25 April 2025
EMA/324858/2025
Committee for Medicinal Products for Human Use (CHMP)
Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

ADCETRIS

International non-proprietary name: Brentuximab vedotin

Procedure No. EMEA/H/C/002455/II/0111

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

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A+AVD	brentuximab vedotin (ADCETRIS®), doxorubicin (Adriamycin®), vinblastine, and dacarbazine
A+CHP	brentuximab vedotin (ADCETRIS) + cyclophosphamide, doxorubicin, and prednisone
ABVD	doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine
ADC	antibody-drug conjugate
ADR	adverse drug reaction
AE	adverse event
alloSCT	allogeneic stem cell transplant(ation)
AML	acute myelogenous leukemia
ASCT	autologous stem cell transplant(ation)
BrECADD	brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone
BrECAPP	brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, procarbazine, prednisone
BSA	body surface area
BV	brentuximab vedotin
CC	central confirmation
CD30+	CD30-positive
CHEP-BV	brentuximab vedotin plus cyclophosphamide, doxorubicin, etoposide, and prednisone
cHL	classical Hodgkin lymphoma
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CMH	Cochran Mantel-Haenszel (test)
CR	complete remission
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	cutaneous T-cell lymphoma
DCO	data cutoff
DOCR	duration of complete response
DOR	duration of response
eBEACOPP	escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone
ECHELON-1	clinical study C25003 of brentuximab vedotin (SGN-35)

ECOG PS	Eastern Cooperative Oncology Group performance status
eCRF	electronic case record form
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study (visit)
EOT	end of treatment
ESMO	European Society for Medical Oncology
EU	European Union
FSH	follicle stimulating hormone
FUP	follow-up
G-CSF	granulocyte colony stimulating factor
GCP	Good Clinical Practice
GHSG	German Hodgkin Study Group
GI	gastrointestinal
HL	Hodgkin lymphoma
HR	hazard ratio
IA	interim analysis
ICU	intensive care unit
IDMC	Independent Data Monitoring Committee
INV	investigator
IPS	International Prognostic Score
IRF	independent review facility
ITT	intent-to-treat
IV	intravenous; intravenously
MAH	marketing authorization holder
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MID	minimally important difference
MMAE	monomethyl auristatin E
mPFS	modified progression-free survival
NA	not applicable
NC	no change
NCCN	National Comprehensive Cancer Network
NE	not estimable

ORR	overall response rate
OS	overall survival
PD	pharmacodynamic
PET	positron emission tomography
PET2	positron emission tomography at Cycle 2
PFS	progression-free survival
PIL	Patient Information Leaflet
PML	progressive multifocal leukoencephalopathy
PN	peripheral neuropathy
PR	partial remission
PRO	patient-reported outcome
PT	preferred term
PTCL	peripheral T-cell lymphoma
PTFU	post-treatment follow-up
QoL	quality of life
QLQ-C30	(EORTC) Quality of Life Questionnaire – Core 30
QLQ-CIPN20	(EORTC) chemotherapy-induced peripheral neuropathy module
QLQ-FA12	(EORTC) cancer-related fatigue questionnaire
SAE	serious adverse event
sALCL	systemic anaplastic large-cell lymphoma
SD	stable disease
SD	standard deviation
SGN-35	brentuximab vedotin, ADCETRIS
SmPC	Summary of Product Characteristics
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TRMB	treatment-related morbidity
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Takeda Pharma A/S submitted to the European Medicines Agency on 10 April 2024 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for ADCETRIS to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV Hodgkin lymphoma (HL) in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD), based on final results from phase 3 study HD21 (NCT02661503). This study is titled 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.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the SmPC.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information relating to orphan designation

ADCETRIS, was designated as an orphan medicinal product (EU/3/08/596) on 15 January 2009 in the following indication:

Treatment of Hodgkin's lymphoma

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decisions (P/0013/2021) on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0013/2021 was completed.

The PDCO issued an opinion on compliance for the PIP P/0013/2021 on 13 Dec 2021.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised

orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek scientific advice from the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: *co-Rapporteur acted as rapporteur* Co-Rapporteur: Jan Mueller-Berghaus

Timetable	Actual dates
Submission date	10 April 2024
Start of procedure:	27 April 2024
CHMP Rapporteur Assessment Report	26 June 2024
PRAC Rapporteur Assessment Report	27 June 2024
PRAC members comments	3 July 2024
PRAC Outcome	11 July 2024
CHMP members comments	15 July 2024
Updated CHMP Rapporteur(s) (Joint) Assessment Report	18 July 2024
Request for supplementary information (RSI)	25 July 2024
CHMP Rapporteur Assessment Report	12 November 2024
PRAC members comments	20 November 2024
PRAC Outcome	28 November 2024
CHMP members comments	2 December 2024
Updated CHMP Rapporteur Assessment Report	5 December 2024
Request for supplementary information (RSI)	12 December 2024
CHMP Rapporteur Assessment Report	24 March 2025
PRAC Rapporteur Assessment Report	24 March 2025
PRAC members comments	
Updated PRAC Rapporteur Assessment Report	
PRAC Outcome	
CHMP members comments	
Updated CHMP Rapporteur Assessment Report	
Opinion	

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

The proposed target indication for this extension of indication is:

Hodgkin lymphoma

*ADCETRIS is indicated for adult patients with **previously untreated** CD30+ **Stage IIB with risk factors, Stage III or Stage IV HL** in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (**BrECADD**) (see sections 4.2 and 5.1).*

Epidemiology

The incidence in Europe is ~ 2.4 cases per 100.000 persons. HL demonstrates a bimodal age distribution with the first peak occurring at about 20-30 years of age and a second peak in patients >65 years of age. In Europe, GLOBOCAN estimates that 19,723 new HL cases were diagnosed and 3,796 HL-related deaths occurred in 2022 (across all ages), with a 5-year prevalence of 79,763 cases in adults. (gco.iarc.who.int/media/globocan/factsheets/cancers/33-hodgkin-lymphoma-fact-sheet.pdf, accessed 26 March 2023).

Clinical presentation, diagnosis and stage/prognosis

Clinical symptoms are present in 2/3 of patients, and could include the presence of B symptoms (fever, night sweats, unexplained weight loss >10% in 6 months), fatigue, pruritus and alcohol-induced pain.

Staging is according to the Ann Arbor criteria, which are based on localisation, the extent of nodal and extranodal involvement and the presence of the classical B symptoms.

For the purposes of treatment planning, classical Hodgkin Lymphoma (cHL) is frequently divided into early-stage (Stage I/II) and advanced-stage (Stage III/IV) disease. In the absence of unfavourable features, the prognosis for early-stage disease is excellent. Thus, the frontline treatment approach for these individuals is focused on minimizing toxicity of therapy while maintaining high cure rates.

Stage at diagnosis predicts long-term outcomes with 5-year OS rates of 92.9% and 78%, respectively, for patients with early- and advanced-stage disease (NIH Cancer stats 2022). In addition to clinical staging, other clinical features can predict outcomes in these patients. The international prognostic score is a tool that assesses 7 potentially unfavourable clinical features in HL at diagnosis: serum albumin <4 g/dL, haemoglobin <10.5 g/dL, male gender, age >45 years, Stage IV disease, white blood cell count ≥15,000/µL, and absolute lymphocyte count <600/µL and/or <8% of the total white blood cell count. When applied retrospectively to patients who were treated with current standard-of-care combination chemotherapy regimens, the 5-year OS for patients with lower scores (0-3) was 93% ±1% and those with higher (≥4) scores was 78% ±4%.

HL prognosis is worse in patients who present with advanced disease and 30-40% relapse within 5 years after initial treatment or have immediate treatment failure. Five-year survival for patients with Stage III cHL is approximately 80%, whereas the 5-year survival rate for patients with Stage IV cHL is

approximately 65%. Multiple large studies demonstrate that about half of patients undergoing ASCT can be cured. However, a significant percentage of patients with relapsed or refractory HL never make it to ASCT because their disease does not respond adequately to salvage therapies or their clinical status, including age, precludes them from undergoing the procedure.

Management

Patients with early-stage disease are typically treated with 2 to 4 cycles of doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD), with or without focal radiotherapy to sites of disease. This approach produces excellent results with 3- to 5-year progression-free and OS rates exceeding 90% and 95%, respectively, in patients with favorable disease (Arakelyan et al. 2010; Engert et al. 2010; Radford et al. 2015), and 85% and 90%, respectively, in patients with unfavorable disease (Bonadonna et al. 2004; Eich et al. 2010).

Patients diagnosed with Stage III/IV cHL are usually treated with 6 to 8 cycles of ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine), with some physicians adding limited field consolidative radiotherapy for bulky mediastinal involvement. In an effort to improve frontline disease control in patients with advanced cHL, more aggressive multiagent chemotherapy regimens have been developed, such as standard-dose and escalated-dose versions of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) (Engert et al. 2009).

Aggregate data support the conclusion that these more aggressive treatment regimens yield better initial disease control (Carde et al. 2016; Merli et al. 2016; Viviani et al. 2011). However, these studies do not demonstrate an OS advantage for the BEACOPP regimens, which are also associated with higher rates of acute toxicities such as febrile neutropenia and long-term morbidities, including infertility and secondary malignancies (Behringer et al. 2013; Merli et al. 2016). Moreover, treatment-related mortality for BEACOPP is unacceptably high in patients 60 years of age and older (Borchmann et al. 2011).

Treatment with salvage chemotherapy followed by high dose chemotherapy and autologous stem cell transplant (ASCT) is standard of care for patients with relapsed or refractory disease after frontline therapy.

2.1.2. About the product

Brentuximab vedotin is a CD30-directed antibody-drug conjugate (ADC) composed of the monoclonal antibody (cAC10) covalently linked, via an enzyme-cleavable linker, to the antimitotic small molecule monomethyl auristatin E (MMAE). Binding of the ADC to CD30 on the cell surface initiates internalisation of the ADC-CD30 complex, which then traffics to the lysosomal compartment. Within the cell, MMAE is released via proteolytic cleavage and degradation of the drug linker. Binding of MMAE to tubulin disrupts the microtubule network within the cell, induces cell cycle arrest and results in apoptotic death of the CD30-expressing tumour cell.

Pharmacological classification (ATC-code): L01XC12.

The first marketing authorization for brentuximab vedotin in the EU was granted in October 2012. Adcetris is currently indicated for:

Hodgkin lymphoma

ADCETRIS is indicated for adult patients with previously untreated CD30+ Stage III or IV Hodgkin lymphoma (HL) in combination with doxorubicin, vinblastine and dacarbazine (AVD) (see sections 4.2 and 5.1).

ADCETRIS is indicated for the treatment of adult patients with CD30+ HL at increased risk of relapse or progression following autologous stem cell transplant (ASCT) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL):

1. *following ASCT, or*
2. *following at least two prior therapies when ASCT or multi agent chemotherapy is not a treatment option.*

Systemic anaplastic large cell lymphoma

ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL) (see section 5.1).

ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL.

Cutaneous T cell lymphoma

ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T cell lymphoma (CTCL) after at least 1 prior systemic therapy (see section 5.1).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

N/A

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

- Tabular overview of clinical studies

Study No. Phase	Design	Diagnosis	Dosage (BV) Frequency Duration	Primary Endpoint	Planned/ Treated/ Analyzed	M:F Median Age (Range)	Status	Sites / Regions
HD21 Phase 3	Open-label, prospective, randomized, 2-arm, BrECADD versus escBEACOPP	advanced-stage cHL (defined as Stage IIB with risk factor, Stage III or Stage IV)	1.8 mg/kg IV q3w 4-6 cycles	Treatment-related morbidity (TRMB), PFS (co-primary)	1500/1500/1500	56 % : 44% 31.0 (18-60)	2016 - ongoing Final PFS analysis 2028	206 EU, Australia, New Zealand

2.3.2. Pharmacokinetics

No new pharmacokinetic data have been submitted in this application.

2.3.3. Pharmacodynamics

No new pharmacodynamic data have been submitted in this application.

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose response studies have been submitted.

The proposed dosing regimen for brentuximab vedotin is 1.8mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks for up to 6 cycles in combination with chemotherapy (etoposide (E), cyclophosphamide (C), doxorubicin (A), dacarbazine (D), dexamethasone (D) [BrECADD]).

2.4.2. Main study

HD-21: 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

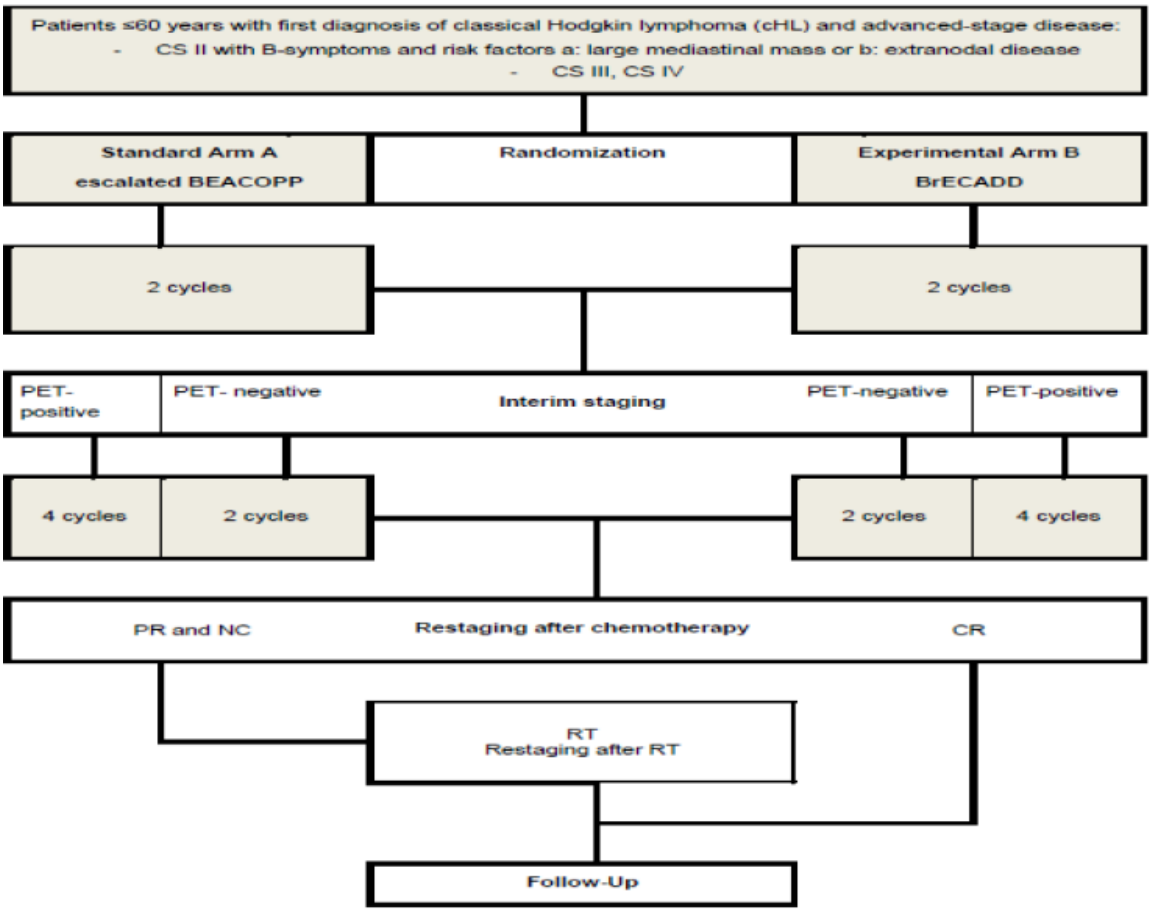

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Figure 1 - Study HD21: Overview of study design; randomised main study

Methods

Study participants

Key inclusion criteria

Each study participant was required to meet all of the following inclusion criteria to be randomised to treatment:

1. Histologically proven cHL.
2. Stage IIB with large mediastinal mass (at least one-third of the maximum transverse thoracic diameter) and/or extranodal disease; Stage III, or Stage IV disease.
3. No previous treatment for HL.
4. Age of 18 to 60 years at randomisation or study entry.
5. Normal organ function (except for HL-related functional disorders).
    - Leukocyte count >3000/mm3 (3.0×10^9/L) and thrombocyte count >100,000/mm3 (100×10^9/L) unless the patient had known marrow involvement of the disease (eg, bone marrow infiltration or splenomegaly).
    - Total bilirubin <1.5×the upper limit of the normal (ULN) unless the elevation was known to be due to Gilbert syndrome.
    - ALT or AST <3×ULN (elevated values due to HL-related liver involvement could be elevated up to 5×ULN).

- Creatinine clearance or calculated creatinine clearance >60 mL/minute (24-hour urine or calculation based on Modification of Diet in Renal Disease formula/Cockcroft-Gault formula).
- Hb of ≥8 g/dL.

Key exclusion criteria

1. Incomplete diagnosis of the disease stage.

2. Prior or concurrent disease that prevented treatment according to the protocol.

3. Nodular lymphocyte-predominant HL or composite lymphoma.

4. Chemotherapy or radiotherapy in medical history.

5. Malignant disease within the last 5 years. (Exceptions included basalioma [basal cell carcinoma], carcinoma in situ eg, of the cervix uteri, completely resected melanoma TNMpT1).

6. Pregnancy; lactation

7. Eastern Cooperative Oncology Group (ECOG) performance status of >2.

8. Long-term administration (>6 months) of corticosteroids (eg, for chronic polyarthritis) or antineoplastic drugs (eg, methotrexate).

9. CTCAE Grade 1 peripheral neuropathy (PN).

10. General intolerance to any of the agents included in the protocol, and known hypersensitivity to recombinant proteins, murine proteins, or to any excipient contained in the drug formulation of brentuximab vedotin

Treatments

Patients in this study were randomised 1:1 to receive up to 6 cycles of either BrECADD or escalated BEACOPP (eBEACOPP) on Day 1 of each 21-day treatment cycle as follows:

BrECADD Treatment Group: 4 cycles of BrECADD for PET2-negative patients or 6 cycles of BrECADD for PET2-positive patients.

eBEACOPP Treatment Group: 4 cycles of eBEACOPP for PET2-negative patients or 6 cycles of eBEACOPP for PET2-positive patients.

The treatment schedules for BrECADD and eBEACOPP are shown in the tables below.

Table 1 - Study HD21: BrECADD Treatment Schedule

Study Drug	Dose	Route of Administration	Cycle Day	Duration
Brentuximab vedotin	1.8 mg/kg	IV	Day 1	Over 30 minutes
Cyclophosphamide [a]	1250 mg/m^2	IV	Day 2	Over 60 minutes
Etoposide or etoposide phosphate [b]	150 mg/m^2	IV	Days 1-3	Over 60 minutes
Doxorubicin	40 mg/m^2	IV	Day 2	Over 30 minutes
Dacarbazine	250 mg/m^2	IV	Days 3-4	Over 120 minutes
Dexamethasone	40 mg	PO	Days 2-5	Not applicable

Source: HD21 protocol Version 9.0 Section 5.4.2.1.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; IV: intravenous; PO: per os (by mouth).
a Administration of Uromitexan was obligatory on the day of administration and the patients was required to ingest 2.5 L of fluid.
b Etoposide phosphate as etoposide-equivalent dose; 113 mg etoposide phosphate equivalent to 100 mg etoposide (difference due to different molecular weights).

Table 2 - Study HD21: eBEACOPP Treatment Schedule

Study Drug	Dose	Route of Administration	Cycle Day	Duration
Cyclophosphamide [a]	1250 mg/m^2	IV	Day 1	Over 60 minutes
Doxorubicin	35 mg/m^2	IV	Day 1	Over 30 minutes
Etoposide or etoposide phosphate [b]	200 mg/m^2	IV	Days 1-3	Over 60 minutes
Procarbazine	100 mg/m^2	PO	Days 1-7	Not applicable
Prednisone	40 mg	PO	Days 1-14	Not applicable
Vincristine	1.4 mg/m^2 (max. 2 mg)	IV	Day 8	Bolus
Bleomycin [c]	10 mg/m^2	IV	Day 8	Bolus

Source: HD21 protocol Version 9.0 Section 5.4.2.1.
eBEACOPP: escalated doses of bleomycin, etoposide, cyclophosphamide, doxorubicin, vincristine, procarbazine, prednisone; IV: intravenous; PO: per os (by mouth).
a Administration of Uromitexan was obligatory on the day of administration and the patients was required to ingest 2.5 L of fluid.
b Etoposide phosphate as etoposide-equivalent dose; 113 mg etoposide phosphate equivalent to 100 mg etoposide (difference due to different molecular weights)
c Bleomycin-induced pneumonitis or pulmonary fibrosis was an identified risk.

Dose adjustments for the BrECADD regimen compared to eBEACOPP

The dose of etoposide was decreased to 150 mg/m2 for patients in the BrECADD treatment group to potentially reduce the risk of late toxicities (AML, MDS) and the dose of doxorubicin was increased from 35 mg/m2 to 40 mg/m2. The 4-day dexamethasone dosage replaced 14 days of prednisone to reduce the risk of infection during the aplastic phase of the treatment cycle, which is considered to occur between Days 6 and 10 of each treatment cycle. The use of prednisone has been shown to be a risk factor for the development of avascular necrosis of the femoral head in patients treated with eBEACOPP (Basic-Kinda et al. 2018). Oral administration of procarbazine for 7 days was substituted with a 2-day IV therapy with dacarbazine on Days 2 and 3 of each treatment cycle. Dacarbazine IV was substituted for procarbazine in consideration of a possible role of procarbazine in gonadal toxicity.

