from interim PET−scan, after 3x BV−DHAP (months)
Number at risk (number censored)
mCR 48 (0) 43 (0) 29 (13) 9 (33)
mPR 5 (0) 2 (0) 1 (1) 1 (1)
B
100%
75%
50%
25%
0%
Progression free survival
p = 0.036
Primary refractory
Relapsed
0
12
24
36
Time from enrollment (months)
Number at risk (number censored)
Primary refractory 24 (0) 17 (0) 12 (3) 4 (11)
Relapsed 37 (0) 32 (2) 22 (10) 9 (23)

# ONLINE APPENDIX

## Title

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

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# On behalf of HOVON and Lunenburg Lymphoma Phase I/II Consortium (LLPC)

## Appendix 1. Study design and statistical analysis (extended methods)

A Bryant and Day two-stage design was used, with early stopping rules for poor response or toxicity.(1) An overall response rate (ORR) of 50% was considered unacceptable and an ORR of 70% was considered acceptable. The maximum rate of patients experiencing significant toxicity was defined as 55% to be unacceptable and 30% to be acceptable. Significant toxicity was defined as a grade 3/4 non-hematological adverse event (AE) according to the dose-limiting toxicity (DLT) criteria [**Supplemental Table 2**]. Error rates were set at 0.1 for both response and toxicity. The recommended sample size for stage 1 was 20 patients of whom at least 11 should have a response and a maximum of 9 could have significant toxicity. Subsequently, a further 30 evaluable patients would be recruited for stage 2, to a total of 50 patients for the entire Phase II study. If a participant were to withdraw from the study, he or she would be replaced by a new participant to reach the target number of participants. Progression free survival (PFS) was defined as time from study entry until progressive disease or death, whichever occurred first. Overall survival (OS) was defined as time from study entry until death from any cause.

**References:**

1. Bryant J, Day R. Incorporating Toxicity Considerations Into the Design of Two-Stage Phase II Clinical Trials. Biometrics. 1995;51(4):1372-1383.

## Supplemental Tables

Supplemental Table 1. Patient selection criteria

| **Inclusion criteria** |
|---|
| Histologically confirmed CD30+ classical HL (central pathology review; results not required to enroll the patient in the study), primarily refractory to first line chemotherapy or in first relapse after any polychemotherapy regimen (e.g. ABVD, baseline BEACOPP or escalated BEACOPP, or other induction regimens) |
| In case of relapse, the relapse must be histologically confirmed. In case histology is not possible, at least confirmation of the relapse by FNA is required. |
| Measurable disease, according to the definitions of response (Cheson 2014), i.e. CT scans showing at least 2 or more clearly demarcated lesions with a long axis ≥ 1.5 cm and a short axis diameter ≥ 1.0 cm, or 1 clearly demarcated lesion with a long axis ≥ 2.0 cm and a short axis diameter ≥ 1.0 cm. These lesions must be FDG-positive |
| Age ≥ 18 years (upper age limit for auto-PBSCT at the discretion of the participating center) |
| WHO Eastern Cooperative Oncology Group Performance Score ≤ 2 |
| Life expectancy of > 3 months with treatment |
| No major organ dysfunction, unless HL-related |
| Total bilirubin < 1.5x ULN (unless due to lymphoma involvement of the liver or a known history of Gilbert's syndrome) |
| ALT/AST < 3x ULN (unless due to lymphoma involvement of the liver; in that case ALT/AST may be elevated up to 5 x ULN) |
| GFR > 60 ml/min as estimated by the Cockroft&Gault formula (1976) |
| Absolute neutrophil count ≥ 1.5x109/L, unless caused by diffuse bone marrow infiltration by the HL |
| Platelets ≥ 100x109/L, unless caused by diffuse bone marrow infiltration by the HL |
| Hemoglobin must be >8 g/dL |
| Written informed consent |
| Able to adhere to the study visit schedule and other protocol requirements |
| Female patient is either post-menopausal for at least 1 year before the screening visit or surgically sterile or if of childbearing potential, agrees to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent through 30 days after the last dose of study drug, or agrees to completely abstain from heterosexual intercourse. |
| Male patients, even if surgically sterilized, (i.e., status post vasectomy) agree to practice effective barrier contraception during the entire study period and through 6 months after the last dose of study drug, or agrees to completely abstain from heterosexual intercourse. |
| Eligible for high dose chemotherapy and autologous peripheral blood stem cell transplantation |
| Resolution of toxicities from first-line therapy |
| **Exclusion criteria** |
| Peripheral sensory or motor neuropathy grade ≥ 2 |
| Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML |
| Symptomatic neurologic disease compromising normal activities of daily living or requiring medications |
| Patients who have been using other investigational agents within at least 5 half lives of the most recent agent used prior to enrollment in the study |
| Patients who were treated with myelosuppressive chemotherapy or biological therapy ≤ 4 weeks before study inclusion |

