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LETTER

Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone for advanced-stage Hodgkin lymphoma in older patients

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Historically, the outcomes among older patients with classic Hodgkin lymphoma (HL) have been inferior compared to younger patients, and 80% of HL-related deaths occur in patients ≥ 55 years of age at diagnosis.[1] These inferior outcomes are in part attributable to comorbidities and frailty, resulting in poorer tolerability of standard multi-agent chemotherapies such as doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD).[2] Even if treatment is administered at standard relative dose intensities, lower progression-free survival (PFS) and overall survival (OS) are observed,[3,4] especially in patients with high comorbidity burden or impaired activities of daily living.[5,6] In light of demographic changes and increased life expectancy in many countries, the growing group of older patients hence constitutes a growing unmet need.[7]

Recently, encouraging results were reported from subgroup analyses and a Phase II trial incorporating either brentuximab vedotin (BV) or nivolumab into first-line treatment.[8] Prospective clinical trials specifically designed to explore novel treatment options specifically in older HL patients remain however scarce. Moreover, patient-reported health-related quality of life (HRQoL) data in patients ≥ 60 years of age remain scarce to absent. Understanding the baseline HRQoL status and treatment-related trajectories in this patient population hence is of immediate interest.

In the international German Hodgkin Study Group (GHSG)-NLH intergroup Phase II BVB trial reported herein, we hypothesized that the combination of the anti-CD30 antibody–drug conjugate BV with cyclophosphamide, doxorubicin, and prednisone (B-CAP) constitutes a feasible and effective first-line treatment.

The Phase II trial (NCT02191930) evaluated six cycles of B-CAP (6xB-CAP), consisting of BV (1.8 mg/kg iv Day 1), cyclophosphamide (750 mg/m^2 iv d1), doxorubicin (50 mg/m^2 iv d1), and prednisone (100 mg po Days 2–6) at 3-weekly intervals as first-line treatment for advanced-stage HL patients ≥ 60 years considered eligible for combination chemotherapy. Patients provided written informed consent, and the trial was conducted according to Good Clinical Practice and in line with the Declaration of Helsinki. Further details are available in the Supplementary Methods.

Between 11/2015 and 09/2017, 50 patients were recruited at 17 centers in 5 European countries. One patient withdrew consent before the start of treatment, and a total of 49 patients with a median age of 66 years (range: 60–84, interquartile range [IQR]

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64–70) were evaluable in the intention-to-treat population (Figure S1 and Table 1).

Before B-CAP treatment, 21 patients (43%) received a protocol-recommended corticosteroid pre-phase (100 mg prednisone/day for ≤5 days). With a median duration of systemic treatment of 111 days, the intended 6xB-CAP were administered in 46/49 patients (94%). Three patients terminated treatment early due to toxicity: One patient deceased after 1xB-CAP due to sepsis and was not evaluable for response, the other two patients both discontinued treatment due to febrile neutropenia with Grade (G) 3 gastrointestinal toxicity after 4x and 5xB-CAP, respectively. Both achieved a PR at interim restaging after 2xB-CAP. With primary granulocyte colony-stimulating factor (G-CSF) support documented in 98% of patients, any treatment delay occurred in 15% of B-CAP cycles, but no cycle was delayed more than 14 days. The maximum dose level was maintained in 86% of patients, and the mean relative dose intensity, defined as relative dose over relative duration, was 93%.

TABLE 1 Patient characteristics.

	B-CAP ITT population (*N* = 49)
Age	
Median, years	66 (range: 60–84, IQR: 64–70)
≥75 years old	4 (8%)
Sex, female	
Female	23 (47%)
Male	26 (53%)
Ann Arbor stage	
IIB	2 (4%)
IIIA	7 (14%)
IIIB	8 (16%)
IVA	7 (14%)
IVB	25 (51%)
GHSG risk factors	
≥3 areas	38 (78%)
Elevated ESR	32 (65%)
Extranodal disease	7 (14%)
Large mediastinal mass	5 (10%)
IPS, *n* = 48, *n* = 1 missing	
1	3 (6%)
2–3	21 (44%)
4–7	24 (50%)
Histologic subtype	
Nodular sclerosis	18 (51%)
Mixed cellularity	12 (34%)
Lymphocyte rich	1 (3%)
Classic HL, not specified	4 (11)
ECOG	
0	13 (27%)
1	30 (61%)
≥2	6 (12%)
CIRS-G summary score	
0	6 (12%)
1–3	25 (51%)
4–6	18 (37%)

Abbreviations: B-CAP, brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisolone; CIRS-G, Cumulative Illness Rating Scale in Geriatrics; ECOG, Eastern Cooperative Oncology Group performance status; ESR, erythrocyte sedimentation rate; GHSG, German Hodgkin Study Group; HL, Hodgkin lymphoma; IPS, international prognostic index; IQR, interquartile range; ITT, intention to treat.