Table 3 - Study HD21: Modification of the eBEACOPP Regimen With Brentuximab Vedotin

Study Drug	eBEACOPP Dose	BrECADD dose	Toxicity
Bleomycin	10 mg/m^2	NA	Pulmonary toxicity; coadministration with brentuximab vedotin contraindicated
Etoposide	200 mg/m^2	150 mg/m^2	Hematologic toxicity; second AML/MDS
Cyclophosphamide	1250 mg/m^2	1250 mg/m^2	--
Doxorubicin	35 mg/m^2	40 mg/m^2	--
Vincristine	1.4 mg/m^2	NA	Neuropathy; also associated with brentuximab vedotin
Procarbazine	100 mg/m^2	NA	Gonadal toxicity; AML, MDS (second malignancies)
Prednisone		NA	Avascular necrosis of the femoral head
Dacarbazine	NA	250 mg/m^2	Replaced procarbazine
Dexamethasone	NA	40 mg	Replaced prednisone
Brentuximab vedotin	NA	1.8 mg/kg	--

HD21 protocol Version 9.0 Section 1.2.2.
AML: acute myeloid leukemia: BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MDS: myelodysplastic syndrome; NA: not applicable.

Premedication

Routine premedication before administration of the first dose of brentuximab vedotin was not recommended but was permissible in subsequent treatment cycles for patients who experienced Grade 1 or Grade 2 infusion-related reactions in a previous cycle as directed in the Adcetris SmPC.

Dose modifications

Dose delay and modification guidance was available for bleomycin and vincristine and brentuximab vedotin-associated peripheral neuropathy (PN) as well as BrECADD and eBEACOPP treatment groups.

Table 4 - Study HD21: Dose Reductions for BrECADD and eBEACOPP Toxicity

Study Drug	Dose level 4	Dose level 3	Dose level 2	Dose level 1	Baseline
BrECADD					
Cyclophosphamide	1250 mg/m^2	1100 mg/m^2	950 mg/m^2	800 mg/m^2	650 mg/m^2
Doxorubicin	40 mg/m^2	40 mg/m^2	40 mg/m^2	40 mg/m^2	35 mg/m^2
Etoposide	150 mg/m^2	125 mg/m^2	100 mg/m^2	100 mg/m^2	100 mg/m^2
eBEACOPP					
Cyclophosphamide	1250 mg/m^2	1100 mg/m^2	950 mg/m^2	800 mg/m^2	650 mg/m^2
Doxorubicin	35 mg/m^2	35 mg/m^2	35 mg/m^2	35 mg/m^2	25 mg/m^2
Etoposide	200 mg/m^2	175 mg/m^2	150 mg/m^2	125 mg/m^2	100 mg/m^2

Source: HD21 protocol Version 9.0 Section 5.4.2.10 and 5.4.2.11.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.

Table 5 - Study HD21: Dose Adjustment for PN Associated With Brentuximab Vedotin

Severity of PN (Signs and Symptoms)	Dose Adjustment
Grade 1 (asymptomatic; only clinical or diagnostic finding; no need for treatment; paresthesia and/or loss of deep tendon reflexes)	Continuation of study treatment at the same dose of brentuximab vedotin.
Grade 2 (mild symptoms; limited activity in daily life) Grade 3 (pronounced symptoms; self-care in daily life only possible to a limited degree).	Discontinuation of treatment until symptoms have subsided to ≤Grade 1 or initial state, then continuation of treatment at reduced dose of 1.2 mg/kg up to a maximum of 120 mg every 3 weeks.
Grade 4 (life-threatening; treatment for PN was required to be initiated immediately)	Termination of brentuximab vedotin administration.

Source: HD21 protocol Version 9.0 Section 5.4.2.8.
PN: peripheral neuropathy.

Co-medication

The following medications and procedures were mandated or allowed during the study:

- Administration of a granulocyte-colony stimulating factor (G-CSF) product was mandatory for patients in both treatment groups
- Antibiotic prophylaxis with trimethoprim/sulfamethoxazole was mandated
- Administration of an intensified antibiotic such as ciprofloxacin was recommended for patients who experienced bone marrow aplasia
- Antiemetic treatment was to be provided using 5-HT3 (serotonin) receptor antagonists primarily and antiemetic treatment could have been intensified to include the use of steroids, if indicated for patients who experienced persistent nausea
- Uromitexan was administered on Day 2 for BrECADD patients and on Day 1 for eBEACOPP patients for hemorrhagic cystitis prophylaxis
- Treatment with allopurinol and H2-receptor blockers was permitted as indicated
- Transfusions of erythrocyte concentrates were permissible for the treatment of patients with anemia if considered necessary according to the physician's judgement. Guidance

Objectives

Co-primary objective (randomised main study)

- To demonstrate reduced toxicity of the BrECADD treatment compared to the eBEACOPP treatment measured by treatment-related morbidity (TRMB).

and

- If reduced toxicity was shown, the co-primary objective was to further demonstrate non-inferior efficacy of 6 cycles of BrECADD compared with 6 cycles of eBEACOPP, each followed by radiotherapy to PET-positive residual lesions, in terms of progression-free survival (PFS).

Outcomes/endpoints

Co-primary endpoint

- The rate of **TRMB** during primary treatment and through the period of up to 30 days after the last dose of either BrECADD or eBEACOPP therapy. On the basis of historical data, the following toxicities were considered clinically relevant:

– Acute severe haematological CTCAE Grade 4 anaemia, thrombocytopenia, and infections.

– Acute non-haematological CTCAE Grade 3 or Grade 4 organ toxicity in the SOCs,

a) Cardiac disorders,

b) GI disorders (excluding vomiting, nausea, and mucositis),

c) Hepatobiliary disorders,

d) Nervous system disorders (except neuropathy),

e) Renal and urinary disorders, and

f) Respiratory, thoracic and mediastinal disorders.

Table 6 - Study HD21: Prespecified Toxicity Terms on the CTCAE Section of the GHSG eCRF

Anaemia
Thrombocytopenia
Leukopenia
Febrile neutropenia
Infection
Cardiac disorders
GI disorders (excluding nausea, vomiting, mucositis)
Nausea/vomiting
Mucositis
Hepatobiliary disorders
Peripheral sensory neuropathy
Peripheral motor neuropathy
Nervous system disorders (other than neuropathy)
Renal and urinary disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Drug fever
Allergy
Avascular necrosis

Source: GHSG std eCRF v13.0 2022-08-08.

- **Progression Free Survival (PFS)**, defined as time from the date of randomisation to the date of the first occurrence of disease progression or relapse or death from any cause. If none of these events occurred, PFS was censored at the date of the last documented restaging or follow-up visit.

Secondary endpoints

- CR (complete response) rate after completion of either BrECADD or eBEACOPP therapy, defined as the proportion of patients who achieved a CR by investigator assessment with central confirmation.

- OS (overall survival), defined as the time from the date of randomisation to the date of death due to any cause.
- Infertility rate at 1 year.
- Second malignancies.
- Incidence of AEs.
- Number of SAEs within 30 days after end of study treatment.
- Therapy adherence.
- Quality Of Life (QOL) before, during, and after therapy.

Sample size

Non-inferiority of PFS

The required sample size was calculated assuming an exponential model without stratification factors and the confidence interval being calculated using normal approximation. The 5-year survival rate was assumed to be 90.5% in both arms. Hence, the hazard ratio was assumed to be 1. With an NI margin of 1.69, the required number of events at a one-sided significance level of = 0.025 and a power of 90% is 154. It was assumed that the trial objective may be reached if 1,500 patients are recruited with a total duration of recruitment plus follow-up of 7.5 years (48 months assumed recruitment, 42 months additional follow up) if the assumptions were correct.

TRMB

Final analysis data from the targeted BEACOPP phase II trial show that 14 of 52 patients treated with 6 cycles BrECADD were affected by TRMB (26.9%, exact 95% CI 16% to 41%). Despite the wide confidence interval due to small numbers, we expect that the true TRMB rate will be at least by 10 percentage points less than with eBEACOPP. Assuming an unadjusted Chi²-test for a conservative power estimate, all reductions of at least 7.25 percentage points result in a power of 80% and above, while a reduction of at least 8.4 percentage points yields a power of at least 90%. Since it was hoped to achieve a reduction of at least 10 percentage points, it was considered sufficient to derive the sample size for the trial from the efficacy endpoint only.

With these assumptions, the combined power for achieving both trial objectives was estimated to be at least 0.9*0.9=81%.

Randomisation

Patients 60 years of age were allocated to the BrECADD and eBEACOPP groups in a 1:1 ratio. Allocation was performed by the German Hodgkin Study Group (GHSG) Trial Coordination Centre before initiation of treatment, according to the minimisation method including a random element. Stratification was performed with respect to the following factors: country of enrolment, age (< 45 years vs ≥ 45 years), sex (male vs female), and IPS (0-2 vs 3-7).

A simple random allocation was used with probability 25% and with probability of 75% the deterministic scoring rule was applied. This score was computed for each newly enrolled subject separately for each treatment arm and the subject was allocated to the treatment arm with the lower score. For each patient, the weighted score for arm (X) was based on

- the number of subjects enrolled within the trial site to arm X multiplied with weight = 1.1,
- the number of subjects in the relevant stratum (based on the 4 stratum variables age, sex, country and IPS score) enrolled to arm X multiplied with weight = 0.25,

- the overall number of subjects enrolled to arm X multiplied with weight = 0.00001,
- and a random factor with weight 0.000001.

Given the very low weight of the random factor, the scoring itself was essentially deterministic and the random factor was only included to allocate the first subject.

Blinding (masking)

There was no blinding in this trial.

Statistical methods

The following methods are described based on SAP Amendment 1.

Estimands

No estimands were specified.

Analyses of co-primary endpoints

TRMB rates was to be compared between groups using a Cochran-Mantel-Haenszel test adjusting for the stratification factors sex (female vs. male), age (< 45 years vs. ≥ 45 years), IPS (0-2 vs. 3-7), and enrollment region (EU vs Non-EU) if sufficient sample size is present in each stratum. BrECADD was to be considered superior if the two-sided test for the stratified *Cochran-Mantel-Haenszel test* was significant at a two-sided level of α = 0.05 and *if the estimated relative risk for BrECADD compared to eBEACOPP is smaller than one*.

The non-inferiority analysis for PFS was to be conducted if and only if a lower TRMB rate of the BrECADD group has been established earlier. To assess non-inferior efficacy of the BrECADD group, the two-sided 95% confidence interval (CI) for the $HR_{BrECADD/eBEACOPP}$ was derived from an unstratified Cox regression. *The confidence level for the HR at the interim analysis was adjusted based on the information fraction observed and the corresponding upper bound of CI was compared to the margin of 1.69 to assess non-inferiority.* If the upper margin of the CI is lower than 1.69, non-inferiority is demonstrated. The primary analysis of PFS was PFS per Investigator (INV) with central confirmation on the ITT population. A sensitivity analysis on PFS per INV (regardless confirmed by central review or not) was also to be performed.

Censoring rules were defined in the SAP as shown below. Additional sensitivity analyses included a PFS analysis which censored patients at the last adequate disease assessment if they had progression of disease (PD) after having had more than one missed assessment.

Definition of censoring rules

Situation	Date of Event or Censoring	Outcome
Progression of disease/relapse	Date of progression/relapse	Event
Death due to any cause	Date of death	Event
No documented PFS event	Date of last adequate disease assessment	Censored
Lost to follow-up or withdraw consent before any documented PFS event	Date of last adequate disease assessment	Censored
No baseline and/or no post baseline assessment, no death	Date of Randomization	Censored

Definition of NI-margin for PFS

The NI margin was defined based on the final analysis of the HD15 trial. This trial with a median follow-up for PFS of four years demonstrated a 4- year PFS of 91.0% and a 5-year PFS of 90.6% after six cycles of

eBEACOPP for the subgroup of patients with classical Hodgkin lymphoma in the intention to treat analysis set. Thus, a 5-year PFS of 90.5% was assumed for the HD21 trial. Clinically relevant inferiority had been defined as an absolute difference of 6 percentage points in 5-year PFS, i.e. a 5-year rate of 84.5% for the BrECADD group. This margin corresponds to a hazard ratio of BrECADD vs. eBEACOPP of ln(0.845)/ln(0.905)=1.69 for the sample size calculation.

Supplementary analyses for PFS

As supplementary analysis, a stratified Cox model adjusting for sex (male vs female), age at randomisation (< 45 years vs. ≥ 45 years), IPS (0-2 vs. 3-7), and enrollment region (EU vs. Non-EU) was to be considered in case sufficient events were available in each stratum.

Subgroup analyses

Subgroup analyses by sex, age, IPS, region, baseline B symptoms, baseline Ann Arbor stage, PET-2 results and baseline ECOG was foreseen.

Interim analyses

An interim analysis of the primary efficacy endpoint PFS was planned to be performed at median follow-up of 36 months. To preserve type I error rate, O'Brien-Fleming method with Lan-DeMets alpha-spending function and the actual information fraction would be used to calculate appropriate critical values. This interim analysis would be performed for the ITT analysis set. If the interim analysis demonstrated non-inferior efficacy, the results would be considered statistically conclusive.

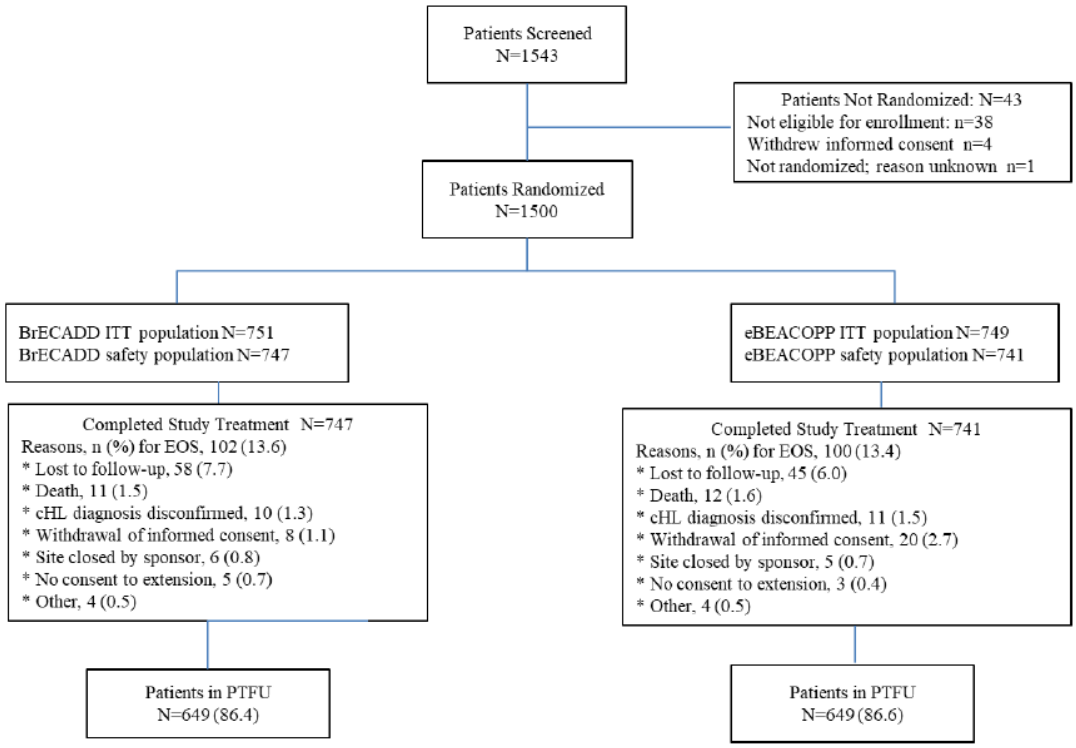
Results

Participant flow

A total of 1543 patients were screened to determine eligibility of which 1500 patients were randomised, 751 patients to the BrECADD treatment group and 749 patients to the eBEACOPP treatment group. Within the ITT population, 4 BrECADD patients and 8 eBEACOPP patients did not receive the study treatment.

As of the 31 December 2022 cutoff for data analysis, 649 patients in each treatment group were reported to be participating in post-treatment follow-up (PTFU). Loss to follow-up was the most commonly reported reason for study discontinuation, reported for 58 BrECADD patients (7.7%) and 45 eBEACOPP patients (6.0%); death and disconfirmation of cHL diagnosis were reported for <2% of patients in each treatment group; and patient's withdrawal of informed consent for 8 BrECADD patients (1.1%) and 20 eBEACOPP patients (2.7%). Other end of study reasons were each reported for <1% of patients across treatment groups.

Figure 2 Participant flow in HD21 trial



Source: Table 15.1.1.1; Listing 16.2.1; enrollment data on file provided to Takeda from the GHSG.

BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL: classical Hodgkin lymphoma; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; EOS: end of study; ITT: intent-to-treat; PTFU: posttreatment follow-up.

Among the 38 patients who did not meet criteria for randomization, 16 patients did not meet 1 inclusion criterion, 8 patients were excluded by an exclusion criterion, and 14 patients were excluded because of an inclusion and exclusion criterion.

4 BrECADD patients and 8 eBEACOPP patients in the ITT population did not receive study treatment.

Early treatment discontinuations (data cutoff 31 October 2023)

Table 7 - HD21 Trial: Summary of Early Treatment Discontinuations (Safety Population, Participants With Early Treatment Discontinuation)

	BrECADD N=747	**eBEACOPP N=741**
Participants with early treatment discontinuation [a]	33 (4.4)	29 (3.9)
Participants who had TRMB events [b]		
Yes	12 (36.4)	17 (58.6)
No	21 (63.6)	12 (41.4)
Participants currently in follow-up	15 (45.5)	11 (37.9)
Reason for End of Trial	18 (54.5)	18 (62.1)
Loss to follow-up	4 (12.1)	2 (6.9)
Participant's withdrawal of informed consent	3 (9.1)	8 (27.6)

	BrECADD N=747	eBEACOPP N=741
Diagnosis of cHL disconfirmed	7 (21.2)	6 (20.7)
Death	2 (6.1)	2 (6.9)
Site closed by sponsor	1 (3.0)	0
Individual trial period ended (no consent to extension)	0	0
Other	1 (3.0)	0
Serious adverse events leading to early treatment discontinuation	9 (27.3)	6 (20.7)
Treatment-emergent [c] serious adverse events leading to early treatment discontinuation	8 (24.2)	6 (20.7)
Death	2 (6.1)	2 (6.9)
On-trial death [d]	2 (6.1)	1 (3.4)
Follow-up death [e]	0	1 (3.4)

Data cut 31 October 2023.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; TRMB: treatment-related morbidity.
a Early treatment discontinuation is derived using a participant's PET status at the end of 2 cycles of chemotherapy and is defined as having received less than 4 cycles of chemotherapy when a participant's PET2 status is negative, and less than 6 cycles when a participant's PET2 status is positive or not done.
b TRMB is defined as any CTCAE organ toxicity of grade 3 or 4 or severe haematological toxicity of grade 4 (Anemia, Thrombocytopenia, Infection) during primary chemotherapy (including a period of 30 days after the last chemotherapy dose).
c Treatment-emergent adverse events are defined as any adverse event that occurs after administration of the first dose of any trial drug and through 30 days after the last dose of any trial drug.
d On-trial deaths are defined as deaths that occur within 30 days after the last dose of chemotherapy.
e Follow-up death refers to those that occurred after 30 days of the last dose.
The denominator for the percentages of participants with early treatment discontinuations is the number of participants in the safety population while for the remaining percentages the denominator is the number of participants with early treatment discontinuation.

Recruitment

First patient enrolled: 19 July 2016

First patient randomised: 22 July 2016

Last patient randomised: 27 August 2020

Data cut off interim analysis coprimary endpoints: 31 December 2022; updated dataset: 31 October 2023

Final data transfer from the GHSG to Takeda: 09 November 2023.

The study is ongoing with patients continuing to be followed during post-treatment follow-up until 5.5 years after enrollment of the last patient into the randomised main study.

Conduct of the study

Protocol amendments

The protocol was amended 9 times. The most important changes are summarized below:

Protocol Version 2.0; Amendment 1 (31 May 2016).

EDC procedures were specified. No patients were randomised into the study until after approval of Version 2.0.

Protocol Version 3.0; Amendment 2 (19 July 2016).

The exclusion criterion, administration of corticosteroids before start of BrECADD or eBEACOPP therapy was removed.

Protocol Version 4.0; Amendment 3 (13 March 2017).

Based on HD18 study results, 4 cycles of eBEACOPP were defined as the new standard of care for PET2-negative patients whereas PET2-positive patents were to receive 6 cycles of eBEACOPP (Borchmann et al. 2017). Only patients with PET-positive residual lesions after completion of either BrECADD or eBEACOPP therapy were treated with 30 Gy of local irradiation. Study conduct was modified by disease restaging with ceCT (CT2) and PET2 after 2 cycles of either BrECADD or eBEACOPP therapy for all patients.

Protocol Version 5.0; Amendment 4 (24 November 2017).