| |
|---|
| Female patients who are both lactating and breast feeding or have a positive serum pregnancy test during the screening period or a positive pregnancy test on Day 1 before first dose of study drug or adults of reproductive potential who are not using effective birth control methods. |
| Patients with any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics within 2 weeks prior to first study drug dose |
| Patients who have a history of another primary malignancy less than 3 years before study inclusion or previously diagnosed with another malignancy and have evidence of residual disease, with the exception of non-melanoma skin cancer, completely resected melanoma TNMpT1 and carcinoma in situ of the uterine cervix |
| Patients with known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin |
| Patients with known HIV seropositivity, known hepatitis B surface antigen-positivity, or known or suspected active hepatitis C infection |
| Patients receiving radiation therapy within 8 weeks prior to start of protocol treatment. Emergency radiation therapy is allowed, as long as measurable disease (at non-irradiated sites) persists. |
| Patients with a serious psychiatric disorder that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol |
| Patients who have any severe and/or uncontrolled medical condition or other conditions that could affect their participation in the study such as: Known history of symptomatic congestive heart failure (NYHA III, IV), myocardial infarction ≤ 6 months prior to first study drug |
| Evidence of current serious uncontrolled cardiac arrhythmia, angina pectoris, electrocardiographic evidence of acute ischemia or active conduction system abnormalities |
| Recent evidence (within 6 months before first dose of study drug) of a left-ventricular ejection fraction <50% |
| severely impaired pulmonary function as defined as spirometry and DLCO (diffusing capacity of the lung for carbon monoxide) that is 50% or less of the normal predicted value and/or O2 saturation that is 90% or less at rest on room air |
| Any active (acute or chronic) or uncontrolled infection/disorders that impair the ability to evaluate the patient or for the patient to complete the study |
| Nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by this study drug, such as severe hypertension that is not controlled with medical management and thyroid abnormalities when thyroid function cannot be maintained in the normal range by medication |

**Abbreviations:** Hodgkin lymphoma (HL); adriamycin, bleomycin, vinblastine, dacarbazine (ABVD); bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP); fine-needle aspiration (FNA); computed tomography (CT); [$^{18}$F]fluorodeoxyglucose (FDG); upper limit of normal (ULN); alanine aminotransferase (ALT); aspartate aminotransferase (AST); glomerular filtration rate (GFR); Progessive Multifocal Leuko-encephalopathy (PML);

Supplemental Table 2. Study endpoints and definitions

| **Endpoint** | **Definition** |
|---|---|
| Metabolic CR rate (PET-CT) after the third cycle of BV-DHAP reinduction therapy | According to the definitions of response (Cheson, 2014). Deauville 1-3 is considered a metabolic CR. |
| Rate of grade 3/4 non-hematological toxicity, including neurotoxicity after each cycle of BV-DHAP | Common Terminology Criteria of Adverse Events (CTCAE) version 4.01 |
| The number of patients who experience significant toxicity during BV-DHAP | Significant toxicity is defined as a dose limiting toxicity (DLT);<br>- grade ≥ 3 non-hematologic toxicity, including neurotoxicity#<br>- death whatever the cause, except death due to Hodgkin lymphoma any of which must occur before day 22 of cycle I-III<br>- postponement of course 2 or 3 of BV-DHAP– despite growth factor prophylaxis- due to neutropenia with more than 10 days and / or neutropenia grade 4 after course 1 , 2 or 3 lasting more than 10 days despite growth factor treatment.<br><br># Exceptions:<br>1. Laboratory abnormalities grade ≥ 3 are only considered to be DLT if they persist for > 2 weeks or if they do not return to ≤ grade 1<br>2. For nausea, vomiting, or diarrhea, subjects must have a grade 3 or 4 event that persists for at least 7 days at this level despite the use of optimal symptomatic treatment, in order for these events to be considered a DLT<br>3. Any infection/fever requiring iv antibiotics is not considered to be a DLT, only grade 4 infection is considered to be a DLT<br>4. Grade 3 thromboembolic events and grade 3 hypertension are not considered to be DLT<br>5. If a DLT is attributed to progressive disease, it will not be counted as DLT.<br>6. Alopecia. |
| Overall response rate (PR + CR) after the third cycle of BV-DHAP reinduction therapy (based on the results of the FDG-PET/CT scan) | |
| Overall response rate (PR + CR) after auto-PBSCT (based on the results of the FDG-PET/CT scan) | |
| Metabolic CR rate (PET-CT) after auto-PBSCT | |
| Fraction of patients (CR/PR) eligible for auto-PBSCT who actually undergo auto-PBSCT | |
| Progression free survival (PFS) | Disease progression or death from any cause, measured from study entry. |