Most patients experienced hematological toxicities (any G: 92%, G3: 8%, G4: 53%), most commonly neutropenia (G3/4: 61%), followed by anemia (G3/4: 18%), and thrombocytopenia (G3/4: 10%; Table S1). At least one red blood cell or platelet transfusion was documented in 3 (6%) and 12 (25%) patients, respectively. Febrile neutropenia occurred in 27% and infections in 61% (G3: 29%, G4: 2%, G5: 2%) of patients, respectively. Acute neuropathy increased with accumulating B-CAP exposure (Figure S2), was mostly sensory, and was reported in 67% of patients (G2: 20%, ≥G3: 0). Dose reduction or omission of BV during B-CAP treatment was documented for three patients each. Persisting peripheral neuropathy was reported in 11/49 (22%) of patients at last available follow-up (G1: 9 patients, G2: 2 patients).

At the first interim restaging after 2xB-CAP, 44/47 centrally evaluable patients had an objective response, including 34% with complete remission (CR) by computed tomography (CT). ^{18}F-fluorodeoxyglucose positron emission tomography with CT (PET/CT) was available for 21 patients after 2xB-CAP, with 17/21 (81%) achieving a metabolic CR defined by Deauville score (DS) ≤ 3.[9] After completion of systemic therapy the predefined primary endpoint was met with a centrally evaluated CT-based objective response rate of 98% (95% CI: 90.5–100) and a CT-based CR rate of 44%. A metabolic CR was achieved in 31/48 evaluable patients (65%), and 10 patients (20%) received consolidative 30-Gy radiotherapy to residues with residual uptake in PET/CT after completion of B-CAP treatment. With a median follow-up of 35 months, 16 patients (33%) experienced disease progression or relapse, and 9 (18%) deceased, mostly from HL (6 patients, 12%). The Kaplan–Meier estimates for 3-year PFS and OS were 64% (95% CI: 50–79) and 91% (95% CI: 82–99), respectively (Figure 1A,B). More favorable 3-year PFS was observed in patients achieving a metabolic CR (82%) after completion of systemic treatment compared to patients with metabolic PR (33%; hazard ratio [HR] 6.7, 95% CI 2.3–19.7; Figure 1C,D). There were two second primary malignancies, with one case each of bladder cancer and colorectal cancer.

A total of 39 patients (80%) provided consent for the collection of patient-reported HRQoL data and completed at least one valid HRQoL questionnaire. Except for a significantly younger median age of 65 (range: 60–84) versus 71 years (range: 68–84; $P < 0.01$), patients with consent for HRQoL analysis did not differ from those without. GHS was impaired compared to age- and sex-matched reference values at diagnosis, but improved already during treatment and normalized during follow-up (Figure S3). Similarly, evaluable patients showed higher symptom burden at baseline for fatigue, dyspnea, insomnia, appetite loss, and constipation compared to the age- and sex-matched control population (Figure S4). Reduced patient-reported functioning was reported for all functioning scales at baseline (Figure S5). In line with GHS trajectories, improvement and normalization to population reference values were seen for most symptom and functioning scales during and after treatment (Figures S3–S5).

This international multicenter Phase II trial showed that first-line treatment with the novel B-CAP regimen is feasible and effective in patients ≥ 60 years of age with first diagnosis of advanced-stage classic HL. The primary endpoint of efficacy was met, and patient-reported HRQoL improved during treatment and follow-up.