The protocol was updated to align with a new version of the EU SmPC.

Protocol Version 6.0; Amendment 5 (20th March 2018).

Updates to a new version of the EU SmPC were implemented. Furthermore, the accompanying clinical scientific investigation was adapted.

Protocol Version 7.0; Amendment 6 (16 December 2019).

Opening of a new cohort for patients aged 61 years to 75 years who were precluded by their age from enrolment in the randomised main study but were eligible for multiagent anticancer therapy. This cohort was not part of the randomised main study. Evaluation and presentation of results were to occur separately without formal comparison with the results from the randomised main study.

Protocol Version 8.0; Amendment 7 (20 July 2021).

Based on the IDMC recommendation (meeting on 21 May 2021), the protocol was amended to bring the analysis of the co-primary endpoint TRMB forward because of its relevance for future choices for the treatment of patients with advanced stage cHL.

Protocol Version 9.0; Amendment 8 (25 August 2022).

The IDMC informed the investigators in March 2022 that the experimental treatment, BrECADD was significantly better tolerated than the GHSG standard of care, eBEACOPP. The IDMC saw great relevance of the results for patients and caregivers and therefore recommended early publication. The IDMC also recommended that publication should, under certain circumstances, include efficacy data (ie, PFS outcomes).

After discussion of the IDMC recommendation as well as the observation of fewer PFS events and slow PFS accrual, the protocol was amended to perform an interim PFS analysis at approximately 3 years of median follow-up for the ITT population.

Changes to the SAP

The SAP was amended primarily to add the interim PFS analysis at a median follow-up of approximately 36 months as described in the HD21 protocol Version 9.0. The SAP was approved on 13 April 2023 before Takeda received the unblinded data for the interim PFS analysis. The approval of the SAP was also planned to precede the GHSG meeting with its IDMC held on 20 April 2023 to discuss the results of the interim PFS analysis.

Protocol compliance

The important protocol deviations identified in the HD21 study included deviations pertaining to eligibility criteria, dose adjustment errors, dose errors, and nonperformance of protocol-defined procedures, SAE reporting timing, and conduct of protocol procedures before signed informed consent.

Dosing errors were related to additional dosing of brentuximab vedotin, higher dosing of etoposide and incorrect dosing of procarbazine (2 patients). Dose adjustment errors were related to missed reductions that would have been required due to PN (2 patients), respiratory distress and thrombocytopenia.

Baseline data

Sex was well-balanced between the treatment arms, with a slight male predominance in each. The patient population was younger, with a median age at randomisation of 31 years (range, 18-60 years), and nearly four fifths of patients were between 18 and 44 years of age.

Table 8 - Study HD21: Baseline Demographics (ITT Population)

No. of patients (%)	BrECADD N=751	eBEACOPP N=749
Sex n (%)		
Male	419 (55.8)	419 (55.9)
Female	332 (44.2)	330 (44.1)
Age at randomization (years)		
Mean (SD)	33.4 (11.77)	33.6 (11.77)
Median	31.0	31.0
Min, max	18, 60	18, 60
Age at randomization categories (years) n (%)		
18-44	590 (78.6)	584 (78.0)
45-60	161 (21.4)	165 (22.0)
Race n (%)		
White	687 (91.5)	678 (90.5)
Other	31 (4.1)	35 (4.7)
Unknown	22 (2.9)	21 (2.8)
Asian	11 (1.5)	13 (1.7)
Black	0	2 (0.3)
Weight (kg)		
Mean (SD)	76.7 (18.34)	75.7 (17.54)
Median	75.0	72.0
Min, max	43, 150	41, 178
BSA [a] (m^2)		
n	748	744
Mean (SD)	1.91 (0.235)	1.90 (0.224)
Median	1.90	1.89
Min, max	1.4, 2.7	1.4, 2.8
Country of Enrollment n (%)		
Europe	692 (92.1)	691 (92.3)
Germany	538 (71.6)	534 (71.3)
Switzerland	67 (8.9)	65 (8.7)
Austria	41 (5.5)	44 (5.9)
Netherlands	17 (2.3)	18 (2.4)
Denmark	11 (1.5)	11 (1.5)
Norway	10 (1.3)	11 (1.5)
Sweden	8 (1.1)	8 (1.1)
Non-Europe	59 (7.9)	58 (7.7)
Australia	54 (7.2)	52 (6.9)
New Zealand	5 (0.7)	6 (0.8)

Source: Table 15.1.4.1; Listing 16.2.4.1.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; BSA: body surface area; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; max: maximum; Min: minimum; SD: standard deviation.
Percentages are based on the number of patients in the ITT population.
a: BSA was calculated using the Du Bois formula: BSA (m^2)=0.007184×Height (cm)$^{0.725}$×weight (kg)$^{0.425}$.

Table 9 - Study HD21: Baseline Disease Characteristics (ITT Population)

Number of patients (%)	BrECADD (N=751)	eBEACOPP (N=749)
Primary histology		
Nodular sclerosis (classical) Hodgkin lymphoma	473 (63.0)	479 (64.0)
Mixed cellularity (classical) Hodgkin lymphoma	129 (17.2)	126 (16.8)
Lymphocyte depleted (classical) Hodgkin lymphoma	5 (0.7)	9 (1.2)
Lymphocyte-rich (classical) Hodgkin lymphoma	22 (2.9)	23 (3.1)
Other (classical) Hodgkin lymphoma	94 (12.5)	80 (10.7)
Hodgkin lymphoma, unspecified	28 (3.7)	32 (4.3)
Ann Arbor stage at initial diagnosis		
Stage II	118 (15.7)	117 (15.6)
Stage III	298 (39.7)	293 (39.1)
Stage IV	332 (44.2)	334 (44.6)
Unknown	3 (0.4)	5 (0.7)
Time from primary histology result to randomization, months		
Mean	0.7 (0.74)	0.7 (0.55)
Median	0.6	0.6
Min, max	0, 12	0, 10
B symptoms		
Yes	517 (68.8)	501 (66.9)
No	231 (30.8)	243 (32.4)
Missing	3 (0.4)	5 (0.7)
Weight loss >10% in 6 months		
Yes	203 (27.0)	224 (29.9)
No	545 (72.6)	520 (69.4)
Missing	3 (0.4)	5 (0.7)
Fever (>38°C)		
Yes	156 (20.8)	165 (22.0)
No	592 (78.8)	579 (77.3)
Missing	3 (0.4)	5 (0.7)
Night sweats		
Yes	436 (58.1)	416 (55.5)
No	312 (41.5)	328 (43.8)
Missing	3 (0.4)	5 (0.7)
Ann Arbor Stage A/B		
A	232 (30.9)	244 (32.6)
B	516 (68.7)	500 (66.8)
Unknown	3 (0.4)	5 (0.7)

Number of patients (%)	BrECADD (N=751)	eBEACOPP (N=749)
ECOG Performance Status		
0	514 (68.4)	521 (69.6)
1	223 (29.7)	205 (27.4)
2	11 (1.5)	18 (2.4)
Unknown	3 (0.4)	5 (0.7)
IPS		
0	48 (6.4)	37 (4.9)
1	148 (19.7)	140 (18.7)
2	198 (26.4)	226 (30.2)
3	198 (26.4)	174 (23.2)
4	99 (13.2)	121 (16.2)
5	42 (5.6)	37 (4.9)
6	16 (2.1)	14 (1.9)
7	2 (0.3)	0
IPS Categories		
0-2	394 (52.5)	403 (53.8)
3-7	357 (47.5)	346 (46.2)

Source: Table 15.1.4.2; Listing 16.2.4.2.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL: classical Hodgkin lymphoma; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ECOG: Eastern Cooperative Oncology Group; IPS: International Prognostic Score; ITT: intent-to-treat; max: maximum; Min: minimum.
Percentages are based on the number of patients in the ITT population.
A patient was considered to have had B symptoms if the patient had any of the 3 symptoms: weight loss of >10% in 6 months, fever (>38°C) of unknown origin or night sweats.

Concomitant medication

Table 10 - Study HD21: Concomitant Medications (Safety Population) (Excerpt)

Number of patients (%)	BrECADD (N=747)	eBEACOPP (N=741)
Patients with any G-CSF use during treatment	747 (100)	741 (100)
Cycle 1	742 (99.3)	741 (100)
Cycle 2	727 (97.3)	725 (97.8)
Cycle 3	720 (96.4)	720 (97.2)
Cycle 4	718 (96.1)	721 (97.3)
Cycle 5	286 (38.3)	285 (38.5)
Cycle 6	282 (37.8)	280 (37.8)
Number of days with G-CSF		
Number of patients	747 (100)	741 (100)
Total days	4785	5662
Mean (SD)	6.4 (6.88)	7.6 (9.31)
Number of days with intensified antibiotic prophylaxis		
Number of patients	508 (68.0)	538 (72.6)
Total days	14699	15546
Mean (SD)	28.9 (21.08)	28.9 (17.97)

Table 11 - Study HD21: Concomitant Blood Products (Safety Population)

Number of patients (%)	BrECADD (N=747)	eBEACOPP (N=741)
Number of platelet infusions		
Number of patients	125 (16.7)	249 (33.6)
Mean (SD)	2.2 (1.79)	2.6 (2.08)
Median	2.0	2.0
Min, max	1, 11	1, 15
Number of RBC transfusions		
Number of patients	179 (24.0)	387 (52.2)
Mean (SD)	3.6 (3.17)	4.3 (3.11)
Median	2.0	4.0
Min, max	1, 20	1, 19
Number of platelet infusions or RBC transfusions		
Number of patients	220 (29.5)	424 (57.2)
Mean (SD)	4.2 (3.99)	5.4 (4.43)
Median	3.0	4.0
Min, max	1, 28	1, 32

Source: HD21 CSR Table 11.c
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; Max: maximum; Min: minimum; RBC: red blood cell; SD: standard deviation.
Percentages are based on the number of patients in the safety population.

Numbers analysed

Efficacy analyses were performed using the ITT analysis set, which included all 1500 randomised patients; 751 patients randomised to BrECADD and 749 patients randomised to eBEACOPP.

In total 92% of the patients derived from sites in the Europe (with the highest proportion (71%) of these patients enrolled at sites located in Germany) and 8% Australia and New Zealand.

	BrECADD N=751 n (%)	eBEACOPP N=749 n (%)	Total N=1500 n (%)
Intent-to-Treat (ITT) population	751 (100)	749 (100)	1500 (100)
Safety population	747 (99.5)	741 (99)	1488 (99.2)
Patients completed study treatment	747 (99.5)	741 (99)	1488 (99.2)
Patients in PTFU	649 (86.4)	649 (86.6)	1298 (86.5)

Outcomes and estimation

Co-primary endpoint - Toxicity Endpoint with Efficacy Impact: TRMB

As of data cutoff 31 Oct 2023 TRMB results showed superiority for patients who received BrECADD over those who received eBEACOPP (descriptive stratified CMH chi square p value of <0.0001; relative risk = 0.712 (95% CI, 0.643 0.789), corresponding to a 28.8% reduced risk of a TRMB event for BrECADD patients compared with eBEACOPP patients.

Table 12 - Study HD21: TRMB (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
Number of patients with TRMB	314 (42.0)	435 (58.7)
Acute Hematologic Toxicity Grade 4	233 (31.2)	386 (52.1)
Anaemia	3 (0.4)	3 (0.4)
Thrombocytopenia	227 (30.4)	383 (51.7)
Infection	13 (1.7)	10 (1.3)
Acute Organ Toxicity; Grade 3 or Grade 4	139 (18.6)	129 (17.4)
Cardiac disorders	18 (2.4)	10 (1.3)
GI disorders (excluding vomiting, nausea, mucositis)	58 (7.8)	32 (4.3)
Hepatobiliary disorders	37 (5.0)	22 (3.0)
Nervous system disorders	20 (2.7)	40 (5.4)
Sensory	9 (1.2)	17 (2.3)
Motor	2 (0.3)	1 (0.1)
Other	11 (1.5)	24 (3.2)
Renal or urinary disorders	7 (0.9)	10 (1.3)
Respiratory, thoracic and mediastinal disorders	25 (3.3)	35 (4.7)
CMH p-value [a]	<0.0001	
RR (Unstratified BrECADD/eBEACOPP) [b]	0.716	
95% CI	(0.646, 0.794)	
RR (Stratified BrECADD/eBEACOPP) [c]	0.712	
95% CI	(0.643, 0.789)	
% Difference (BrECADD-eBEACOPP)	-16.7	
Exact 95% CI	(-21.7, -11.5)	

Source: Table 15.2.1.1; Data cut 31 October 2023.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CMH: Cochran-Mantel-Haenszel; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GI: gastrointestinal; IPS: International Prognostic Score; RR: relative risk; TRMB: treatment-related morbidity.
Percentages are calculated using the safety population as denominator.
a: Descriptive p-value is based on CMH test comparing BrECADD with eBEACOPP stratified by enrollment region (Europe vs non-Europe), age at randomization (18-44 years vs 45-60 years), biologic sex (female vs male), and IPS risk group (0-2 vs 3-7).
b: RR calculated by using unstratified CMH test.
c: RR calculated by using stratified CMH test.

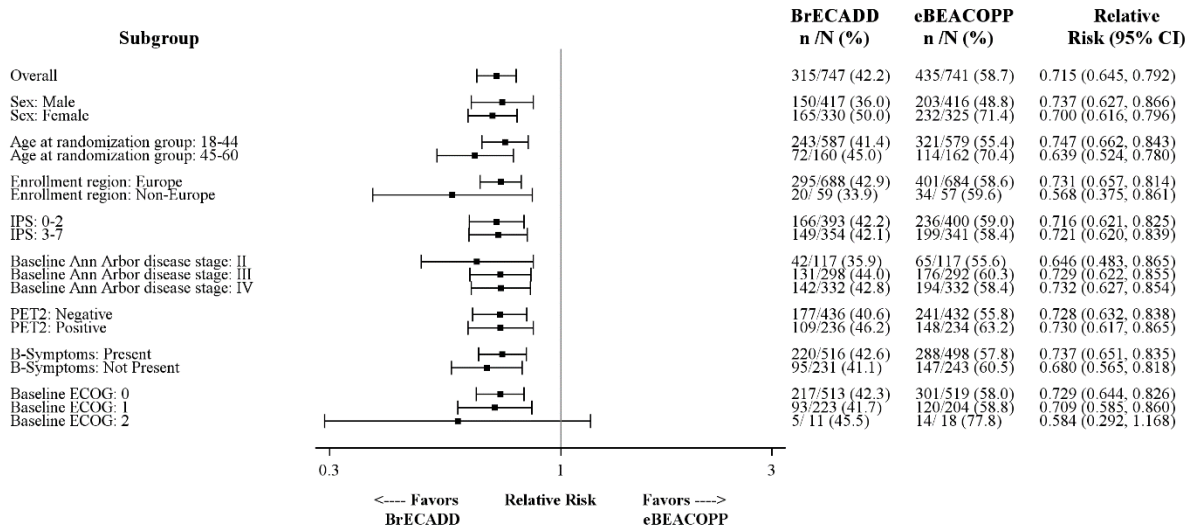
Table 13 - TRMB Including Premature Treatment Discontinuation

No of patients (%)	BrECADD N=747	eBEACOPP N=741
No. of patients with TRMB	336 (45.0)	447 (60.3)
Acute Hematologic Toxicity Grade 4	233 (31.2)	386 (52.1)
Anaemia	3 (0.4)	3 (0.4)
Thrombocytopenia	227 (30.4)	383 (51.7)
Infection	13 (1.7)	10 (1.3)
Acute Organ Toxicity; Grade 3 or Grade 4	140 (18.7)	129 (17.4)
Cardiac disorders	18 (2.4)	10 (1.3)
GI disorders (excluding vomiting, nausea, mucositis)	58 (7.8)	32 (4.3)
Hepatobiliary disorders	37 (5.0)	22 (3.0)
Nervous system disorders (sensory, motor, and other)	21 (2.8)	40 (5.4)
Sensory	10 (1.3)	17 (2.3)
Motor	3 (0.4)	1 (0.1)
Other	12 (1.6)	24 (3.2)
Renal or urinary disorders	7 (0.9)	10 (1.3)
Respiratory, thoracic and mediastinal disorders	25 (3.3)	35 (4.7)

CMH p-value [a]	<0.0001
Relative risk (unstratified BrECADD/eBEACOPP) [b]	0.746
95% CI	(0.676, 0.823)
Relative risk (stratified BrECADD/eBEACOPP) [c]	0.744
95% CI	(0.675, 0.820)
% Difference (BrECADD-eBEACOPP)	-15.3
Exact 95% CI	(-20.4, -10.1)

Source: Table 15.2.1.1b.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CMH: Cochran-Mantel-Haenszel; CTCAE: Common Terminology Criteria for Adverse Events; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GI: gastrointestinal; IPS: International Prognostic Score; PET: positron emission tomography; RR: relative risk; TRMB: treatment-related morbidity.
This sensitivity analysis included all patients with TRMB events per prespecified CTCAE terms and early discontinuation of treatment as an event (for PET2-negative patients, the total number of treated cycles was fewer than 4 and for PET2-positive patients, the total number of treated cycles was fewer than 6).
a: p-value is based on CMH test comparing BrECADD with eBEACOPP stratified by enrollment region (Europe vs non-Europe), age (18-44 years vs 45-60 years), biologic sex (female vs male), and IPS risk group (0-2 vs 3-7).
b: RR calculated by using unstratified CMH test.
c: RR calculated by using stratified CMH test.

Subgroup analyses



- Data cutoff date 31 December 2022.
- CI = Confidence Interval; IPS = International Prognostic Score; ECOG = Eastern Cooperative Oncology Group; TRMB = Treatment-Related Morbidity.
- TRMB is defined as any CTCAE organ toxicity of grade 3 or 4 or severe haematological toxicity of grade 4 (Anemia, Thrombocytopenia, Infection) during primary chemotherapy (including a period of 30 days after the last chemotherapy dose).
- n is number of subjects with TRMB. N is number of total subjects in the safety population within the respective subgroup.
- Relative risk for overall safety population is based on the Cochran-Mantel-Haenszel statistic comparing BrECADD to eBEACOPP, stratified by sex (female vs male), age at randomisation (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe). Relative risk of subgroups is from the unstratified analysis.
- PET2 Negative is defined as Deauville score <= 3 at the end of cycle 2 and PET2 Positive is defined as Deauville score = 4 or 5 at the end of cycle 2.
- A patient is considered to have B symptoms if the patient has any of the three symptoms: weight loss of > 10% in 6 months, fever of unknown origin > 38ºC or night sweats.

Figure 3 - Study HD21: Forest Plot of TRMB by Baseline Prognostic Factor Groups and Cycle 2 PET Status (Safety Population)

TRMB by 4 versus 6 treatment cycles

Receipt of 4 vs 6 cycles was well balanced between the treatment groups. Among participants receiving BrECADD, a somewhat smaller proportion of participants receiving 4 cycles experienced any TRMB event (40.3%) compared with those receiving 6 cycles (45.8%). This was also true among participants receiving eBEACOPP (56.2% [4 cycles] vs 62.8% [6 cycles]).

Table 14 - HD21 Trial: Summary of TRMB by 4 versus 6 Cycles of Treatment (Safety Population, Participants Receiving 4 Cycles)

	BrECADD N=434 n (%)	**eBEACOPP N=436 n (%)**
Number of Participants with TRMB	175 (40.3)	245 (56.2)
Acute haematological toxicity - Grade 4	130 (30.0)	209 (47.9)
Anemia	2 (0.5)	2 (0.5)
Thrombocytopenia	127 (29.3)	207 (47.5)
Infection	5 (1.2)	4 (0.9)
Acute organ toxicity - Grade 3 or 4	77 (17.7)	75 (17.2)

	BrECADD N=434 n (%)	eBEACOPP N=436 n (%)
Cardiac Disorders	9 (2.1)	7 (1.6)
Gastrointestinal disorders (excluding vomiting, nausea and mucositis)	34 (7.8)	13 (3.0)
Hepatobiliary disorders	18 (4.1)	13 (3.0)
Nervous system disorders (sensory, motor and other)	8 (1.8)	23 (5.3)
Sensory	3 (0.7)	10 (2.3)
Motor	1 (0.2)	0
Other	6 (1.4)	15 (3.4)
Renal or urinary disorders	4 (0.9)	6 (1.4)
Respiratory, thoracic or mediastinal disorders	13 (3.0)	18 (4.1)
CMH p-value [a]	<.0001	
Relative Risk (unstratified analysis)[b] (BrECADD/eBEACOPP)	0.718	
(95% CI)	(0.623, 0.826)	
Relative Risk (stratified analysis)[c] (BrECADD/eBEACOPP)	0.727	
(95% CI)	(0.633, 0.834)	
% Difference (unstratified)[b] (BrECADD-eBEACOPP)	-15.9	
Exact 95% CI	(-22.5, -8.8)	

- data cutoff date 31 December 2022.
- CI = Confidence Interval; IPS = International Prognostic Score; TRMB = Treatment Related Morbidity.
- TRMB is defined as any CTCAE organ toxicity of grade 3 or 4 or severe haematological toxicity of grade 4 (Anemia, Thrombocytopenia, Infection) during primary chemotherapy (including a period of 30 days after the last chemotherapy dose).
- a p-value is based on Cochran-Mantel-Haenszel statistic comparing BrECADD to eBEACOPP, stratified by sex (female vs male), age at randomisation (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe).
- b Relative Risk is calculated by using unstratified Cochran-Mantel-Haenszel test.
- c Relative Risk is based on Cochran-Mantel-Haenszel statistic comparing BrECADD to eBEACOPP, stratified by sex (female vs male), age at randomisation (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe).
- Percentages are calculated using safety population in each corresponding group (N) as denominator.