| | |
|---|---|
| Event free survival (EFS) | Failure of treatment (no CR or PR, no stem cell harvest or auto-PBSCT possible or relapse), measured from study entry. |
| Overall survival (OS) | Death as a result of any cause, measured from study entry. |
| Serious Adverse Events (SAE)s during the combination treatment | An SAE is any untoward medical occurrence or effect that:<br>- Results in death;<br>- Is life threatening (at the time of the event);<br>- Requires hospitalization or prolongation of existing inpatients' hospitalization;<br>- Results in persistent or significant disability or incapacity;<br>- is a congenital anomaly or birth defect;<br>- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc. |
| Time to hematological recovery after each cycle of BV + DHAP | Absolute neutrophil count (ANC) recovery is defined as $\geq 0.5 \times 10^9$/L for three consecutive laboratory values obtained on different days.<br>Platelet recovery is defined as $\geq 20 \times 10^9$/L for three untransfused platelet counts over 7 days with rising counts during the week. |
| Rate of successful PBSC collection ($\geq 2 \times 10^6$ CD34+ cells/kg) after the second cycle of BV-DHAP | |
| Time to hematological recovery after auto-PBSCT | Absolute neutrophil count (ANC) recovery is defined as $\geq 0.5 \times 10^9$/L for three consecutive laboratory values obtained on different days.<br>Platelet recovery is defined as $\geq 20 \times 10^9$/L for three untransfused platelet counts over 7 days with rising counts during the week. |

**Abbreviations:** complete response (CR); positron emission tomography (PET); computed tomography (CT); brentuximab vedotin (BV); dexamethasone, high-dose cytarabine, cisplatin (DHAP); partial response (PR); autologous peripheral blood stem-cell transplant (auto-PBSCT); Investigational Medicinal Product (IMP);

Supplemental Table 3. Hematological toxicity and recovery

| Grade (n(%)) Recovery (median days [range]) | | Cycle 1 (n=55) | Cycle 2 (n=53) | Cycle 3 (n=51) | BEAM + auto-PBSCT (n=47) |
|---|---|---|---|---|---|
| **Neutropenia** | **Grade 3** | 5 (9) | 7 (13) | 10 (20) | |
| | **Grade 4** | 29 (53) | 24 (45) | 23 (45) | |
| | **Recovery†** | 13 [9 – 21] | 15 [12 – 21] | 17 [12 – 33] | 12 [8 – 29] |
| **Thrombocytopenia** | **Grade 3** | 16 (29) | 15 (28) | 11 (22) | |
| | **Grade 4** | 21 (38) | 27 (53) | 31 (61) | |
| | **Recovery‡** | 14 [11 – 22] | 18 [12 – 26] | 19 [13 – 37] | 15 [6 – 46] |
| **Anemia** | **Grade 3** | 1 (2) | 9 (17) | 13 (25) | |
| | **Grade 4** | 0 (0) | 0 (0) | 0 (0) | |
| | No grade 4 anemia, so no recovery measured. | | | | |

**†**Neutrophil recovery was defined as absolute neutrophil count (ANC) ≥0.5 x $10^9$/L for three consecutive laboratory values obtained on different days and was measured from the start of BV-DHAP cycle 1-3 or from reinfusion of stem cells after BEAM, until the date of the first of three consecutive laboratory values where the ANC is ≥0.5 x $10^9$/L in patients with grade 4 neutropenia.

**‡**Platelet recovery was defined as platelet count ≥20 x $10^9$/L for three untransfused platelet counts over 7 days with rising counts during the week and was measured from the start of BV-DHAP cycle 1-3 or from reinfusion of stem cells after BEAM, until the date of the first of three consecutive laboratory values where the platelet count is ≥20 x $10^9$/L in patients with grade 4 thrombocytopenia.

**Abbreviations:** carmustine, etoposide, high-dose cytarabine, melphalan (BEAM); autologous peripheral blood stem-cell transplant (auto-PBSCT).

