0.2 PROTOCOL SYNOPSIS

SPONSOR	University of Cologne Albertus-Magnus Platz 50923 Köln Represented by: Prof. P. Borchmann (Trial Chairman) Cologne University Hospital Department of Internal Medicine I Kerpener Str. 62 50937 Köln
TRIAL CHAIRMAN	Prof. P. Borchmann
TRIAL SECRETARY	Dr. J. Ferdinandus
HEAD STATISTICIAN	Gundolf Schneider
TITLE	Treatment optimization trial in the first-line treatment of advanced stage Hodgkin lymphoma; comparison of 4-6 cycles of escalated BEACOPP with 4-6 cycles of BrECADD.
SCHEDULE	Entry of first patient - randomized cohort (FPI): 22 July 2016 End of recruitment - randomized cohort (LPI): 27 August 2020 Start of recruitment – elderly cohort: 22 July 2020 End of recruitment- elderly cohort: 31 July 2022 Analysis of primary toxicity endpoint (16 months after LPI): 30 November 2021 Analysis of elderly cohort: 01 April 2023 Interim analysis of efficacy endpoint (randomized cohort): approximately 36 months of median Follow-Up Analysis of efficacy and secondary endpoints (randomized cohort): after reaching 154 events

	Last patient, last visit 31 December 2025 Follow up analysis of efficacy and secondary endpoints (within 6 months after LPLV) 30 June 2026 Subsequent follow-up observation of patients outside the trial.
PHASE	III
TRIAL CENTERS	Approx. 250 in Germany and other countries
PRIMARY ENDPOINTS	Randomized main study: • Treatment-related morbidity (TRMB) • Progression-free survival (PFS) Cohort of older patients: • Complete remission (CR) rate after chemotherapy
SECONDARY ENDPOINTS	Randomized main study: • Tumor response (CR rate) • Overall survival (OS) • Infertility rate at 1 year • Second malignancies • Quality of life (QoL) • Frequency of adverse events • Therapy adherence Cohort of older patients: • TRMB • PFS • OS • Time to progression (PFSHL) and HL-specific survival (OSHL)
NUMBER OF PATIENTS	Randomized main study: 1,500 Cohort of older patients: 85
MAIN ENTRY CRITERIA	• Histologically proven classical Hodgkin lymphoma • First diagnosis, no previous treatment • Stage IIB with large mediastinal mass and/or extranodal lesions, stage III or IV • Randomized main study: 18 to 60 years of age • Cohort of older patients: 61 to 75 years of age
MAIN EXCLUSION CRITERIA	• Composite lymphoma or nodular lymphocyte-predominant Hodgkin lymphoma • Previous malignancy (exceptions: basalioma, carcinoma in situ of the cervix uteri, completely resected melanoma TNMpT1)

	• Prior chemotherapy or radiotherapy (prephase is allowed as outlined in the protocol) • Concurrent disease which precludes protocol treatment • Pregnancy, lactation • Non-Compliance
TREATMENT GROUPS	In the main study, patients are randomized to receive chemotherapy with escalated BEACOPP (standard group) or with BrECADD (experimental group). After the first two cycles, a restaging is performed by contrast-enhanced computed tomography (ceCT) and positron-emission tomography (FDG PET/CT) in all patients in order to guide response-adapted continuation of therapy consisting of 4 or only 2 additional cycles of randomized chemotherapy in case of a PET positive or negative staging result, respectively. A second restaging will be performed after completion of chemotherapy; Patients with PET-positive residual disease will receive local irradiation, while patients in complete remission do not receive radiotherapy. All patients older than 60 years receive PET-guided therapy with BrECADD and radiotherapy, if applicable, as described above (experimental group).
TRIAL DESIGN	Open-label, prospective, multicenter trial with central stratified randomization between two parallel groups (minimization method) with an additional, independent, non-randomized cohort for older patients not eligible for the randomized main study
STATISTICAL METHODS	**Randomized main study:** Hierarchical design with two primary endpoints. At first, superiority in terms of less serious treatment-related adverse events during treatment will be tested using the Cochran-Mantel-Hanszel test. If successful, non-inferiority in terms of PFS will be tested using the 95% confidence interval of the hazard ratio adjusted for stratification factors. The intention-to-treat analysis set will be primary analysis set in both cases. **Cohort of older patients:** In order to meaningfully describe the outcome of the BrECADD regimen in older patients, the CR rate will be estimated with its two-sided exact 95% confidence interval. With 85 evaluable patients,

	the exact 95% CI for the CR rate will have a half width of less than 12%. Secondary endpoints will be analyzed descriptively, including rates and corresponding 95% confidence intervals.
GCP CONFORMITY	This trial is conducted in conformity with the international Guidelines for Good Clinical Practice (ICH-GCP) including the storage of essential documents.
FINANCIAL SUPPORT	The trial is financially supported and brentuximab vedotin is supplied free of charge by Millennium Pharmaceuticals, Inc.