Table 15 - HD21 Trial: Summary of TRMB by 4 versus 6 Cycles of Treatment (Safety Population, Participants Receiving 6 Cycles)

	BrECADD N=284 n (%)	**eBEACOPP N=282 n (%)**
Number of Participants with TRMB	130 (45.8)	177 (62.8)
Acute haematological toxicity - Grade 4	99 (34.9)	168 (59.6)
Anemia	1 (0.4)	0
Thrombocytopenia	96 (33.8)	168 (59.6)
Infection	6 (2.1)	4 (1.4)
Acute organ toxicity - Grade 3 or 4	54 (19.0)	47 (16.7)
Cardiac Disorders	7 (2.5)	3 (1.1)
Gastrointestinal disorders (excluding vomiting, nausea and mucositis)	21 (7.4)	16 (5.7)
Hepatobiliary disorders	17 (6.0)	7 (2.5)
Nervous system disorders (sensory, motor and other)	11 (3.9)	14 (5.0)
Sensory	6 (2.1)	7 (2.5)
Motor	2 (0.7)	0
Other	5 (1.8)	7 (2.5)
Renal or urinary disorders	3 (1.1)	3 (1.1)
Respiratory, thoracic or mediastinal disorders	10 (3.5)	14 (5.0)
CMH p-value [a]	<.0001	
Relative Risk (unstratified analysis)[b] (BrECADD/eBEACOPP)	0.729	
(95% CI)	(0.624, 0.852)	
Relative Risk (stratified analysis)[c] (BrECADD/eBEACOPP)	0.719	
(95% CI)	(0.616, 0.841)	
% Difference (unstratified)[b] (BrECADD-eBEACOPP)	-17.0	
Exact 95% CI	(-25.1, -8.1)	

	BrECADD N=284 n (%)	eBEACOPP N=282 n (%)

- Source: Table 15.2.1.3.9; data cutoff date 31 December 2022, run time 05 August 2024 11:32.CI = Confidence Interval; IPS = International Prognostic Score; TRMB = Treatment Related Morbidity.
- TRMB is defined as any CTCAE organ toxicity of grade 3 or 4 or severe haematological toxicity of grade 4 (Anemia, Thrombocytopenia, Infection) during primary chemotherapy (including a period of 30 days after the last chemotherapy dose).
- a p-value is based on Cochran-Mantel-Haenszel statistic comparing BrECADD to eBEACOPP, stratified by sex (female vs male), age at randomisation (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe).
- b Relative Risk is calculated by using unstratified Cochran-Mantel-Haenszel test.
- c Relative Risk is based on Cochran-Mantel-Haenszel statistic comparing BrECADD to eBEACOPP, stratified by sex (female vs male), age at randomisation (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe).
- Percentages are calculated using safety population in each corresponding group (N) as denominator.

Co-primary endpoint – PFS

As of the 31 December 2022 data cutoff date for the PFS IA, a total of 101 PFS events per INV with central confirmation (CC) (7% of possible events) were reported for the ITT population, with 39 PFS events (5%) reported for the BrECADD group and 62 PFS events (8%) for the eBEACOPP group.

PFS per INV with CC results met statistical significance for noninferiority with an upper confidence bound of 1.04 based on the 98.87% CI, which was below the prespecified noninferiority margin of 1.69.

This 98.87% confidence level was adjusted by the O'Brien-Fleming method with Lan- DeMets alpha-spending function and the 65.6% information fraction at IA to control for type-1 error.

The HR by unstratified Cox proportional hazards modeling was 0.619 (multiplicity adjusted 95% CI: 0.369, 1.040), indicating a 38% reduction in risk of a PFS event for BrECADD patients compared with eBEACOPP patients. At a median follow-up of 40.6 months (95% CI, 39.82-42.22 months) for BrECADD patients and 40.4 months (95% CI, 39.85-41.36 months) for eBEACOPP patients, median PFS was not estimable (NE) for either treatment group but was consistent with previous analyses from October 2023 (presented in Table 16 and Figure 4).

Table 16 - Study HD21: PFS per INV With CC (ITT Population; Updated data cutoff 31 Oct 2023)

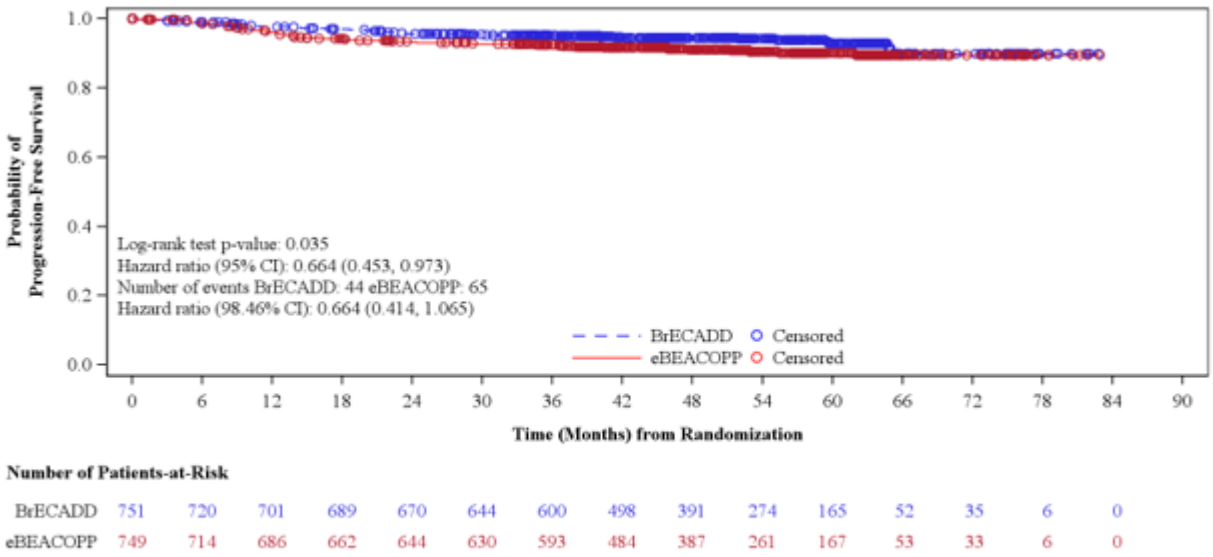
	BrECADD N=751	eBEACOPP N=749
PFS, months		
Number with events (%)	44 (5.9)	65 (8.7)
Number censored (%)	707 (94.1)	684 (91.3)

	BrECADD N=751	eBEACOPP N=749
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 82.8*	0.0*, 82.9*
Hazard ratio (95% CI) [b]	0.664 (0.453, 0.973)	
Log rank p-value [c]	0.035	
Kaplan-Meier estimates, % (95% CI) [d]		
12 months	97.5 (96.1, 98.4) [n=701]	96.0 (94.3, 97.2) [n=686]
24 months	95.7 (93.9, 96.9) [n=670]	93.3 (91.2, 94.9) [n=644]
36 months	95.2 (93.4, 96.6) [n=600]	92.4 (90.2, 94.1) [n=593]
48 months	94.5 (92.6, 96.0) [n=391]	91.1 (88.7, 93.0) [n=387]
60 months	92.8 (90.0, 94.9) [n=165]	90.2 (87.5, 92.3) [n=167]
Median PFS follow-up, months (95% CI) [e]	50.8 (49.15, 51.35)	51.1 (49.84, 51.91)
Reason for PFS event		
PD or relapse	37 (4.9)	57 (7.6)
Death due to any cause	7 (0.9)	8 (1.1)
Reason for censoring, n (%)		
Lost to follow-up	71 (9.5)	50 (6.7)
Withdrawal of consent	8 (1.1)	19 (2.5)
No documented PFS event	618 (82.3)	607 (81.0)
No postbaseline PFS assessment	10 (1.3)	8 (1.1)

- data cut 31 October 2023.
  BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CC: central confirmation; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; INV: investigator; ITT: intent-to-treat; NE: not estimable; PD: progressive disease; PFS: progression-free survival.
- * Denotes a censored observation.
- Percentages are based on the number of patients in the ITT population.
- p-value was calculated using unstratified log-rank test comparing PFS between the 2 treatment groups.

	BrECADD N=751	eBEACOPP N=749

- a: The hazard ratio was derived from unstratified Cox proportional hazards model. Confidence level was adjusted by the O'Brien-Fleming method with Lan-DeMets alpha-spending function, and the actual information fraction observed at the interim analysis.
  b: The hazard ratio is derived from unstratified Cox proportional hazards model.
  c: p-value is calculated using unstratified log-rank test comparing PFS between the 2 treatment groups.
  d: Based on Kaplan-Meier product limit estimates [n=number of patients at risk].
  e: Median PFS follow-up (months) was calculated based on the reverse Kaplan-Meier method.



Source: Figure 15.2.2.1. Data cut 31 October 2023.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI: confidence interval; CC: central confirmation; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; INV: investigator (assessment); ITT: intent-to-treat; PFS: progression-free survival.

Figure 4 - Study HD21: PFS by Investigator Assessment With Central Confirmation (ITT Population; Updated data cutoff 31 Oct 2023)

Sensitivity analyses of co-primary endpoint PFS

As of the 31 October 2023 data cut, a total of 33 participants were noted to have received subsequent anticancer therapy (ACT) without a prior PFS event. To assess the impact of subsequent ACT without subsequent progression, these events were treated either as competing events (Table 17) or as progression events (Table 18). Participants who received a subsequent anticancer therapy as their HL diagnosis was disconfirmed (N = 8) or who needed to switch their care provider away from a trial site were not considered as progressors ("clinically reviewed ACT population").

Table 17 - HD21 Trial: Competing Risk Analysis of PFS per INV with CC (ITT Population, Receipt of Subsequent New Anticancer Therapy Without a Prior PFS Event Treated as a Competing Event, Clinically Reviewed ACT Population; Updated data cutoff 31 Oct 2023)

	BrECADD (N=751)	eBEACOPP (N=749)
PFS, months		
Number with event of interest [a], n (%)	40 (5.3)	62 (8.3)
Number with competing risk events [b], n (%)	15 (2.0)	9 (1.2)
Number censored, n (%)	696 (92.7)	678 (90.5)
Hazard ratio (95% CI) [c]	0.633 (0.426, 0.941)	
p-value	0.0239	

- data cut date 31 October 2023.
- BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, CI: confidence interval; dexamethasone; eBEACOPP: escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; max: maximum; PFS: progression-free survival.
- PFS is defined as time from the date of randomisation until the date of the first occurrence of progression/relapse of the disease, initiation of new anticancer therapy, or the date of death from any cause. Initiation of new anticancer therapy refers to any new cancer treatment, given for any reason other than prescribed per protocol, to participants whose HL was confirmed per the trial protocol including treatment given to treat other emerging diseases.
- Percentages are based on the number of participants in the ITT population.
  a: Event of interest includes progression/relapse of disease or death from any cause without new anti-cancer therapy prior to these events of interest.
  b: Initiation of new anticancer therapy without prior event of interest is treated as a competing event.
  c: The hazard ratio is derived from unstratified subdistribution hazards model by Fine and Gray (1999).

Table 18 - HD21 Trial: Sensitivity Analysis of PFS per INV With CC Counting Subsequent ACT in the Absence of Documented PD as an Event (ITT Population with Clinically Reviewed ACT Population; Updated data cutoff 31 Oct 2023)

	BrECADD N=751	eBEACOPP N=749
PFS, months		
Number with events (%)	55 (7.3)	71 (9.5)
Number censored (%)	696 (92.7)	678 (90.5)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	0.0*, 82.8*	0.0*, 82.9*
Hazard ratio (95% CI) [a]	0.766 (0.539, 1.089)	
Kaplan-Meier estimates, % (95% CI) [b]		
12 months	96.0 (94.3, 97.2) [n=691]	95.0 (93.2, 96.4) [n=681]

	BrECADD N=751	eBEACOPP N=749
24 months	94.2 (92.2, 95.7) [n=660]	92.5 (90.3, 94.2) [n=640]
36 months	93.8 (91.7, 95.3) [n=593]	91.6 (89.3, 93.4) [n=589]
48 months	93.1 (90.9, 94.7) [n=388]	90.3 (87.8, 92.3) [n=385]
60 months	91.3 (88.4, 93.5) [n=165]	89.4 (86.6, 91.6) [n=166]
Median PFS follow-up, months (95% CI) [c]	50.8 (49.74, 51.58)	51.1 (49.84, 51.91)
Reason for PFS event		
PD or relapse	33 (4.4)	54 (7.2)
New anti-cancer therapy regardless of PD/relapse	15 (2.0)	9 (1.2)
Death due to any cause	7 (0.9)	8 (1.1)
Reason for censoring, n (%)		
Loss to follow-up	69 (9.2)	49 (6.5)
Withdrawal of consent	7 (0.9)	18 (2.4)
No documented PFS event	610 (81.2)	603 (80.5)
No postbaseline PFS assessment	10 (1.3)	8 (1.1)

- data cut 31 October 2023, ACT: anticancer therapy; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CC: central confirmation; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; INV: investigator; ITT: intent-to-treat; NE: not estimable; PD: progressive disease; PFS: progression-free survival.
- * Denotes a censored observation.
- Percentages are based on the number of participants in the ITT population.
- PFS is defined as time from the date of randomisation until the date of the first occurrence of progression/relapse of the disease, the date of a subsequent new anti-cancer therapy regardless of progression of disease, or the date of death from any cause. Initiation of new anti-cancer therapy refers to any new cancer treatment, given for any reason other than prescribed per protocol, to participants whose HL was confirmed per the trial protocol including treatment given to treat other emerging diseases.
- a: The hazard ratio was derived from unstratified Cox proportional hazards model. Confidence level was adjusted by the O'Brien-Fleming method with Lan-DeMets alpha-spending function, and the actual information fraction observed at the interim analysis.
  b: Based on Kaplan-Meier product limit estimates [n=number of participants at risk].
  c: Median PFS follow-up (months) was calculated based on the reverse Kaplan-Meier method.

Stratified Analysis

Table 19 - Study HD21: Stratified Cox Regression Analysis of PFS per Investigator With Central Confirmation (ITT Population; Initial data cutoff 31 Dec 2022)

Factor	Parameter Estimate (SE)	Hazard Ratio (98.87% CI) [a]	Hazard Ratio (95% CI) [b]	P-value [c]
Treatment (BrECADD vs eBEACOPP)	-0.478 (0.2057)	0.620 (0.368, 1.044)	0.620 (0.414, 0.928)	0.020

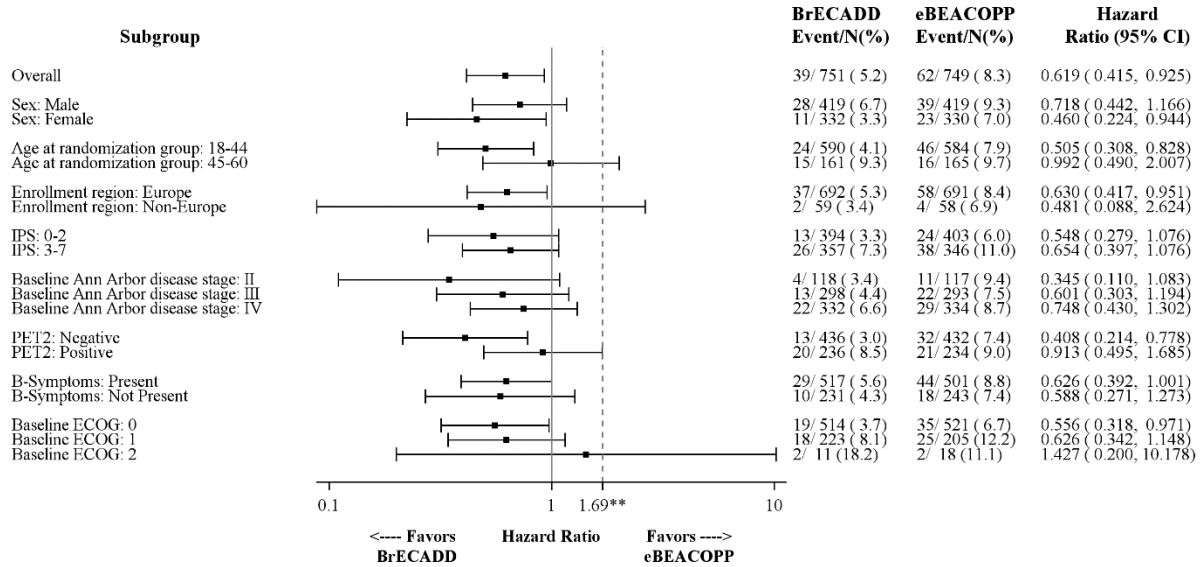
Source: Table 15.2.2.2; data cutoff 31 December 2022.
BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; IPS: International Prognostic Score; SE: standard error; PFS: progression-free survival.

[a] The hazard ratio is derived from Cox proportional hazards model stratified by sex (female vs male), age at randomization (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe). Confidence level was adjusted by the O'Brien-Fleming method with Lan-DeMets alpha-spending function and the actual information fraction observed at the interim analysis with the planned 154 PFS events at the final analysis.

[b] The hazard ratio is derived from Cox proportional hazards model stratified by sex (female vs male), age at randomization (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe).

[c] p-value is calculated using log-rank test stratified by sex (female vs male), age at randomization (age 18-44 vs age 45-60), IPS (0-2 vs 3-7), and enrollment region (Europe vs Non-Europe) comparing PFS between the 2 treatment groups.

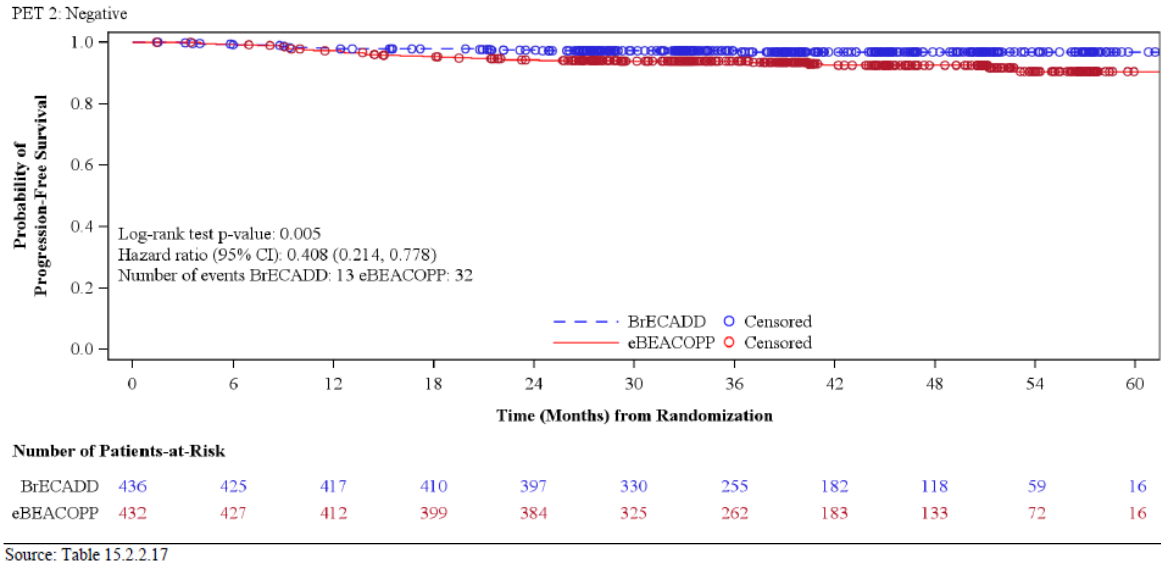
Subgroup Analyses of PFS



- data cutoff date 31 December 2022
- CI = Confidence Interval; IPS = International Prognostic Score; ECOG = Eastern Cooperative Oncology Group; PFS = Progression-Free Survival.
- PFS is defined as time from the date of randomisation until the date of the first occurrence of progression or relapse of the disease or death from any cause. If none of these occurred, PFS is censored at the date of the last documented restaging or follow-up visit.
- The hazard ratio is derived from unstratified Cox proportional hazards model.
- PET2 Negative is defined as Deauville score <= 3 at the end of cycle 2 and PET2 Positive is defined as Deauville score = 4 or 5 at the end of cycle 2.
- A patient is considered to have B symptoms if the patient has any of the three symptoms: weight loss of > 10% in 6 months, fever of unknown origin > 38ºC or night sweats.
- **non-inferiority margin=1.69.