Supplemental Table 4. Neurotoxicity

| | PNP not present at baseline (n=21) | Resolved | PNP present at baseline (n=11) | Resolved | Total (n=32) | Resolved |
|---|---|---|---|---|---|---|
| **Highest CTCAE grade during BV-DHAP [n; (% resolved)]** | | | | | | |
| **0** | 3 | . | 0 | . | 3 | . |
| **1** | 15 | 15 (100%) | 10 | 8 (80%) | 25 | 23 (88%) |
| **2** | 3 | 3 (100%) | 1 | 0 (0%) | 4 | 3 (75%) |
| **Highest CTCAE grade during BEAM/auto-PBSCT [n; (% resolved)]** | | | | | | |
| **0** | 6 | . | 4 | . | 10 | . |
| **1** | 12 | 8 (67%) | 2 | 0 (0%) | 14 | 8 (57%) |
| **2** | 1 | 0 (0%) | 2 | 1 (50%) | 3 | 1 (33%) |
| **Unknown** | 2 | . | 3 | . | 5 | . |
| **Muscle weakness during BV-DHAP [n; (% resolved)]** | | | | | | |
| **No** | 13 | . | 7 | . | 20 | . |
| **Yes** | 8 | 8 (100%) | 4 | 3 (75%) | 12 | 11 (92%) |
| **Muscle weakness during BEAM/auto-PBSCT [n; (% resolved)]** | | | | | | |
| **No** | 19 | . | 10 | . | 29 | . |
| **Yes** | 2 | 2 (100%) | 1 | 0 (0%) | 3 | 2 (67%) |

**Abbreviations:** Peripheral neuropathy (PNP); number of patients (n); Common Terminology Criteria for Adverse Events (CTCAE); Brentuximab vedotin (BV); dexamethasone, high-dose cytarabine, cisplatin (DHAP); carmustine, etoposide, high-dose cytarabine, melphalan (BEAM); autologous peripheral blood stem-cell transplant (auto-PBSCT).

Supplemental Table 5. Cox proportional hazard regression on progression free survival

| Univariable Cox models for PFS from enrollment | | | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Events** | **N** | **HR** | **Lower 95% CI** | **Upper 95% CI** | **P-value** |
| **Age** | | | | | | |
| Per unit | 14 | 61 | 1.010 | 0.970 | 1.051 | 0.635 |
| **Age (grouped)** | | | | | | |
| < 45 | 10 | 45 | 1 (ref) | | | |
| ≥ 45 | 4 | 16 | 1.634 | 0.512 | 5.215 | 0.407 |
| **Relapse 3 groups** | | | | | | |
| Primary refractory | 9 | 24 | 1 (ref) | | | |
| Relapse < 1 year (not refractory) | 3 | 17 | 0.424 | 0.115 | 1.567 | 0.198 |
| Relapse ≥ 1 year | 2 | 20 | 0.245 | 0.053 | 1.133 | 0.072 |
| **Relapse 2 groups** | | | | | | |
| Primary refractory | 9 | 24 | 1 (ref) | | | |
| Relapse | 5 | 37 | 0.328 | 0.110 | 0.980 | 0.046 |
| **B-symptoms** | | | | | | |
| No | 8 | 38 | 1 (ref) | | | |
| Yes | 6 | 23 | 1.392 | 0.483 | 4.016 | 0.540 |
| **Ann Arbor Stage at first diagnosis** | | | | | | |
| I / II | 3 | 22 | 1 (ref) | | | |
| III / IV | 10 | 36 | 2.025 | 0.557 | 7.366 | 0.284 |
| (3 unknown) | | | | | | |
| **Ann Arbor Stage at relapse** | | | | | | |
| I / II | 5 | 28 | 1 (ref) | | | |
| III / IV | 9 | 32 | 1.756 | 0.588 | 5.244 | 0.313 |
| (1 unknown) | | | | | | |
| **First line treatment** | | | | | | |
| ABVD | 9 | 45 | 1 (ref) | | | |
| BEACOPP (escalated/baseline) | 2 | 11 | 0.903 | 0.195 | 4.179 | 0.896 |
| Other | 3 | 5 | 3.878 | 1.039 | 14.474 | 0.044 |
| **Interim PET status*** | | | | | | |
| mCR | 6 | 48 | 1 (ref) | | | |
| mPR | 3 | 5 | 6.02 | 1.499 | 24.2 | 0.011 |
| PD (censored from cox analysis) | 5 | 5 | - | | | |
| (3 not evaluable for response) | - | 3 | - | | | |

| Multivariable Cox model for PFS, measured from interim PET | | | | | | |
|---|---|---|---|---|---|---|
| **Characteristic** | **Events** | **N** | **HR** | **Lower 95% CI** | **Upper 95% CI** | **P-value** |
| **Interim PET status*** | | | | | | |
| mCR | 6 | 48 | 1 (ref) | | | |
| mPR | 3 | 5 | 4.785 | 1.167 | 19.628 | 0.030 |
| **Relapse 2 groups** | | | | | | |
| Primary refractory | 6 | 20 | 1 (ref) | | | |
| Relapse | 3 | 33 | 0.311 | 0.076 | 1.271 | 0.104 |

*For interim PET status analysis, the PFS was defined as time from interim PET-scan after 3 cycles of BV-DHAP, until progression or death, and patients with PD at time of the interim PET were excluded from this subanalysis.