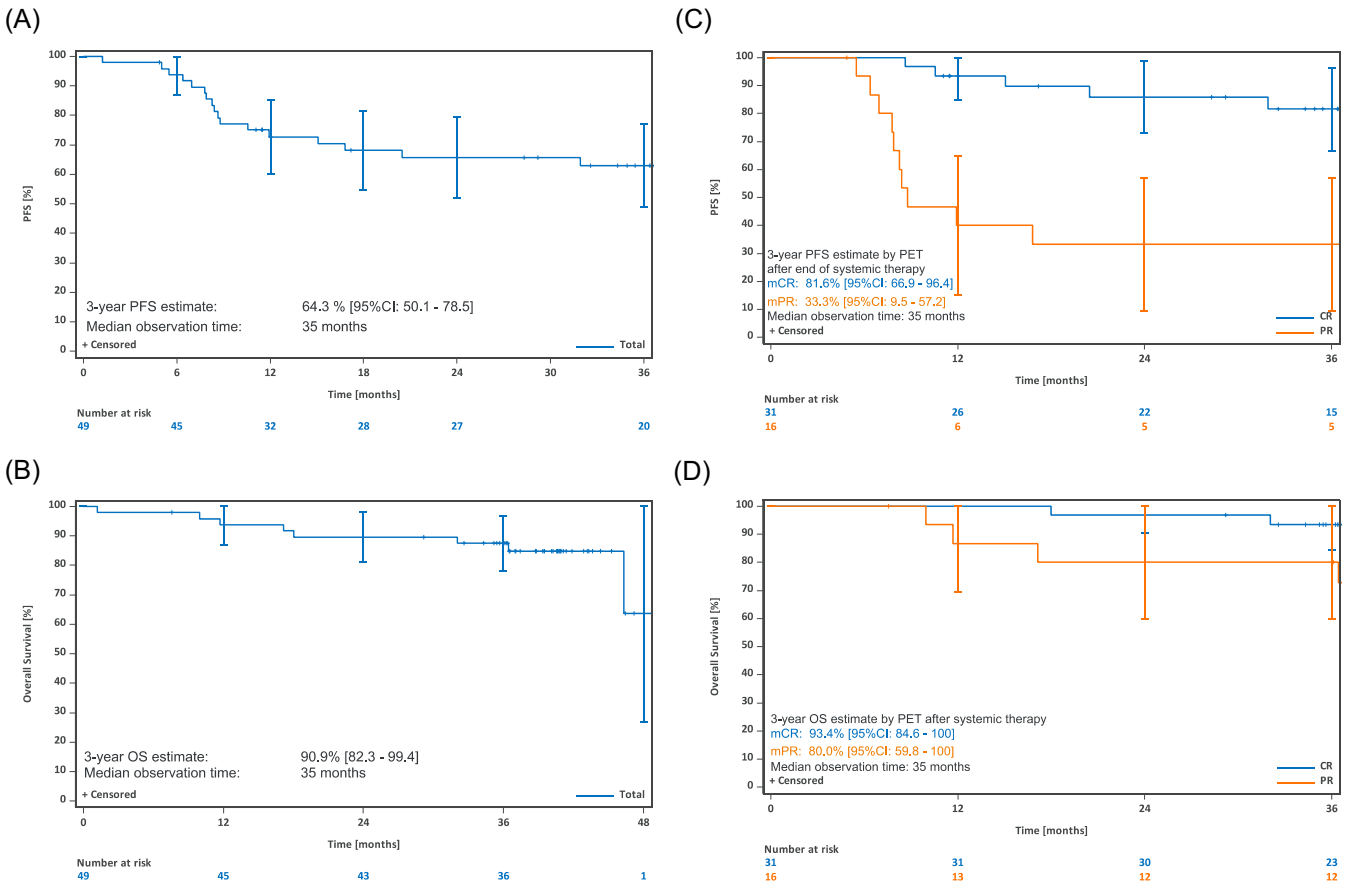

FIGURE 1 **Progression-free survival (PFS) and overall survival (OS).** PFS **(A)** and OS **(B)** after start of brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone treatment in the intention-to-treat cohort. PFS **(C)** and OS **(D)** in patients with and without a complete metabolic remission after the end of treatment among the subset of patients with available PET. CI, confidence interval; mCR, metabolic complete remission; mPR, metabolic partial remission; PET, ^{18}F-fluorodeoxyglucose positron emission tomography with computed tomography.

Since the conduct of our trial, data on other approaches for treatment with curative intent such as PET-guided 4–6 cycles of BrECADD or 6 cycles of N-AVD have been reported from subgroups of older patients included in larger Phase III trials.[8,10] The currently available 2-year PFS rates of 92% (95% CI: 85–95) with BrECADD and 89% (95% CI: 74–95) with N-AVD, respectively, are higher than the 3-year PFS rate of 64% (95% CI: 50–79) reported with B-CAP herein. More recently, a Phase II trial reported a 3-year PFS rate of 79% (95% CI: 66–95) with six cycles of N-AVD.[11] Given the heterogeneous population of older HL patients, there might be patients in whom neither BrECADD nor N-AVD may be feasible, for example, due to lack of fitness, higher comorbidity burden (including active autoimmune disease), or local unavailability. B-CAP hence adds to the therapeutic options in this growing patient population. Other novel therapeutic approaches specifically designed for older patients, such as single-agent pembrolizumab,[12] single-agent BV,[13] or BV in combination with dacarbazine or nivolumab,[14] have been explored mostly in less fit patients with usually inferior outcomes. Indirect comparisons to these regimens are, however, limited by the often-substantial differences in the trial populations.