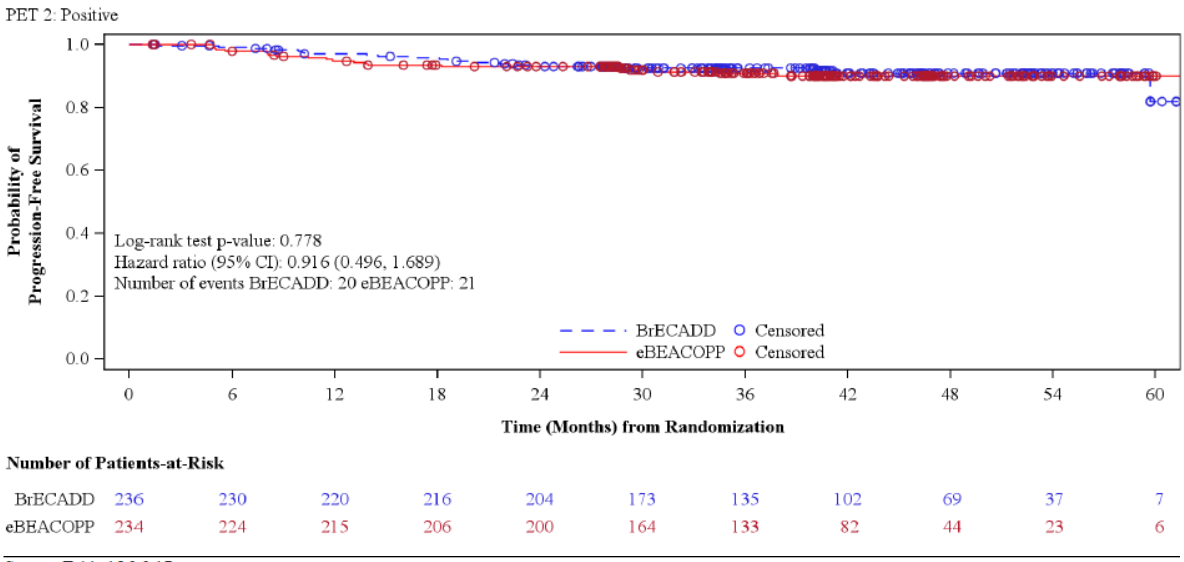
Figure 5 - Study HD21: Forest Plot of PFS per INV with CC by Baseline Prognostic Factor Groups and Cycle 2 PET Status (Safety Population; Initial data cutoff 31 Dec 2022)

PFS by PET-status



Source: Table 15.2.2.17

Figure 6 - Kaplan-Meier Plot of PFS per Investigator Assessment by PET Status at Cycle 2 of Chemotherapy (ITT Population) – PET Negative (data cutoff: 31 DEC 2022)



Source: Table 15.2.2.17

Figure 7 - Kaplan-Meier Plot of PFS per Investigator Assessment by PET Status at Cycle 2 of Chemotherapy) ITT Population – PET Positive (data cutoff: 31 DEC 2022)

PFS by 4 versus 6 treatment cycles

Table 20 - Study HD21: PFS per INV With CC (ITT Population Receiving 4 Treatment Cycles; Initial data cutoff 31 Dec 2022)

	BrECADD N=434	eBEACOPP N=436
PFS, months		
Number with events (%)	13 (3.0)	33 (7.6)
Number censored (%)	421 (97.0)	403 (92.4)
25th percentile (95% CI)	NE (NE, NE)	NE (61.9, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	1.4*, 64.6*	3.4*, 65.0*
Hazard ratio (95% CI) [a]	0.403 (0.212, 0.767)	
Log rank p-value [b]	0.004	
Kaplan-Meier estimates [c], % (95% CI)		
12 months	97.9 (96.0, 98.9) [n = 414]	97.4 (95.4, 98.6) [n = 416]
24 months	97.4 (95.4, 98.6) [n = 395]	94.4 (91.7, 96.2) [n = 387]
36 months	97.2 (95.0, 98.4) [n = 253]	93.8 (91.1, 95.8) [n = 265]
48 months	96.8 (94.5, 98.1) [n = 116]	91.8 (88.2, 94.4) [n = 132]
60 months	96.8 (94.5, 98.1) [n = 15]	89.8 (84.8, 93.2) [n = 16]
Median PFS follow-up, months (95% CI) [d]	39.6 (38.83, 40.74)	39.9 (39.10, 43.04)
Reason for PFS event		
PD or relapse	9 (2.1)	30 (6.9)
Death due to any cause	4 (0.9)	3 (0.7)
Reason for censoring, n (%)		
Lost to follow-up	25 (5.8)	21 (4.8)
Withdrawal of consent	3 (0.7)	5 (1.1)
No documented PFS event	393 (90.6)	377 (86.5)
No postbaseline PFS assessment	0	0

Source: Table 15.2.2.24, run time 05 August 2024 11:42; data cut 31 December 2022.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CC: central confirmation; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; INV: investigator; ITT: intent-to-treat; NE: not estimable; PD: progressive disease; PFS: progression-free survival.
PFS is defined as time from the date of randomization until the date of the first occurrence of progression or relapse of the disease or death from any cause. If none of these occurred, PFS is censored at the date of the last documented restaging or follow-up visit.
Percentages are based on the number of patients in the ITT population.
a The hazard ratio is derived from unstratified Cox proportional hazards model.
b p-value is calculated using unstratified log-rank test comparing PFS between the 2 treatment groups.
c Based on Kaplan-Meier product limit estimates [n = number of patients at risk].
d Median PFS follow-up (months) is calculated based on the reverse Kaplan-Meier method.
* Denotes a censored observation.

Table 21 - Study HD21: PFS per INV With CC (ITT Population Receiving 6 Treatment Cycles; Initial data cutoff 31 Dec 2022)

	BrECADD N=284	eBEACOPP N=282
PFS, months		
Number with events (%)	21 (7.4)	27 (9.6)
Number censored (%)	263 (92.6)	255 (90.4)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Minimum, maximum	1.3*, 70.3*	4.7*, 70.3*
Hazard ratio (95% CI) [a]	0.752 (0.425, 1.330)	
Log rank p-value [b]	0.325	
Kaplan-Meier estimates [c], % (95% CI)		
12 months	98.2 (95.8, 99.3) [n = 272]	94.3 (90.8, 96.5) [n = 262]
24 months	94.5 (91.1, 96.7) [n = 251]	92.1 (88.2, 94.7) [n = 244]
36 months	93.7 (90.0, 96.0) [n = 180]	90.3 (86.1, 93.3) [n = 175]
48 months	92.5 (88.4, 95.2) [n = 114]	89.8 (85.4, 92.9) [n = 88]
60 months	88.6 (80.6, 93.4) [n = 42]	89.8 (85.4, 92.9) [n = 44]
Median PFS follow-up, months (95% CI) [d]	45.7 (41.33, 47.47)	41.4 (40.54, 46.06)
Reason for PFS event		
PD or relapse	20 (7.0)	24 (8.5)
Death due to any cause	1 (0.4)	3 (1.1)
Reason for censoring, n (%)		
Lost to follow-up	28 (9.9)	15 (5.3)
Withdrawal of consent	2 (0.7)	3 (1.1)
No documented PFS event	233 (82.0)	237 (84.0)
No postbaseline PFS assessment	0	0

Source: Table 15.2.2.24, run time 05 August 2024 11:42; data cut 31 December 2022.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CC: central confirmation; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; INV: investigator; ITT: intent-to-treat; NE: not estimable; PD: progressive disease; PFS: progression-free survival.
PFS is defined as time from the date of randomization until the date of the first occurrence of progression or relapse of the disease or death from any cause. If none of these occurred, PFS is censored at the date of the last documented restaging or follow-up visit.
Percentages are based on the number of patients in the ITT population.
a The hazard ratio is derived from unstratified Cox proportional hazards model.
b p-value is calculated using unstratified log-rank test comparing PFS between the 2 treatment groups.
c Based on Kaplan-Meier product limit estimates [n = number of patients at risk].
d Median PFS follow-up (months) is calculated based on the reverse Kaplan-Meier method.
* Denotes a censored observation.

Secondary endpoints

CR Rate and ORR at End of Chemotherapy

Table 22 - Study HD21: Response per Central Review (ITT Population)

	BrECADD N=751	eBEACOPP N=749
Response rate at the end of chemotherapy (n [%])		
Complete remission	585 (77.9)	570 (76.1)
Partial remission	131 (17.4)	140 (18.7)
No change [a]	0	0
Progressive disease (PD)	1 (0.1)	5 (0.7)
ORR at the end of chemotherapy (CR+PR)	716 (95.3)	710 (94.8)
95% CI	(93.8, 96.8)	(93.2, 96.4)
Response rate difference (95% CI)	0.5 (-1.6, 2.7)	
Stratified CMH p-value [b] for ORR	0.650	
CR rate at the end of chemotherapy	585 (77.9)	570 (76.1)
95% CI for CR rate	(74.9, 80.9)	(73.0, 79.2)
Response rate difference (95% CI)	1.8 (-2.5, 6.1)	
Stratified CMH p-value [b] for CR	0.391	

Source: Table 15.2.3.1; Listing 16.2.6.3; Data cutoff date 31 December 2022.

BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; ITT: intent-to treat.

ORR per central assessment is defined as the proportion of patients who achieve CR or PR per central assessment at the end of chemotherapy per central PET panel with randomized regimen (BrECADD or eBEACOPP).

Percentages are based on the number of patients in the ITT population.

Sensitivity Analyses: CR Rate and ORR per INV at End of Chemotherapy

Assessments per INV tended to be somewhat more bimodal than those per central assessment, with more patients assigned to CR or PD and fewer patients assigned to PR or NC, a consistent trend between the treatment groups. The rates of ORR were slightly lower per INV than per central assessment but retained similar trends. As observed for CR rate at EOT per central assessment, BrECADD also showed a slight improvement in CR rate at EOT per INV that was not associated with a descriptive p-value of <0.05.

DOR per Central Review

Median duration of response (DOR) was not reached for either treatment group, with fewer subsequent relapses recorded for patients randomised to BrECADD (BrECADD 30 relapses, 4% versus eBEACOPP 54 relapses, 7%; descriptive unstratified p-value 0.007).

Sensitivity Analysis: DOR per INV

Response duration results per INV were similar to and supportive of those determined by CC, with a similar number of relapses identified in each treatment group and a similar HR for the reduction in the risk of a subsequent progression event among responding patients (HR=0.587, 95% CI, 0.376-0.915, descriptive p-value 0.017).

DOCR per Central Review

While the median duration of complete response (DOCR) was not reached for either treatment group, fewer subsequent relapses were recorded for BrECADD patients (BrECADD 21 relapses, 3% versus eBEACOPP 40 relapses, 7%; descriptive unstratified p-value of 0.008).

Sensitivity Analysis: DOCR per INV

CR duration results per INV were similar to and supportive of those determined per central confirmation. Investigators identified slightly more relapses in both treatment groups but a trend favoring BrECADD was maintained, with a similar HR for the reduction in the risk of a subsequent progression event among patients attaining a CR (HR=0.513, 95% CI, 0.312-0.842, descriptive p-value 0.007).

Overall Survival

With the data cutoff 31 Dec 2023 a similar number of OS events was reported across treatment groups. At a median follow up of 52.6 months (range, 0 86.7 months), 12 deaths (1.6%) were reported for BrECADD patients, and at a median follow up of 53.2 months (range, 0 85.9 months), 13 deaths (1.7%) were reported for eBEACOPP patients.

Median OS was not reached for either treatment group. The HR, derived from unstratified Cox proportional hazards model, was 0.919 (95% CI, 0.419 2.015), and unstratified log-rank p value was 0.83 (Table 19).

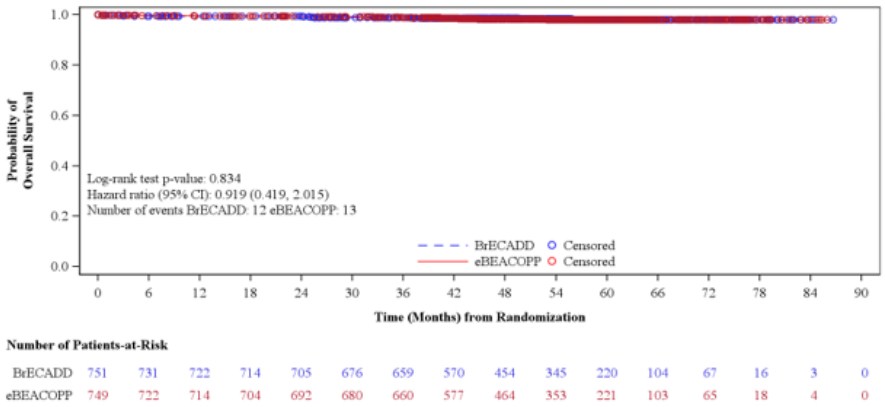
Estimated OS rates were comparable across treatment groups and ranged from 98.9% (95% CI, 97.8% 99.4%) across the 2 treatment groups at 36 months to 98.1% (95% CI, 96.5% 98.9%) for BrECADD patients and 97.9% (95% CI, 96.4% 98.8%) for eBEACOPP patients at 60 months.

Table 23 - Study HD21: OS (ITT Populatio; data cutoff 31 Oct 2023)

	BrECADD (N=751)	eBEACOPP (N=749)
OS, months		
Number of OS events, n (%)	12 (1.6)	13 (1.7)
Number censored, n (%)	739 (98.4)	736 (98.3)
25th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, Max	0.0*, 86.7*	0.0*, 85.9*
Median OS follow-up, months [a] (95% CI)	52.6 (51.15, 54.18)	53.2 (52.14, 54.51)
Kaplan-Meier estimates [b], % (95% CI)		
12 months	99.5 (98.6, 99.8) [n=722]	99.5 (98.5, 99.8) [n=714]
24 months	99.3 (98.4, 99.7) [n=705]	99.3 (98.4, 99.7) [n=692]
36 months	98.9 (97.8, 99.4) [n=659]	98.9 (97.8, 99.4) [n=660]
48 months	98.6 (97.4, 99.2) [n=454]	98.2 (96.8, 99.0) [n=464]
60 months	98.1 (96.5, 98.9) [n=220]	97.9 (96.4, 98.8) [n=221]
Reason for censoring, n (%)		
End of study	118 (15.7)	115 (15.4)
Individual trial period ended (no consent to extension)	14 (1.9)	10 (1.3)
Lost to follow-up	76 (10.1)	61 (8.1)
Withdrawal by patient	8 (1.1)	21 (2.8)
Other	20 (2.7)	23 (3.1)
Still alive at time of last contact	621 (82.7)	621 (82.7)
Hazard ratio (95% CI) [c]	0.919 (0.419, 2.015)	
Log-rank p-value [d]	0.834	

Source: Table 15.2.5.1; Listing 16.2.6.6; Data cut 31 October 2023.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; Max: maximum; Min: minimum; NE: not estimable; OS: overall survival.

Percentages are based on the number of patients in the ITT population.
a: Median OS calculated by reverse Kaplan-Meier method.
b: Based on Kaplan-Meier product limit estimates [n=number of patients at risk].
c: The hazard ratio is derived from unstratified Cox proportional hazards model.
d: p-value calculated using unstratified log-rank test to compare OS between the 2 treatment groups.



Source: Figure 15.2.5.1.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CI: confidence interval; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; Max: maximum; Min: minimum; NE: not estimable; OS: overall survival.

Figure 8 - Study HD21: OS (ITT Population)

PET Negativity Rate at Cycle 2

PET2-negativity was defined by a Deauville score of ≤3 at the Cycle 2 assessment. A PET2-negativity rate of 58.1% was reported for BrECADD patients and 57.7% for eBEACOPP patients. The stratified CMH p-value was 0.799, indicating no difference in the PET2 negativity rate between the 2 treatment groups at Cycle 2.

Table 24 - Study HD21: PET Status After 2 Cycles of Therapy (ITT Population)

Number of patients (%)	BrECADD (N=751)	eBEACOPP (N=749)
PET-negativity at Cycle 2	436 (58.1)	432 (57.7)
Deauville score		
1	25 (3.3)	30 (4.0)
2	119 (15.8)	150 (20.0)
3	292 (38.9)	252 (33.6)
4	235 (31.3)	234 (31.2)
5	1 (0.1)	0
% Difference BrECADD/eBEACOPP (95% CI)	0.4 (-4.6, 5.4)	
Stratified CMH p-value [a]	0.799	

Source: Table 15.2.6.1; Listing 16.2.6.7; data cutoff 31 December 2022.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; CMH: Cochran-Mantel-Haenszel; ITT: intent-to-treat; PET: positron emission tomography.
PET negative was defined as a Deauville score of ≤3.
Percentages are based on the number of patients in the ITT population.
a: p-value is based on CMH statistic comparing BrECADD and eBEACOPP, stratified by enrollment region (Europe vs Non-Europe), age at randomization (18-44 vs 45-60), biologic sex (female vs male), IPS risk category (0-2 vs 3-7).

Rates of Radiotherapy

PET-positive residual lesions were reported for 127 BrECADD patients (16.9%) and 137 eBEACOPP patients (18.3%) after completion of primary study therapy.

Primary radiotherapy was reported for 90 BrECADD patients (12%) and 103 eBEACOPP patients (13.8%). The p-value based on the stratified log-rank CMH test was 0.282, indicating no difference in the rates of radiotherapy between the 2 treatment groups.

Table 25 - Study HD21: Primary Radiotherapy After Completion of Therapy (ITT Population)

Number of patients (%)	BrECADD (N=751)	eBEACOPP (N=749)
PET-positivity after completion of therapy	127 (16.9)	137 (18.3)
Radiotherapy after completion of therapy	90 (12.0)	103 (13.8)
Rate Difference (95% CI)	-1.77 (-5.16, 1.62)	
Stratified CMH p-value [a]	0.282	

Source: Table 15.2.7.1; Listing 16.2.6.8; data cutoff 31 December 2022.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CMH: Cochran-Mantel-Haenszel; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; PET: positron emission tomography.
Completion of therapy refers to either BrECADD or eBEACOPP.
PET-positive was defined as a Deauville score of >3.
Percentages are based on the number of patients in the ITT population.
a: p-value is based on CMH statistic comparing BrECADD and eBEACOPP, stratified by enrollment region (Europe vs Non-Europe), age at randomization (18-44 vs 45-60), biologic sex (female vs male), IPS risk category (0-2 vs 3-7).

Subsequent Anticancer Therapy

Fewer BrECADD patients had received salvage therapy or any further treatment for cHL as of this analysis. At least 1 subsequent anticancer therapy was reported for 46 BrECADD patients (6.2%) and 63 eBEACOPP patients (8.5%). The most commonly reported subsequent therapies were ASCT, reported for 26 BrECADD patients (3.5%) and 46 eBEACOPP patients (6.2%), and high-dose chemotherapy, reported for 24 BrECADD patients (3.2%) and 45 eBEACOPP patients (6.1%).

Table 26 - Study HD21: Subsequent Anticancer Therapy (Safety Population)

Number of patients (%)	BrECADD (N=747)	eBEACOPP (N=741)
At least 1 subsequent anticancer therapy	46 (6.2)	63 (8.5)
At least 1 salvage therapy	31 (4.1)	52 (7.0)
Type of therapy		
Reintroduction	8 (1.1)	11 (1.5)
Conventional polychemotherapy or monotherapy	20 (2.7)	41 (5.5)
Other conventional chemotherapy	17 (2.3)	8 (1.1)
High-dose chemotherapy	24 (3.2)	45 (6.1)
Antibody/immunotherapy	21 (2.8)	28 (3.8)
Autologous SCT	26 (3.5)	46 (6.2)
Allogeneic SCT	5 (0.7)	4 (0.5)
Radiotherapy	7 (0.9)	12 (1.6)

Source: T15.2.8.1; Listing 16.2.6.9.; data cutoff 31 December 2022.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; cHL: classical Hodgkin lymphoma; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; SCT: stem cell transplantation.
Percentages are based on the number of treated patients in the denominator.

Patient-related outcome (PRO) – Quality of Life

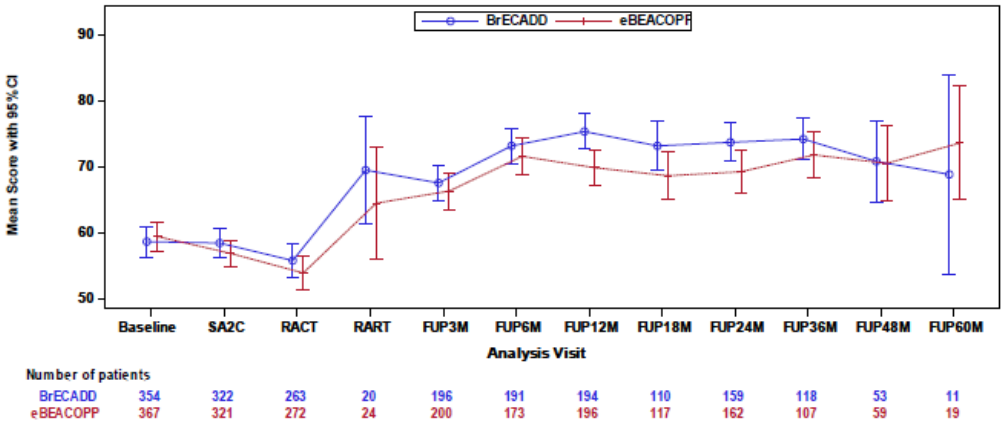
Compliance rates

In the BrECADD and BEACOPP treatment groups, compliance rates for patients consenting to the EORTC QLQ-C30, EORTC QLQ-FA12, and EORTC QLQ-CIPN20 questionnaires were higher at baseline (74% and 76%, respectively) and during treatment (68% each), then decreased notably during PTFU (46% and 45%, respectively).

