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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ONLINE APPENDIX

Title

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Authors and affiliation

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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); - grade ≥ 3 non-hematologic toxicity, including neurotoxicity# - death whatever the cause, except death due to Hodgkin lymphoma any of which must occur before day 22 of cycle I-III - 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. # Exceptions: 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 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 3. Any infection/fever requiring iv antibiotics is not considered to be a DLT, only grade 4 infection is considered to be a DLT 4. Grade 3 thromboembolic events and grade 3 hypertension are not considered to be DLT 5. If a DLT is attributed to progressive disease, it will not be counted as DLT. 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: - Results in death; - Is life threatening (at the time of the event); - Requires hospitalization or prolongation of existing inpatients' hospitalization; - Results in persistent or significant disability or incapacity; - is a congenital anomaly or birth defect; - 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. 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. 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) 57 – AITL (PD1/CD21)	44 – PTCL 53 – PTCL		
TcR equivocal (poor DNA quality)	45 – PTCL (T-cell marker loss)	6 – cHL 43 – cHL 18 – cHL		
TcR polyclonal	42 – PTCL (T-cell marker loss)	67 – cHL (PD1+ only)		
Ig-R monoclonal			11 – IA-B-LPD	21 – cHL 24 – cHL
Ig-R polyclonal				61 – cHL 64 – cHL
No Ig- and TcR information available				51 – cHL 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).