Longitudinal patient-reported HRQoL data in the context of first-line treatment in older patients have, to our knowledge, not been reported. We report impaired GHS at baseline, and the underlying HL-associated changes in older patients include symptoms such as fatigue, dyspnea, insomnia, loss of appetite, or constipation as well as reduced role and social functioning. Importantly, initiation of B-CAP does not lead to further HRQoL deterioration but rather marks the beginning of a steady improvement, with most HRQoL domains approaching age- and sex-matched reference values during follow-up. Besides establishing B-CAP as a treatment option, our results provide a benchmark for HRQoL trajectories in older HL patients. Additionally, our results show that curatively intended multi-agent treatment given to appropriately selected older HL patients may have a profound and sustained positive impact on HRQoL up until 3 years after treatment.

Interpretability of our study findings is, however, limited by the lack of more comprehensive geriatric assessments, including, for example, activities of daily living. Also, despite a relatively high response rate in the sub-study of PRO HRQoL, attrition and selection bias may have hampered generalizability. Lastly, although the relatively long median follow-up of 35 months is a strength of our study, the latency between trial conduct and reporting in a meanwhile changed therapeutic landscape potentially limits the applicability of the results.

In summary, first-line treatment with up to six cycles of the B-CAP regimen results in high response rates already after two cycles and favorable 3-year PFS in patients achieving a metabolic CR. Importantly, patients reported early and sustained improvement of HRQoL during and after first-line treatment with B-CAP. B-CAP

hence is a feasible and effective treatment option for older patients with advanced-stage classic HL.

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AUTHOR CONTRIBUTIONS

Paul J. Bröckelmann: Investigation; writing—original draft; conceptualization. **Boris Böll**: Conceptualization; funding acquisition; investigation; writing—review and editing. **Daniel Molin**: Writing—review and editing. **Gundolf Schneider**: Formal analysis; writing—review and editing. **Sirpa Leppä**: Investigation; writing—review and editing. **Julia Meissner**: Investigation; writing—review and editing. **Peter Kamper**: Investigation; writing—review and editing. **Martin Hutchings**: Investigation; writing—review and editing. **Jacob H. Christensen**: Investigation; writing—review and editing. **Ulf Schnetzke**: Investigation; writing—review and editing. **Michael Fuchs**: Investigation; funding acquisition; writing—review and editing. **Janina Jablonski**: Formal analysis; writing—review and editing. **Dennis A. Eichenauer**: Investigation; writing—review and editing. **Bastian von Tresckow**: Investigation; writing—review and editing. **Wolfram Klapper**: Investigation; writing—review and editing. **Carsten Kobe**: Investigation; writing—review and editing. **Peter Borchmann**: Investigation; conceptualization; funding acquisition; writing—review and editing. **Alexander Fosså**: Conceptualization; investigation; funding acquisition; writing—review and editing.

CONFLICT OF INTEREST STATEMENT

P.J.B. is an advisor or consultant for Hexal, Merck Sharp & Dohme (MSD), Need Inc., Stemline, and Takeda; holds stock options in Need Inc.; has received honoraria from AstraZeneca, BeiGene, Bristol-Myers Squibb (BMS)/Celgene, Eli Lilly, MSD, Need Inc., Stemline, and Takeda; and reports research funding from BeiGene (institution), BMS (institution), MSD (institution), and Takeda (institution). D.M. received honoraria from Roche. J.H.C. received honoraria from Takeda. D.A.E. has received honoraria from Takeda. B.v.T. is an advisor or consultant for Allogene, Amgen, BMS/Celgene, Cerus, Gilead Kite, Incyte, IQVIA, Janssen-Cilag, Lilly, MSD, Miltenyi, Novartis, Noscendo, Pentixapharm, Pfizer, Pierre Fabre, Qualworld, Regeneron, Roche, SOBI, and Takeda; has received honoraria from AbbVie, AstraZeneca, BMS/Celgene, Gilead Kite, Incyte, Janssen-Cilag, Lilly, MSD, Novartis, Roche, Serb, and Takeda; reports research funding from Esteve (institution), MSD (institution), Novartis (institution), and Takeda (institution); reports travel support from AbbVie, AstraZeneca, Gilead Kite, Janssen-Cilag, Lilly, MSD, Pierre Fabre, Roche, Takeda, and Novartis; and is member of steering committees for Regeneron (institution) and Takeda. A.F. has acted as a consultant for Takeda, Kite Gilead, and SOBI; has received honoraria from Johnson and Johnson, Roche, Takeda, MSD, BMS, Eusapharma, Kite Gilead, Kyowa Kirin, and SOBI; and reports research support from Takeda (outside of the submitted work) and Roche. The other authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The BVB Phase II trial reported herein was registered at ClinicalTrials.gov (NCT02191930) and approved by the respective ethics committees and responsible authorities. All patients provided written informed consent, and the trial was conducted according to Good Clinical Practice and in line with the Declaration of Helsinki. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found in the online version of this article.

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