EORTC QLQ-C30

Analysis of the change from baseline in global health status scores using linear mixed models generally showed a similar change in scores during treatment and a change to higher scores for BrECADD patients compared with eBEACOPP patients at 12-24 months PTFU.

The estimated mean change from baseline for BrECADD at 36 months PTFU and for eBEACOPP at 36 months PTFU was considered clinically meaningful using the published minimally important difference (MID) of 10 (Musoro et al. 2023; Osoba et al. 1998; Osoba et al. 2023). The estimated mean change from baseline in the eBEACOPP treatment group reached the MID of 10 at 36 and 60 months PTFU. However, the number of patients at 60 months PTFU was too small for drawing meaningful conclusions.



Source: Figure 15.2.10.1a.

Analysis Visits: SA2C=Staging after 2 Cycles; RACT=Restaging after Chemotherapy; RART=Restaging after Radiotherapy; FUP3M=3 months follow-up; FUP6M=6 months follow-up; FUP12M=12 months follow-up; FUP18M=18 months follow-up; FUP24M=24 months follow-up; FUP36M=36 months follow-up; FUP48M=48 months follow-up; FUP60M=60 months follow-up.
Baseline was defined as the value collected at the time closest to, but before, the start of study drug administration.
The score range is 0-100. A high score for the global scale represents a high QOL or functioning.
All patients with PRO measurements at baseline and at least 1 postbaseline visit were included.
All patients were from Europe.

Figure 9 - Study HD21: Mean EORTC QLQ-C30 Subscale Scores Over Time: Global Health Status/QOL (ITT Population)

EORTC QLQ-FA12

No consistent differences between treatment groups in EORTC QLQ-FA12 physical fatigue subscale scores were noted over time but change from baseline analysis showed lower scores in favor of BrECADD during and after treatment. Analysis of the change from baseline based on linear mixed models showed a trend in favor of BrECADD at 18 to 36 months PTFU.

EORTC QLQ-CIPN20

Mean scores and mean change from baseline scores for the sensory symptoms subscale generally trended lower (indicating favorable scores) for BrECADD compared with eBEACOPP during treatment and at 12,

36, and 48 months PTFU. Analyses of the change from baseline in scores using linear mixed models showed lower scores in favor of BrECADD at staging after 2 cycles and at 12 and 36 months PTFU. These differences between the 2 treatment groups were clinically meaningful as they reached the published MID of 2.5 to 5.9 for the sensory subscale.

Mean scores for the EORTC QLQ-CIPN20 motor, and autonomic symptom subscales indicated worsening of symptoms during treatment and then improvement during PTFU in both treatment groups. A trend toward improved change from baseline subscale scores in favor of BrECADD was observed for motor symptoms at multiple time points.

Medical Resource Utilization Results

At least 1 hospitalization was reported for 576 BrECADD patients (76.7%) during 2708.08 patient-years of follow-up and 553 eBEACOPP patients (73.8%) during 2699.10 patient-years of follow-up. No substantive difference between treatment groups was observed in the rate of hospitalization (0.61 vs 0.57 per patient-year for BrECADD and eBEACOPP, respectively) or median number of hospitalizations (3.0 vs 2.0 per patient, respectively). The median number of days of hospitalization among hospitalized patients was 15 (range, 1-109) days for BrECADD and 14 (range, 1-103) days for eBEACOPP.

At least 1 ICU stay was reported for 24 BrECADD patients (3.2%) during 233.65 patient-years of follow-up and 22 eBEACOPP patients (2.9%) during 251.93 patient-years of follow-up. The rate of ICU stays per patient-year (0.10 for BrECADD and 0.09 for eBEACOPP) and the median number of ICU stays per patient (1.0 [range, 1-1] for BrECADD and 1.0 [range, 1-2] for eBEACOPP) were similar in the 2 treatment groups. The median stay for patients hospitalized in the ICU was 3.0 (range, 1-14) days for BrECADD and 3.5 (range, 1-21) days for eBEACOPP.

A higher proportion of BrECADD patients (163 patients, 21.7%) than eBEACOPP patients (116 patients, 15.5%) were hospitalized for neutropenic fever (febrile neutropenia). This was consistent with the higher incidence of febrile neutropenia in BrECADD patients compared with eBEACOPP patients, with febrile neutropenia being the most commonly reported SAE. The median stay for patients hospitalized for neutropenic fever was similar for BrECADD (6.0 days, range: 1-41 days) and eBEACOPP (6.0 days, range: 1-51 days).

Ancillary analyses

The MAH performed a tipping point analysis that assumed that the remaining 53 PFS events occurred 1 day after the interim analysis in the BrECADD treatment group.

Given that 101 of 154 PFS events have been observed, the analysis was based on the PFS events ranging from 0 events (best case scenario) to 53 events (worst case scenario) in the BrECADD group, with a corresponding PFS event range for the eBEACOPP group of 53 to 0. Figure 2 and Figure 3 depict the results of the HR point estimates along with 95% CIs and 95.35% CIs, respectively.

Figure 10 Study HD21: Hazard Ratios and 95% Confidence Intervals When 0-53 Additional PFS Events of 53 Possible Events Happen in the BrECADD Group

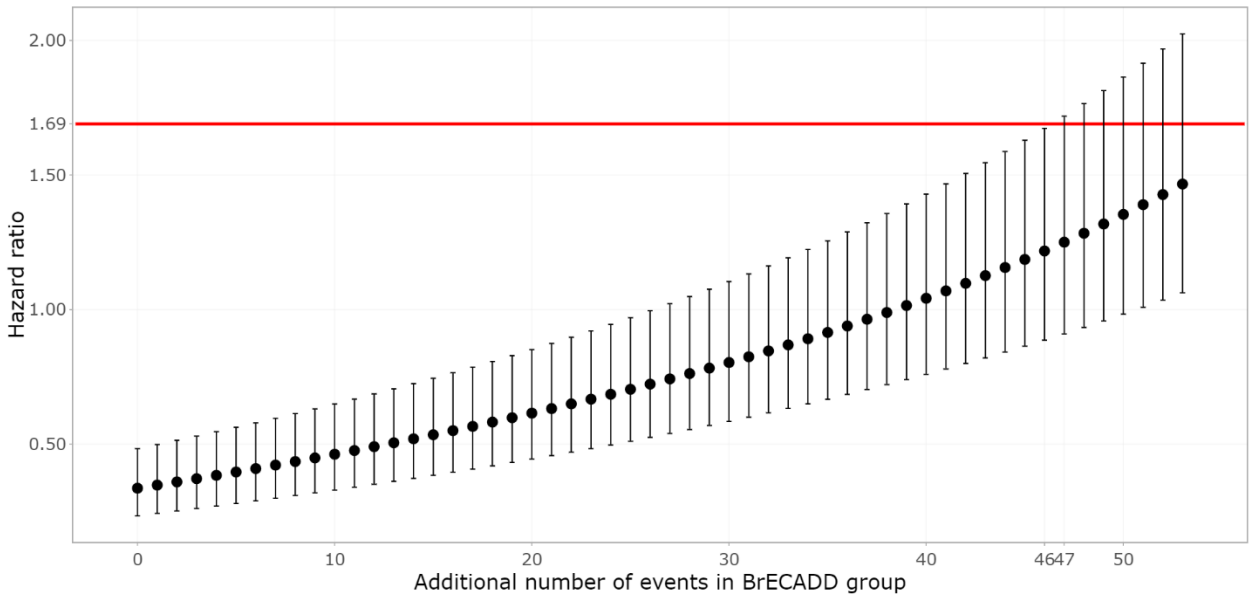
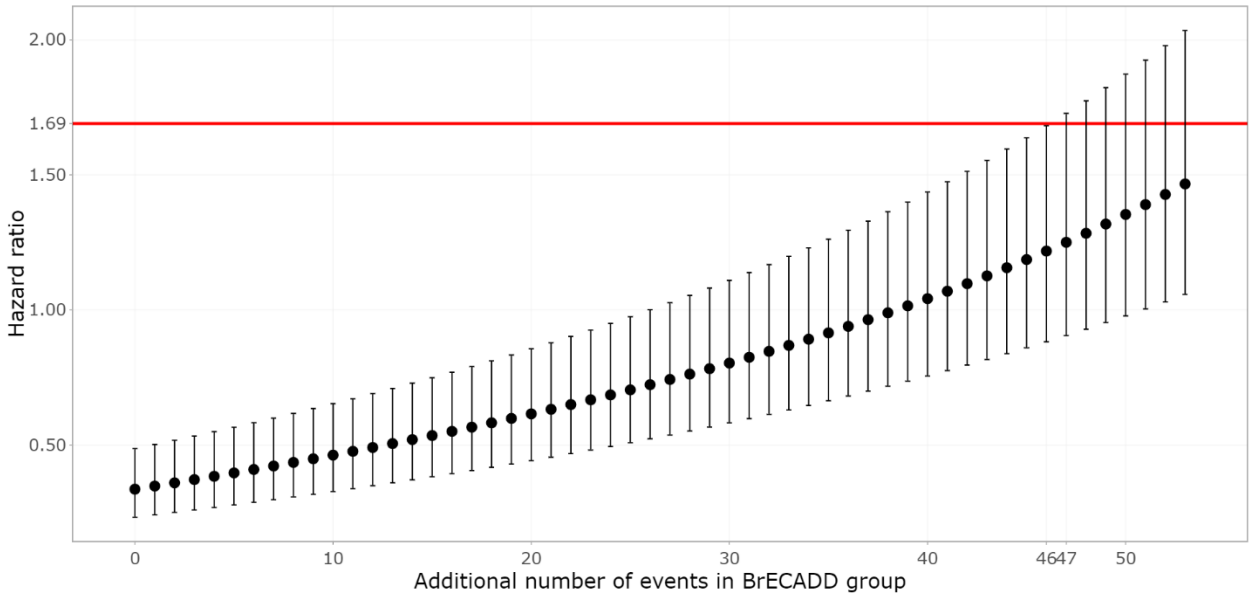


Figure 11 Study HD21: Hazard Ratios and 95.35% Confidence Intervals When 0-53 Additional PFS Events of 53 Possible Events Happen in the BrECADD Group



BrECADD is noninferior when, of the 53 possible events, the additional number of events is less than 47. With 46 PFS events in the BrECADD group, the upper limit of 95% CI for HR is 1.674 and the upper limit of 95.35% CI for HR is 1.681. Both are less than the pre-specified noninferiority margin of 1.69 (marked by the red horizontal line). On the other hand, with 47 PFS events in the BrECADD group, the upper limit of the 95% CI for the HR is 1.719, which is greater than 1.69. Therefore, 47 PFS events represents the tipping point for the noninferiority of BrECADD.

In addition, based on the number of PFS events observed as of the interim analysis (39 in the BrECADD group and 62 in the eBEACOPP group), the probability of observing inferiority of BrECADD group at 154 events with the tipping point of 47 events can be calculated using a generalized hypergeometric distribution:

P(Inferiority of BrECADD arm at 154 events)=P(X≥47)=2.98×〖10〗^(-14)

In this equation, X denotes the number of events in the BrECADD group 1 day after the interim analysis.

This probability is extremely small, indicating that it is highly unlikely that the BrECADD group will be inferior to eBEACOPP after the remaining 53 PFS events are observed.

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27 - Summary of Efficacy for trial HD21

Title: Clinical trials for adults: HD21 for advanced stages: 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			
Study identifier	Sponsor code: Uni-Koeln-1762 (HD21) ClinicalTrials.gov ID: NCT02661503 EudraCT no.: 2014-005130-55		
Design	Prospective, multicenter, randomised, Cycle 2 PET-guided open-label trial receiving 4 or 6 cycles of eBEACOPP or BrECADD. Patients in either group with PET+ residual tumor at the end of chemotherapy receive 30 Gy radiation; otherwise no further treatment is given. Assessments from the interim staging (PET2) and restaging after chemotherapy (PET4 or PET6) underwent central review.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		As planned, 4 years of enrollment, analysis of TRMB at ~5.5 years, ~ 8 years to analysis of PFS/OS. not applicable not applicable
Hypothesis	Superiority (TRMB) and Non-inferiority (PFS)		
Treatments groups	BrECADD		4-6 cycles of brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone, n=751
	eBEACOPP		4-6 cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone, n=749
Endpoints and definitions	Co-Primary endpoint	TRMB	Treatment-related morbidity, defined as the rate of treatment-related toxicities during primary treatment (CTCAE Grade 3 and 4 acute organ toxicity, by predefined SOC and Grade 4 acute hematologic toxicity [anemia, thrombocytopenia, infections]) occurring from first dose through 30 days post last dose.

	Co-Primary endpoint	PFS	Progression-free survival defined as time from the date of randomisation to the date of the first occurrence of disease progression or relapse or death from any cause. If none of these events occurred, PFS was censored at the date of the last documented restaging or follow up visit.
	Secondary endpoint	CR rate	Complete remission rate after completion of either BrECADD or eBEACOPP therapy, defined as the proportion of patients who achieved a CR by investigator assessment with central confirmation.
	Secondary endpoint	OS	Overall survival, defined as the time from the date of randomisation to the date of death due to any cause.

Database lock	Data cut for analysis of coprimary endpoints: 31 December 2022 Data extract date 06 November 2023 Final data transfer from GHSG to Takeda: 09 November 2023 Data cut for updated analysis: 31 October 2023 Data transfer from GHSG to Takeda for updated analysis: 05 July 2024.

Results and Analysis

Analysis description	**Coprimary Analysis - TRMB**	
Analysis population and time point description	Safety population 2+ years after randomisation of the last patient	
Descriptive statistics and estimate variability	BrECADD	eBEACOPP
	n=747 n (%)	n=741 n (%)
	Number of Patients with TRMB 315 (42.2)	 435 (58.7)
	Acute hematologic toxicity-Gr 4 233 (31.2) Anemia 3 (0.4) Thrombocytopenia 227 (30.4) Infection 13 (1.7)	 386 (52.1) 3 (0.4) 383 (51.7) 10 (1.3)

	Acute Organ toxicity-Gr 3 or 4 140 (18.7) Cardiac 18 (2.4) GI (excl. nausea/vomiting/mucositis) 58 (7.8) Hepatobiliary 37 (5.0) Nervous system 21 (2.8) Sensory 10 (1.3) Motor 3 (0.4) Other 12 (1.6) Renal or urinary 7 (0.9) Respiratory, thoracic or mediastinal 25 (3.3)	129 (17.4) 10 (1.3) 32 (4.3) 22 (3.0) 40 (5.4) 17 (2.3) 1 (0.1) 24 (3.2) 10 (1.3) 35 (4.7)
Analysis description	**Coprimary Analysis - PFS**	
Analysis population and time point description	Intent-to-treat population 2+ years after randomisation of the last patient (Interim Analysis data cutoff of 31 December 2022).	
Descriptive statistics and estimate variability	BrECADD	eBEACOPP
	n=751 n (%)	n=749 n (%)

	PFS (months) Number with events n (%) 39 (5.2) Number censored n (%) 712 (94.8) 25th percentile (95% CI) NE (NE, NE) Median NE (NE, NE) 75th percentile (95% CI) NE (NE, NE) Min, Max 0.0*, 70.3* Kaplan-Meier Estimates % (95% CI) 12 months 97.5 (96.1, 98.4) 24 months 95.7 (93.9, 96.9) 36 months 95.2 (93.3, 96.5) 48 months 94.4 (92.4, 96.0) 60 months 91.5 (85.8, 94.9)	 62 (8.3) 687 (91.7) NE (NE, NE) NE (NE, NE) NE (NE, NE) 0.0*, 70.3* 96.0 (94.3, 97.2) 93.3 (91.2, 94.9) 92.3 (90.0, 94.0) 90.9 (88.3, 93.0) 89.8 (86.8, 92.2)
Analysis description	**Coprimary Analysis - PFS**	
Analysis population and time point description	Intent-to-treat population 3+ years after randomisation of the last patient (Updated data cutoff of 31 October 2023).	
Descriptive statistics and estimate variability	BrECADD	eBEACOPP
	n=751 n (%)	n=749 n (%)

	PFS (months) Number with events n (%) 44 (5.9) Number censored n (%) 707 (94.1) 25th percentile (95% CI) NE (NE, NE) Median NE (NE, NE) 75th percentile (95% CI) NE (NE, NE) Min, Max 0.0*, 82.8* Kaplan-Meier Estimates % (95% CI) 12 months 97.5 (96.1, 98.4) 24 months 95.7 (93.9, 96.9) 36 months 95.2 (93.4, 96.6) 48 months 94.5 (92.6, 96.0) 60 months 92.8 (90.0, 94.9)	 65 (8.2) 684 (91.3) NE (NE, NE) NE (NE, NE) NE (NE, NE) 0.0*, 82.9* 96.0 (94.3, 97.2) 93.3 (91.2, 94.9) 92.4 (90.2, 94.1) 91.1 (88.7, 93.0) 90.2 (87.5, 92.3)
Analysis description	**Secondary Analysis – CR Rate at the End of Chemotherapy**	
Analysis population and time point description	Intent-to-treat population 2+ years after randomisation of the last patient (31 December 2022)	
Descriptive statistics and estimate variability	BrECADD n=751 n (%)	eBEACOPP n=749 n (%)

	CR Rate 585 (77.9) 95% CI (74.9, 80.9)	 570 (76.1) (73.0, 79.2)
Analysis description	**Secondary Analysis – OS**	
Analysis population and time point description	Intent-to-treat population 2+ years after randomisation of the last patient (Data cutoff 31 December 2022)	
Descriptive statistics and estimate variability	BrECADD	eBEACOPP
	n=751 n (%)	n=749 n (%)
	OS (months) Number with events n (%) 11 (1.5) Number censored n (%) 740 (98.5) 25th percentile (95% CI) NE (NE, NE) Median (95% CI) NE (NE, NE) 75th percentile (95% CI) NE (NE, NE) Min, max 0.0*, 76.7* Kaplan-Meier Estimates % (95% CI) 12 months 99.5 (98.6, 99.8) 24 months 99.3 (98.4, 99.7) 36 months 98.9 (97.8, 99.4) 48 months 98.7 (97.5, 99.3)	 12 (1.6) 737 (98.4) NE (NE, NE) NE (NE, NE) NE (NE, NE) 0.0*, 76.0* 99.5 (98.5, 99.8) 99.3 (98.4, 99.7) 98.8 (97.6, 99.4) 98.1 (96.6, 99.0)

Analysis description	**Secondary Analysis – OS**	
Analysis population and time point description	Intent-to-treat population 3+ years after randomisation of the last patient (Updated data cutoff of 31 October 2023).	
Descriptive statistics and estimate variability	BrECADD	eBEACOPP
	n=751 n (%)	n=749 n (%)
	OS (months)	
	Number with events n (%)	
	12 (1.6)	13 (1.7)
	Number censored n (%)	
	739 (98.4)	736 (98.3)
	25th percentile (95% CI)	
	NE (NE, NE)	NE (NE, NE)
	Median (95% CI)	
	NE (NE, NE)	NE (NE, NE)
	75th percentile (95% CI)	
	NE (NE, NE)	NE (NE, NE)
	Min, max	
	0.0*, 86.7*	0.0*, 85.9*
	Kaplan-Meier Estimates % (95% CI)	
	12 months	
	99.5 (98.6, 99.8)	99.5 (98.5, 99.8)
	24 months	
	99.3 (98.4, 99.7)	99.3 (98.4, 99.7)
	36 months	
	98.9 (97.8, 99.4)	98.9 (97.8, 99.4)
	48 months	
	98.6 (97.4, 99.2)	98.2 (96.8, 99.0)
	60 months	
	98.1 (96.5, 98.9)	97.9 (96.4, 98.8)

Effect estimate per comparison	Co-Primary endpoint: TRMB	Comparison groups	BrECADD vs eBEACOPP
		Number of patients with TRMB n (%)	301 (40.3) vs 418 (56.4)
		Relative Risk (stratified analysis) (BrECADD/eBEACOPP)	0.711
		95% CI	(0.639, 0.791)
		Relative Risk (unstratified analysis) (BrECADD/eBEACOPP)	0.714
		95% CI	(0.641, 0.796)
		CMH P-value	<0.0001
		% Difference (unstratified) (BrECADD-eBEACOPP)	-16.1
		Exact 95% CI	(-21.1, -10.9)
	Co-Primary endpoint: PFS IA (2022 data cut)	Comparison groups	BrECADD vs eBEACOPP
		Number of patients with PFS events n (%)	39 (5.2) vs 62 (8.3)
		Hazard ratio	0.619
		95% CI	(0.415, 0.925)
		Multiplicity adjusted 98.87% CI	(0.369, 1.040)
		Unstratified log-rank P-value	0.018
	Note: *indicates censored value		
	Co->Primary endpoint: Updated PFS analysis with 2023 data cut	Comparison groups	BrECADD vs eBEACOPP
		Number of patients with PFS events n (%)	44 (5.9) vs 65 (8.7)

Hazard ratio	0.664
95% CI	(0.453, 0.973)
Unstratified log-rank P-value	0.035
Note: *indicates censored value	

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analyses or meta-analysis have been submitted.