**Abbreviations:** Number of patients (N); Hazard Ratio (HR); Confidence Interval (CI); reference (ref); progression free survival (PFS); progressive disease (PD); metabolic complete response (mCR); metabolic partial response (mPR); adriamycin, bleomycin, vinblastine, dacarbazine (ABVD); bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone (BEACOPP); positron emission tomography (PET).

Supplemental Table 6: Central pathology review

| Table 6: Central pathology review of EBER positive cases (n=17) | | | | |
|---|---|---|---|---|
| | **IHC unequivocal** | **IHC non-conclusive** | **(iatrogenic) immunodeficiency highly suggestive** | **No proof for (iatrogenic) immunodeficiency** |
| **TcR monoclonal** | 46 – PTCL (PD1)<br>57 – AITL (PD1/CD21) | 44 – PTCL<br>53 – PTCL | | |
| **TcR equivocal (poor DNA quality)** | 45 – PTCL (T-cell marker loss) | 6 – cHL<br>43 – cHL<br>18 – cHL | | |
| **TcR polyclonal** | 42 – PTCL (T-cell marker loss) | 67 – cHL (PD1+ only) | | |
| **Ig-R monoclonal** | | | 11 – IA-B-LPD | 21 – cHL<br>24 – cHL |
| **Ig-R polyclonal** | | | | 61 – cHL<br>64 – cHL |
| **No Ig- and TcR information available** | | | | 51 – cHL<br>10 – cHL |

Diagnostic biopsy samples at relapse were available for review for all of the 67 patients (100%) included in the phase I and/or phase II of this study. In 34 cases also the primary diagnostic biopsy sample was submitted for review (51%). At review, at least the following immunohistochemical stains were available in all cases: CD30, CD15, PAX5, CD20, CD3 as well as EBER-ISH. In one case cHL and synchronous lymphoplasmacytic lymphoma was diagnosed (case 60) and in another case the material was not diagnostic for cHL due to absence of tumor cells (case 50).

In 4 of the cases, the cHL-cells expressed CD20, but lacked further arguments for a classification as “mediastinal grey zone lymphoma”. All 17 cases with EBER positive Hodgkin-type cells and/or small lymphocytes were scrutinized to dissect the difficult differential diagnosis of cHL, T-cell lymphoma with secondary EBV+ Hodgkin-like blasts (either angio-immunoblastic T-cell lymphoma or peripheral T-cell lymphoma) and immunodeficiency-associated B-lymphoproliferative disorder (IA-B-LPD) (**Table 6**). T-cell receptor (TcR)- and immunoglobulin heavy (IgH) and kappa light chain (IgK) gene rearrangement studies according to standard methods (IgH, IgK, TcR beta and gamma standard BIOMED assays) and complementary immunohistochemistry was performed to include at least CD21 and PD1 and if sufficient material was available also CD79a, CD2, CD5, CD7, CD8, CD4, CD23.

Of these 17 cases, 3 showed only EBER positivity in small cells and were considered fully consistent with cHL (cases 10, 24, 51). Only in case of unequivocal monoclonal TcR rearrangement (case 46 and 57) and/or immunohistochemical patterns (T-cell marker loss case 45 and 42), in the context of a fitting morphology, a diagnosis of T-cell lymphoma was rendered. Only in case of unequivocal (iatrogenic) immunodeficiency, the diagnosis IA-B-LPD was made (long history of steroid use). Equivocal cases were considered as cHL for this review. In conclusion, in 59/67 cases (88%), a diagnosis of cHL could be confirmed.

**Abbreviations**: Epstein-Barr virus encoded RNAs (EBER), in situ hybridization (ISH), Epstein-Barr virus (EBV), immunohistochemistry (IHC), T-cell receptor (TcR), immunoglobulin receptor (Ig-R), peripheral T-cell lymphoma, not otherwise specified (PTCL), angio-immunoblastic T-cell lymphoma (AITL), classical Hodgkin lymphoma (cHL), immunodeficiency-associated B-lymphoproliferative disorder (IA-B-LPD), programmed cell death protein1 (PD1).