Clinical studies in special populations

Elderly

The main study (randomised cohort) was restricted to patients aged 18 to 60 years.

More than 7 years after initiation of the randomised main study an additional, independent, nonrandomised cohort was introduced that enrolled 85 patients aged between 60 years and 75 years with newly diagnosed, advanced-stage cHL who were precluded by their age from enrolment in the randomised main study. As the BrECADD regimen was shown to be associated with a more favorable toxicity profile (Eichenauer et al. 2017), it was considered that PET-guided BrECADD might be a promising treatment strategy in this older patient population. Study entry criteria, objectives, and endpoints for the older, nonrandomised cohort were defined separately from those of the randomised main study.

The treatment period of the study was ongoing for this cohort at the time of the 31 December 2022 data cut and results for this cohort are to be presented separately from the results for the randomised cohort.

Paediatric patients

Eligibility was restricted to patients aged ≥18 years.

Pregnancy and lactation

No data is available in pregnant or lactating woman.

Supportive study

Comparative study of targeted BEACOPP Variants (BrECADD vs. BrECAPP)[1]

A randomised, open-label phase 2 study of patients with newly diagnosed advanced classical Hodgkin's lymphoma aged 18–60 years. 20 study sites in Germany participated.

Disease

Advanced classical Hodgkin's lymphoma was defined as either: stage IIB disease, defined according to the Ann Arbor staging system, with one or both of the risk factors mediastinal mass (greater than a third of the maximum intrathoracic diameter) and extranodal involvement; or as stage III or IV disease.

Study design

[1] Eichenauer et al. 2017 (NCT01569204)

Patients received six 21-day cycles of either BrECAPP or BrECADD, according to their random assignment.

PET and CT scans for interim staging were conducted between day 17 and day 21 of the second chemotherapy cycle, and these were reviewed by the central response evaluation panel (CREP). Restaging after chemotherapy was CT-based and investigator-assessed, but an additional PET scan and central review of all initial staging and restaging images were indicated in case of residual lymphoma of 2.5 cm or larger.

Patients with either residual lymphoma less than 2.5 cm or PET-negative (ie, Deauville score 1–3) residual lymphoma of 2.5 cm or larger at the restaging after chemotherapy had no further treatment. Patients with PET-positive (ie, Deauville score 4) residual lymphoma of 2.5 cm or larger received consolidating radiotherapy and had their definite CT-based and investigator-assessed restaging 3 months after the end of radiotherapy. Patients with disease progression (ie, Deauville score 5) received off-study salvage treatment according to individual recommendations by the CREP.

Outcomes/Endpoints

Co-primary endpoints:

- proportion of patients achieving a complete response after chemotherapy
    - complete response was defined as achievement of either complete remission, partial remission with residual lymphoma less than 2·5 cm, or PET negativity after chemotherapy, according to the CREP
- proportion of patients achieving complete remission at end of treatment.
    - complete remission was defined as complete remission after completion of study treatment or, in case of residual lymphoma after completion of study treatment, freedom from progression without additional treatment for at least 6 months

Dose and regimen

In the BrECAPP protocol, brentuximab vedotin was administered at 1.8 mg/kg on day 1 in combination with 200 mg/m² etoposide on days 2–4, 1250 mg/m² cyclophosphamide on day 2, 35 mg/m² doxorubicin on day 2, 100 mg/m² procarbazine on days 2–8, and 40 mg/m² prednisone on days 2–15.

In the BrECADD protocol, brentuximab vedotin was administered at 1.8 mg/kg on day 1 in combination with with 150 mg/m² etoposide on days 2–4, 1250 mg/m² cyclophosphamide on day 2, 40 mg/m² doxorubicin on day 2, 250 mg/m² dacarbazine on days 3 and 4, and 40 mg dexamethasone on days 2–5.

Concomitant medication

Application of granulocyte colony stimulating factor and intake of an antibiotic prophylaxis (trimethoprim and sulfamethoxazole [co-trimoxazole], and ciprofloxacin) were mandatory.

Statistical analysis

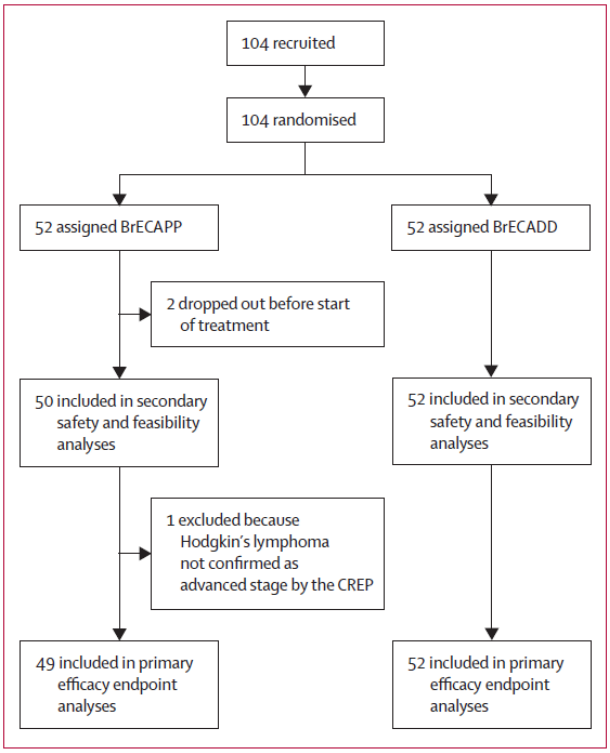
The co-primary efficacy endpoints were tested against fixed response values based on a one sided 97.5% Clopper-Pearson exact binominal CIs for each study group separately. There was no a-priori hypothesis about differences between study groups. Apart from the hypothesis tests described below, all statistical analyses were exploratory.

For *complete response* a threshold of 70% or lower was to be excluded. The second co-primary efficacy endpoint was only to be tested if the null hypothesis for complete response could not be rejected. In this

case, the null hypothesis—ie, *complete remission* of 80% or lower— was tested against a one-sided alternative. The co-primary and secondary endpoint analyses were analysed in the ITT population.

Results

Participant flow



Baseline and disease characteristics

	BrECAPP (n=52)	BrECADD (n=52)
Demographics		
Age (years)	29·5 (18–60)	28·5 (18–59)
Sex		
Women	21 (40%)	20 (38%)
Men	31 (60%)	32 (62%)
WHO activity index		
0 (fully active)	23 (44%)	18 (35%)
1 (able to do light work)	27 (525%)	34 (65%)
2 (unable to do light work)	2 (4%)	0
Ann Arbor stage		
IIB	10 (19%)	8 (15%)
With organ involvement	2	3
IIIA	15 (29%)	9 (17%)
With organ involvement	2	3
IIIB	8 (15%)	12 (23%)
With organ involvement	2	3
IVA	5 (10%)	5 (10%)
With organ involvement	0	0
IVB	14 (27%)	18 (35%)
With organ involvement	5	6
Risk factors		
Large mediastinal mass	21 (40%)	21 (40%)
Extranodal involvement	11 (21%)	15 (29%)
≥3 lymph node areas	44 (85%)	42 (81%)
High erythrocyte sedimentation rate	31 (60%)	39 (75%)
International Prognostic Score[17] (grouped)		
0–2	35 (67%)	33 (63%)
3–7	17 (33%)	19 (37%)

Efficacy results

42 (86%, 95% CI 73–94) of 49 patients assigned to BrECAPP achieved a complete response after chemotherapy and 46 (94%, 95% CI 83–99) had complete remission as their final treatment outcome. In the BrECADD group, 46 (88%, 95% CI 77–96) of 52 patients achieved both a complete response after chemotherapy and complete remission as their final treatment outcome.

	BrECAPP	BrECADD
Restaging after two cycles*		
CR	2/50 (4%)	0/52
CRu	4/50 (8%)	6/52 (12%)
PR	40/50 (80%)	45/52 (87%)
NC	4/50 (8%)	1/52 (2%)
PET after two cycles (Deauville score)		
1	13/49 (27%)	9/52 (17%)
2	7/49 (14%)	14/52 (27%)
3	18/49 (37%)	18/52 (35%)
4–5	11/49 (22%)	11/52 (21%)
Restaging after six cycles†		
CR	4/48 (8%)	3/52 (6%)
CRu	3/48 (6%)	7/52 (13%)
PR	1/48 (2%)	2/52 (4%)
PR (residual ≥2·5 cm)	40/48 (83%)	39/52 (75%)
PD (residual ≥2·5cm)	0/48	1/52 (2%)
PET after chemotherapy (Deauville score)‡		
1	10/40 (25%)	13/40 (33%)
2	9/40 (23%)	13/40 (33%)
3	14/40 (35%)	8/40 (20%)
4–5	7/40 (18%)	6/40 (15%)
Complete response to chemotherapy		
No (further treatment recommended by CREP)	7/49 (14%)	6/52 (12%)
Yes (CR or PR <2·5 cm [local investigator] or no indication for further treatment [CREP])	42/49 (86%)	46/52 (88%)

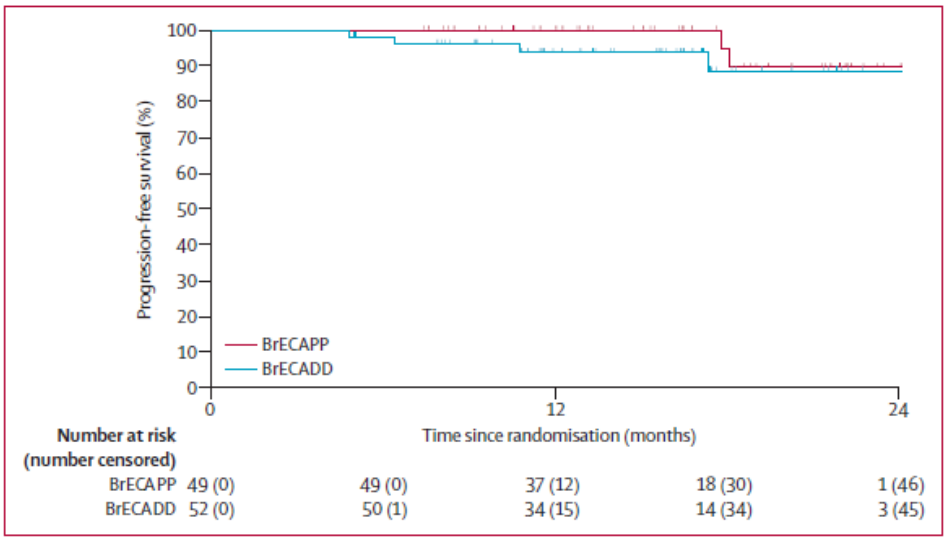


Figure 12 - Progression-free survival in patients treated with BrECAPP or BrECADD

Safety

Table 28 - Randomised Phase 2 Trial and Study HD15 (used 6 cycles of eBEACOPP): Acute Toxicities of Chemotherapy and Dose Reduction

	BrECAPP (n=50)			BrECADD (n=52)			HD15 arm B* (n=695)	
	Grade 1-2	Grade 3	Grade 4	Grade 1-2	Grade 3	Grade 4	Grade 3	Grade 4
Any toxicity	2 (4%)	7 (14%)	40 (80%)	3 (6%)	5 (10%)	41 (79%)	99 (14.4%)	571 (82.0%)
Hematological toxicity	2 (4%)	6 (12%)	40 (80%)	4 (8%)	4 (8%)	41 (79%)	3 (10.5%)	564 (82.0%)
Anemia	25 (59%)	19 (38%)	3 (6%)	29 (60%)	18 (35%)	0	292 (42%)	79 (11.4%)
Thrombocytopenia	12 (24%)	12 (24%)	20 (40%)	17 (32%)	12 (23%)	15 (29%)	143 (20.6%)	228 (32.8%)
Leukopenia	5 (10%)	4 (8%)	40 (80%)	8 (15%)	3 (6%)	41 (79%)	67 (9.8%)	550 (79.0%)
Drug fever	4 (8%)	1 (2%)	0	2 (4%)	0	0		
Infection	7 (14)	3 (6%)	1 (2%)	5 (10%)	7 (13%)	1 (2%)	116 (16.7%)	39 (5.6%)
Renal/urinary toxicity**	0	0	0	3 (6%)	0	0		
Hepatobiliary toxicity**	4 (8%)	3 (6%)	1 (2%)	6 (12%)	1 (2%)	0		
Nervous system, sensory	15 (30%)	1 (2%)	0	0	0	0	32 (4.6%)#	3 (0.4%)#
Nervous system, motory	1 (2%)	0	0	0	0	0		
Heart	0	0	0	0	0	0	4 (0.6%)	1 (0.1%)
Mucositis	10 (20%)	2 (4%)	0	7 (13%)	2 (4%)	0	62 (8.9%)	11 (1.6%)
Gastrointestinal tract	11 (22%)	2 (4%)	1 (2%)	16 (31%)	0	0	39 (5.6%)	6 (0.9%)
Urogenital tract	2 (4%)	0	0	(4%)	1 (2%)	0	3 (0.4%)	0
Respiratory tract	5 (10%)	0	0	8 (15%)	0	0	17 (2.4%)	9 (1.3%)
Treatment at reduced dose in at least one cycle***	19 (40%)			16 (31%)			343 (51%)	

Data are number (%). No death occurred in patients treated with BrECAPP or BrECADD.
* 6 x eBEACOPP
** The documentation of renal/urinary and hepatobiliary toxicities was introduced with a CRF change during the trial. Thus, 88 of 102 patients have complete information, 11 have incomplete information and 3 patients have no information at all regarding these toxicities.
# nervous system, sensory or motory
*** subjects with 6 cycles administered (n=48 with BrECAPP, n=52 with BrECADD, n=672 with eBEACOPP)

3-year follow-up data[2] (2022)

	6 × BrECAPP (*N* = 49)		6 × BrECADD (*N* = 52)	
Observation time				
Observation time for disease status, median	31 months		34 months	
Observation time for survival status, median	35 months		34 months	
3-year survival estimates				
Progression-free survival	90.2% (80.9–99.5%)		89.7% (81.0–98.3%)	
Overall survival	100%		95.4% (89.2–100%)	
Hodgkin lymphoma events[a]				
Any Hodgkin lymphoma event	4	(8%)	4	(8%)
Progression[b]	0		3	(6%)
Relapse[c]	4	(8%)	1	(2%)
Number of Hodgkin lymphoma events				
1	4	(8%)	2	(4%)
2	0		2	(4%)
Second-line treatment				
High-dose chemotherapy and autologous stem cell transplantation	4	(8%)	4	(8%)
Causes of death				
Any event	0		2	(4%)
Hodgkin lymphoma	0		1	(2%)
Accident	0		1	(2%)
Second primary malignancies				
Any event	0		0	

[2] Damaschin et al. 2022

2.4.3. Discussion on clinical efficacy

An extension of indication is sought for brentuximab vedotin to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV Hodgkin Lymphoma (HL) in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD).

Design and conduct of clinical studies

The main clinical data are derived from the phase 3 study HD21, an investigator-initiated, randomised, open-label trial that measured the efficacy vs toxicity of BrECADD versus that of eBEACOPP in terms of a novel coprimary endpoint, treatment-related morbidity (TRMB) along with PFS.

Patients were randomised 1:1 to receive up to 6 cycles of either BrECADD or eBEACOPP on Day 1 of each 21-day treatment cycle. Based on results from the HD18 trial, Protocol Amendment 3 (13 March 2017) altered the study design to include a disease restaging after 2 treatment cycles with PET2-negative patients receiving 2 additional cycles of their allocated treatment and PET2-positive patients receiving 4 additional cycles. This is in accordance with current treatment guideline recommendations (eg. ESMO, NCCN, DGHO) and allows for adequate comparison between treatment arms.

Choice of comparator

eBEACOPP is an effective and established frontline treatment regimen in advanced-stage HL (ESMO, DGHO). Compared to ABVD (doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine), another established treatment option in this clinical setting, eBEACOPP has shown superior initial disease control and prolonged time-to-relapse but is associated with higher rates of early and late toxicities.

For the selection of adequate candidates for improving the B/R comparing to eBEACOPP, a study that investigated two modifications of eBEACOPP was used. This was a Phase 2 study (targeted BEACOPP Variants): BrECADD vs. BrECAPP (Eichenauer et al. 2017, Damaschin et al. 2022). In both regimens brentuximab vedotin replaced bleomycin and vincristine. While BrECAPP used the exact same backbone as eBEACOPP there were several modifications to the backbone chemotherapy of BrECADD to optimise the safety profile (see discussion of results).

Both regimens met the co-primary endpoint for complete response to chemotherapy (complete response rate significantly > 70%) and BrECAPP also met the second co-primary endpoint for complete remission at the end of treatment (complete remission rate significantly > 80%).

Both regimens showed an improved safety profile for Grade 3 and 4 events compared to 6 cycles of eBEACOPP (data presented from the HD15 trial) with a slight tendency in favour of BrECAPP in terms of acute toxicities (fewer Grade 4 non-haematological toxicities and Grade 3 haematological toxicities). Interestingly, although vincristine has been replaced by BV in both the BrECADD and BrECAPP regimen, peripheral neuropathy was only observed in the BrECAPP group while no events occurred in the BrECADD group. Furthermore, compared to eBEACOPP the incidence of PN was considerably higher for BrECAPP (4.6% vs 30%) which will likely have impacted the decision towards BrECADD as comparator in the HD21 trial instead of BrECAPP.

Considering the anticipated effect on long-term toxicities such as fertility and second malignancies along with the largely similar efficacy observed in the Phase 2 trial, the choice of BrECADD (with an adapted backbone regimen) over BrECAPP as comparator for the HD21 trial is deemed comprehensible. The lower number of patients who received a treatment cycle at a reduced dose in the BrECADD arm (31% vs BreCAPP 40% vs eBEACOPP 51%) is also considered supportive in this regard.

Choice of endpoints

The primary objective of this trial was to reduce toxicity without sacrificing efficacy. While PFS is an established outcome measure in clinical oncology trials, the same does not apply to TRMB which was introduced as a parameter that includes relevant toxicities of primary chemotherapy.

For organ toxicities, Grade 3 and 4 events were included as those occurred in approximately 15% of patients treated with eBEACOPP (trials HD15 and HD18) and are often associated with severe or irreversible symptoms in need of medical intervention that may be potential life-threatening. These toxicities may also result in treatment delay and/or dose reduction, which may ultimately impact treatment efficacy.

For haematological toxicity, only grade 4 events were included in the TRMB endpoint although almost all patients experience grade 3/4 events after treatment with eBEACOPP. This was justified by the good handling of grades 1-3 toxicities in clinical practice whereas grade 4 anemia and thrombocytopenia may cause life-threatening events that require medical intervention and hemosubstitution as preventive measures.

The chosen toxicities – especially the haematological toxicities - are deemed of relevance in the frontline treatment of patients with newly diagnosed HL. Thus, a reduction of these toxicities is considered to be a favourable effect of BrECADD.

The secondary endpoints, which included CR, OS, infertility rate at 1 year, second malignancies, incidence of AEs, therapy adherence and QoL, are acceptable.

Choice of non-inferiority margin for PFS

PFS was to be tested for non-inferiority. The margin was derived based on results from a previous trial (HD15) from which a 5-year PFS rate of 90.5% was deduced. Additionally, it was assumed that a 6% (absolute) difference in 5-year PFS would be clinically meaningful, leading to a non-inferiority margin for the HR of 1.69. The size of the margin on the HR scale is considered large and not well justified. The observed HR, however, deviated substantially from the assumed HR of 1 (see Efficacy data and additional analyses section below) and thus the selection of the NI margin is not an issue impacting this application. This led to an upper bound of the multiplicity-adjusted confidence interval of 1.040 in the inferential PFS analysis (data cutoff 31 Dec 2022). The observed margin is hence much smaller and not of concern. Non-inferiority was clearly achieved in the overall population.

Blinding

The study was an open-label study. As the DMC was not blinded to treatment allocation and the trial statistician was unblinded as well and was a participant of the closed session of the DMC meetings, concerns were raised on the conduct of a (pivotal) study. The decision on the endpoint hierarchy and introduction of a PFS interim analysis was based on the maturity of the TRMB data which seems to confirm that all data for TRMB and rather mature data for PFS was indeed known at the time of these changes and hence these changes can be considered data driven. This is not in line with the guideline on data monitoring committees (EMEA/CHMP/EWP/5872/03 Corr), which requires pre-specification of potential changes which might be recommended by the DMC. The unplanned ad-hoc changes in this study mean that type 1 error control was no longer maintained and hence these changes are not supported. Also the MAH might have been unblinded before finalizing the SAP – see *Data cutoff and transfer*.

Given the reported effect of the investigational arm on TRMB and PFS was shown to be non-inferior (see Efficacy data and additional analyses section below) the overall trial outcome seemingly was not meaningfully impacted by these changes in the given situation.

Randomisation

Treatment allocation was based on a minimisation approach. The details show that the scoring itself, which was used with a probability of 75%, was essentially deterministic. Only with a probability of 25%, a simple random sample was used to allocate subjects. The MAH claimed that randomisation was stratified by age, sex, country and IPS score. The details of the minimisation algorithm, however, revealed that the most important stratification factor was the study centre which had a weight of 1.1 in the scoring rule, while the other strata had a combined weight of 0.25 only. The relatively high weight of trial site in the scoring rule leads to a reasonably predictable allocation at a given site, based on the scoring rule. Given that the minimisation algorithm has a relevantly large random component as in 25% of all cases a simple random allocation is used, the predictability of subsequent treatment allocation is partially concealed. Overall, the approach is considered acceptable.

Statistical aspects

Overall, the finally defined analyses are endorsed. Censoring rules of the primary analysis are overall endorsed. Sensitivity analyses censoring progressions after missed visits are not considered relevant as highlighted in Appendix 1 to the guideline on the evaluation of anticancer medicinal products in man (EMA/CHMP/27994/2008/Rev.1). In the primary analysis, the initiation of a new anticancer therapy was ignored and PFS was recorded regardless of whether a patient had received an additional therapy. The initiation of a subsequent therapy could be a sign of inadequate response or even progression, and it impacts the progression of patients thereafter. No estimands were defined in the protocol or SAP; upon request the MAH specified the targeted estimands post hoc. For TRMB the targeted estimand does not align with the estimate. While it is postulated that the estimand addressed the relative difference in TRMB *in all eligible patients*, the primary estimate seems to rather target the relative difference in TRMB *in all patients who received at least one dose of treatment*. It is furthermore noted that some patients did prematurely terminate treatment. No toxicities were recorded for these patients, who hence could not contribute to TRMB. For PFS, the primary estimand in which the initialization of subsequent anticancer therapy was ignored (treatment policy strategy) does not seem to reflect a clinically meaningful question for the PFS endpoint. Sensitivity analyses are discussed below.

Conduct of the trial

The study protocol was amended 9 times. Not all protocol amendments might have influenced the conduct of trial in the same way. Notably, with Protocol Version 4 (13 March 2017) the treatment schedule of the trial was modified. Two PET/CT scans one after two cycles and one after the end of chemotherapy were added and a decision for the subsequent treatment was based on these PET/CT scan results (PET2 negative subjects were to receive 2 additional cycles versus 4 additional cycles for PET2 positive subjects; an additional radiotherapy was given after completion of all cycles based on PET/CT positivity). Additional subgroup analyses were provided to assess the impact of this change.

With Amendment 7 (20 July 2021) the test hierarchy for the primary endpoints was reversed. Previously, TRMB was planned to be tested only after PFS was shown to be non-inferior; the meeting minutes of the DMC Meeting on 03 March 2022 were provided, where PFS results were qualitatively reported to the Sponsor. The DMC raised the problem that the publication of interim results might induce bias and impact the conduct of study. This is supported. However, it was also stated that "*PFS as a measure of efficacy can only provide information, that the non-inferiority is very likely but not yet statistically significant*". – which implies information was shared to the core study group that might have impacted the conduct of study. Indeed the subsequent protocol amendment included an interim analysis for PFS, introducing substantial uncertainties with respect to the credibility and robustness of the results. To rule out or at least minimize the impact of data-driven decisions, the MAH was asked to provide tipping point analyses for PFS. These showed that given the interim results, only in very extreme cases non-inferiority would not have been met (i.e., if 47 out of the remaining 53 events would have occurred in the BrECADD arm) at

the initially pre-planned primary analysis and in reasonable, although not extreme, scenarios (with up to 25 of 53 events in the BrECADD arm) even superiority would have been met.

The final amended SAP was finalized on 13 Apr 2023, which is much later than Protocol Amendment 8 and after the primary data cut, which was on 31 Dec 2022.

Data sets and planned analyses

Data from an interim analysis with data cutoff 31 December 2022 along with updated data from a cutoff 31 October 2023 form the basis of the current application. Study closure is planned for December 2024 after approximately 5 years of median follow-up. About 6 months afterwards, a descriptive analysis of PFS is planned. The MAH committed to submit the final results as CSR addendum as a post-authorisation measure (REC).

Supportive study – targeted BEACOPP variants (BreCADD versus BrECAPP)

The study of targeted BEACOPP Variants compared the modified regimens BrECADD and BrECAPP in patients with advanced Hodgkin lymphoma defined as Stage IIB with one or both risk factors mediastinal mass and extranodal involvement, Stage III or IV disease. Patients received 6 cycles of either BrECADD or BrECAPP with interim staging after two cycles of chemotherapy. The co-primary endpoints were the proportion of patients achieving a complete response after chemotherapy and the proportion of patients achieving complete remission at end of treatment. The overall study design is acceptable and the study population is representative of patients with advanced HL.

Efficacy data and additional analyses

Data cutoff and transfer

Data cut for analysis was 31 December 2022. Analysis of TRMB was to be performed approximately 1 year after randomization of the last patient. The last patient was randomized on 27 August 2020. According to the CSR, study results for the primary endpoint were reviewed by the DMC in March 2022. The MAH was asked to provide the initial analyses for TRMB and PFS as conducted by the DMC, as these were the analyses which led to the actual rejection of the null hypothesis and hence are the only analyses under type 1 error control. All further analyses with different analysis sets or different data cutoffs are deemed descriptive updates. It is noted, that these updates are very relevant to understand the impact of data cleaning, the used analysis sets and to substantiate the observed treatment effect, especially for the early PFS analysis. However, type 1 error control is no longer possible in these analyses, neither for TRMB with a single analysis time point, nor for the group sequential analyses of PFS. Unfortunately, the MAH was not able to provide these analyses without any relevant justification. Given the overall effect sizes and assumingly small changes due to the updates, the issue was not further pursued.

The data was transferred from the GHSG to the MAH at multiple times: A partial masked data transfer (plan dated 03 Jan 2023, data transfer on 20 Jan 2023), a full masked data transfer (plan dated 24 Feb 2023, data transfer on 24 Mar 2023), and an unmasked data transfer (plan dated 26 Apr 2023, data transfer on 11 May 2023); the final data transfer took place on 09 Nov 2023 based on data extracted on 06 Nov 2023. The data cutoff was defined as a much earlier date (31 Dez 2022, i.e. ~ 10 months earlier). It was noted during assessment that it remains unclear if the masking was adequate given that the data transfer plans only requested that data which contained information on the treatment allocation was to be separated from the core data sets. No request to shuffle or modify this data (e.g. by using dummy data) was specified in the data transfer plans. It might have hence been possible that the MAH was unblinded before finalizing the SAP given that the final data cutoff was before the first data transfer and given that the SAP was finalized only after the full masked data transfer.

Study population

The ITT population consisted of 751 patients in the BrECADD treatment group and 749 patients in the eBEACOPP treatment group. The demographic and baseline characteristics of the HD21 study population were well balanced between the treatment groups. The majority of patients was between the ages of 18 and 44, had nodular sclerosis cHL with Ann Arbor Stages III and IV and B-symptoms present. The study population is deemed to be representative of newly diagnosed patients with Stage IIB, III or IV cHL who would be considered suitable for treatment with escalated polychemotherapy.

In the BrECADD arm distinctly fewer patients received RBC transfusions and platelet infusions (differences of 28.2% and 27.7%, respectively) compared to eBEACOPP. This is deemed of clinical relevance as haematological toxicity is a predominant and known side effect of several chemotherapeutic components. In the eBEACOPP regimen this would in particular apply to etoposide, which was reduced in the BrECADD regimen. Anemia and thrombocytopenia are known (common/very common) adverse drug reactions of brentuximab vedotin. A reduction of RBC infusions or platelet infusions is therefore considered of relevance in the B/R evaluation of the BrECADD regimen.

Co-primary endpoint TRMB

The co-primary endpoint TRMB was met as a statistically significant reduction in TRMB was demonstrated (TRMB BrECADD: 42.0%, eBEACOPP 58.7%).

The main improvement of the safety profile was attributed to the reduction of haematological toxicities (BrECADD: 31.2% vs eBEACOPP: 52.1%) while organ toxicity was slightly increased in the BrECADD arm compared to the eBEACOPP arm (18.6% vs 17.4%).

GI and hepatobiliary disorders, which were the main drivers for the observed imbalances between the treatment arms, are identified adverse events associated with brentuximab vedotin. SAEs such as diarrhea, abdominal pain, colitis and neutropenic colitis were observed with a higher frequency in the BrECADD arm, although these events occurred overall with low frequencies (between 0.8 and 2.8%). Interestingly, the number of patients requiring dose modification or treatment delay was low and similar between the treatment arms which suggests that these toxicities seem to be manageable in clinical practice. The SmPC of Adcetris already includes information about gastrointestinal complications and hepatotoxicity, which is considered sufficient.

As most GI events were transient and patients were able to receive full treatment courses (which will ultimately impact the outcome of the patients), the slight increase in organ toxicity appears to be acceptable in light of the generally improved safety profile.

Interestingly, peripheral neuropathy as TRMB occurred almost twice as often in the eBEACOPP arm. Hence, although this is a common known toxicity associated with brentuximab vedotin, its replacement of vincristine led to a distinct reduction of peripheral neuropathies in the BrECADD arm compared to eBAECOPP thereby improving the safety profile.

For the remaining organ toxicities “renal or urinary disorders” and “respiratory, thoracic and mediastinal disorders” TRMB was lower in the BrECADD arm. The latter may be attributed to the omission of bleomycin which is known for its pulmonary toxicity. Consequently, due to its contraindication for concomitant use with brentuximab vedotin, the safety profile of BrECADD was further improved.

Regarding the reduction of haematological toxicity, apparently this effect is primarily driven by the replacement of procarbazine with dacarbazine and also potentially due to the etoposide dose reduction. A contribution of brentuximab vedotin is not likely considering that anemia and thrombocytopenia are common ADRs associated with brentuximab vedotin. The lower incidence of haematological toxicity is accompanied by a reduction of red cell transfusions and platelet infusions. This is deemed of clinical relevance.

In conclusion, although brentuximab vedotin only partially contributed to the improved safety profile, the modifications to the backbone of the BreCADD regimen are nevertheless considered meaningful for HL patients receiving first-line treatment as it offers a reduction of clinically relevant toxicities.

The subgroup analyses for TRMB were all supportive of the results in the overall safety population. The only exception are patients with ECOG2 at baseline. However, this effect is attributed to the very small number of patients (N=11 BrECADD and N=18 eBEACOPP). In general, it appears that organ toxicity is higher compared to the overall population in patients with less favourable baseline or disease factors such as age (45-60 years), Ann Arbor Stage 4, Pet-positivity, B-symptoms and ECOG 1. For all of these subgroups the main toxicity drivers are GI and hepatobiliary toxicities. Analysis according to PET status were comparable for PET-positive and PET-negative patients. The same applies for the analysis according to number of treatment cycles (4 vs 6 cycles).

Co-primary endpoint PFS

The co-primary endpoint of PFS was met with 39 PFS events (5%) reported for the BrECADD group and 62 PFS events (8%) for the eBEACOPP group. PFS was even numerically superior in the BrECADD arm, despite non-inferiority being the objective of the trial. For a detailed discussion of the non-inferiority margin, see above.

Updated PFS data were provided. Only few additional PFS events were reported since the last cutoff of 31 December 2022 (BrECADD N=5 and eBEACOPP N=3) which was to be expected considering the disease and treatment line. PFS results were still in favour of BrECADD with a HR of 0.664 (95% CI 0.543, 0.973).

PFS was assessed by investigator but was centrally confirmed. PFS results were in favour of BrECADD up to 48 months. It is noted that both in the overall PFS analysis as well as in the subgroup analyses that the numbers reported with and without central confirmation seemed identical. The MAH clarified that blinded central review was used for all cases to confirm response at end of treatment and that at all other time points for which scans were obtained upon investigators' clinical suspicion of disease progression, only cases for which progression had been determined were then sent for central review.

Further sensitivity analyses of PFS were conducted with censoring at >1 consecutively missing assessment and receipt of subsequent anticancer therapy before PFS event, respectively, all of which are supporting the results of the primary analysis. Censoring subjects when receiving a subsequent therapy without prior confirmed disease progression leads to the assumption that the initiation of a new therapy is rather an indicator of disease progression. In any case it is not plausible that patients who received a new anticancer therapy would have behaved as all other subjects. A competing risk analysis was provided where subsequent anticancer therapy without prior PD was considered a competing event and an analysis where these events were considered as PD. These analyses showed that of the 33 subjects who received subsequent anticancer therapy prior to PD, 24 might be considered related to treatment and could be considered either as a competing event or as PD. The competing risk analysis showed a slightly stronger benefit of BrECADD as compared to eBEACOPP (HR = 0.633; 95% CI: 0.426, 0.941), while the analysis treating these events as progression showed a slightly reduced benefit (HR = 0.766; 95% CI: 0.539, 1.089).

Overall PFS results were clearly in favour of the BrECADD regimen thereby supporting that BV contributes to a certain and relevant extent to the efficacy of this regimen. Moreover, the modifications to the chemotherapy backbone are not expected to have a major impact on efficacy that would lead to the observed PFS rates in favour of the BrECADD regimen. Procarbazine and dacarbazine have shown to exert

similar efficacy in patients with HL[3]. The replacement of procarbazine with dacarbazine was mainly because of a different safety profile which has also led to its replacement in other regimen[4]. Moreover, bleomycin and vincristine have been omitted which would consequently lead to a "loss" in efficacy. The etoposide dose was reduced. Hence, no increase in efficacy is to be expected from this change. The slight increase of doxorubicin from 35mg/m² to 40 mg/m² is very likely not the sole driver of the observed improvement in PFS for BrECADD compared to eBEACOPP.

Taking all these aspects into account, BV is deemed to have a relevant part in the efficacy of the BrECADD regimen.

Subgroup analyses of PFS by INV were supportive of ITT results. Results for patients in the age group 45-60 years (HR 0.992) as well as for PET-positive patients (HR 0.913) deviated from those of the overall population with a HR closer to 1. For PET positivity the 95%CI was still within the predefined non-inferiority margin of 1.69, which is reassuring. For the age group the 95%CI was slightly outside the margin. However, as the point estimate was below 1 benefit is still demonstrated. Interestingly, results for TRMB were slightly in favour of this age group compared to younger patients (18-44 years).

Secondary endpoints

Responses measured by CR and ORR are comparable between the treatment arms slightly favouring BrECADD. Results for DOR and DOCR are in accordance with the PFS results which are also favouring the BrECADD arm.

As expected in this indication and line of treatment the number of deaths was low and comparable between the treatment arms at both data cutoffs of 31 December 2022, and with the updated data on OS with a cut off of 31 October 2023.

There was no major difference in PET2-negativity between the treatment arms.

Slightly fewer patients in the BrECADD arm had PET-positive residual lesions as well as subsequent radiotherapy (in accordance with current treatment guidelines) after completion of therapy. The same effect was observed for the number of patients with subsequent anticancer therapy indicating that BrECADD provides good initial disease control.

Patient-reported outcome assessments were overall showing a slight trend in favour of BrECADD from 12/18 to 36 months.

Slightly more patients in the BrECADD arm were overall hospitalized as well as hospitalised due to neutropenic fever which is reasonable considering the higher rate of febrile neutropenia (see section 5.5 of this AR) in the BrECADD arm. However, in both cases the median number of days of hospitalisation was comparable between the treatment groups.

Supportive study – targeted BEACOPP variants (BreCADD versus BrECAPP)

The observed outcomes were largely comparable although results for complete remission were slightly more favourable for BrECAPP: complete response (BrECADD 88%, BrECAPP 86%), complete remission (BrECADD 88%, BrECAPP 94%). This may be attributed to the fact that patients in the BrECADD arm had slightly more advanced disease (Ann Arbor stages IIIB and IVB) and risk factors (extranodal involvement and high ESR) compared to the BrECAPP arm.

In a 3-way comparison with eBEACOPP data from the HD15 trial, the number of patients with any toxicity is overall comparable. Fewer patients reported non-hematologic Grade 4 events in the BrECADD arm

[3] Christine Mauz-Körholz et al., Procarbazine-Free OEPA-COPDAC Chemotherapy in Boys and Standard OPPA-COPP in Girls Have Comparable Effectiveness in Pediatric Hodgkin's Lymphoma: The GPOH-HD-2002 Study. JCO 28, 3680-3686(2010).DOI:10.1200/JCO.2009.26.9381
[4] https://doi.org/10.1182/blood-2022-166543, last accessed 09 Nov 2024

compared to BrECAPP and eBEACOPP. In addition, the overall number of patients with any Grade 3 hematologic events is also lower in the BrECADD group (8% vs BrECAPP 12% vs eBEACOPP 10.5%) while Grade 4 haematological toxicitiy has been oberserved in a similar high frequency of around 80%. Toxicties that occurred more frequently in the BrECADD group compared to BrECAPP included Grade 3 infection (13% vs 6%) and the Grade 1-2 events renal toxicity (6% vs 0%) and respiratory tract toxicity (15% vs 10%). Conversely, Grade 1-2 drug fever (4% vs 8%) and mucositis (13% vs 20%) were reported for fewer patients in BrECADD. Moreover, there was a shift from Grade 3 events to Grade 1-2 events in favour of BrECADD for GI and hepatobiliary toxicity.

Overall, both BrECADD and BrECAPP showed an improved safety profile for Grade 3 and 4 events compared to 6 cycles of eBEACOPP with a slight tendency in favour of BrECAPP in terms of acute toxicities.

2.4.4. Conclusions on the clinical efficacy

Brentuximab vedotin has already demonstrated efficacy in the frontline setting of cHL (in combination with AVD) as well as in the relapsed/refractory setting as monotherapy. The co-primary endpoints TRMB and PFS with the new proposed treatment regime, have been met in study HD21. The clinical relevance of the altered and to some extent improved safety profile of BrECADD compared to eBEACOPP is considered meaningful for HL patients receiving first-line treatment. Following a recommendation from the CHMP, the MAH will provide the final results from study HD21.

2.5. Clinical safety

Introduction

The safety results for study HD21 (randomised main cohort) are presented from analysis of accumulated data as of the 31 December 2022 cutoff for data analysis and with updated data at the cut off of 31st October 2023, at which time all patients in the safety population had completed the treatment period of the randomised main study.

The safety profile of the 2 treatment regimens administered to study participants was defined by TRMB (see Section 2.4.2 of this report) and the other AEs that reflected acute and late toxicities.

In addition to acute toxicities defined by TRMB, the study also included assessments to evaluate late toxicities (including second malignancies and fertility assessment) associated with frontline treatment regimens for patients with advanced stage cHL.

AEs that were not documented by the 19 prespecified CTCAE toxicity terms previously described were classified according to MedDRA Version 25.1 and their severity graded according to CTCAE version 4.0, effective 29 Aug 2009.

Safety assessments are ongoing during PTFU until planned study end. LPLV is currently defined as a time point 5.5 years after the last patient was randomised to treatment in the randomised main study.

Patient exposure

A total of 747 BrECADD patients and 741 eBEACOPP patients received at least 1 dose of any study drug in the protocol-defined treatment regimen. A treated cycle was a 21-day period in which the patient received any amount of the individual drugs in the treatment regimen.

Treated patients across the 2 treatment groups received a median of 4 cycles of study treatment (range, 1-6 cycles) over a median of 72 days (range, 5-166 days) for BrECADD patients and 82 days (range, 1-172 days) for eBEACOPP patients.

The PET2-negative patients received a median of 4 cycles of therapy (range, 2-6 cycles for BrECADD patients; 3-6 cycles for eBEACOPP patients), and PET2-positive patients received a median of 6 cycles (range, 3-6 cycles across treatment groups).

Approximately 58% of patients in the safety population were PET2 negative and 31% of patients were PET2 positive. Almost all of PET2-negative patients (98.2% of BrECADD patients and 99.5% of eBEACOPP patients) received 4 cycles of therapy. Similarly, 96.6% of PET2-positive patients across treatment groups received 6 cycles of therapy.

Table 29 - Study HD21: Dose Levels by Cycle (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
All Cycles	747	741
Cycle 1		
Dose level 4 (full dose)	745 (99.7)	738 (99.6)
Dose level 3	0	0
Dose Level 2	0	0
Dose level 1	1 (0.1)	0
Baseline	1 (0.1)	3 (0.4)
Cycle 2		
Dose level 4 (full dose)	669 (89.6)	582 (78.5)
Dose level 3	63 (8.4)	143 (19.3)
Dose level 2	0	2 (0.3)
Dose level 1	0	1 (0.1)
Baseline	1 (0.1)	2 (0.3)
Cycle 3		
Dose level 4 (full dose)	634 (84.9)	522 (70.4)
Dose level 3	75 (10.0)	157 (21.2)
Dose level 2	9 (1.2)	23 (3.1)
Dose level 1	0	1 (0.1)
Baseline	11 (1.5)	24 (3.2)
Cycle 4		
Dose level 4 (full dose)	563 (75.4)	426 (57.5)
Dose level 3	115 (15.4)	181 (24.4)
Dose level 2	20 (2.7)	52 (7.0)
Dose level 1	0	9 (1.2)
Baseline	25 (3.3)	56 (7.6)
Cycle 5		
Dose level 4 (full dose)	206 (27.6)	144 (19.4)
Dose level 3	50 (6.7)	64 (8.6)
Dose level 2	13 (1.7)	32 (4.3)
Dose level 1	1 (0.1)	2 (0.3)
Baseline	19 (2.5)	46 (6.2)
Cycle 6		
Dose level 4 (full dose)	191 (25.6)	121 (16.3)
Dose level 3	49 (6.6)	65 (8.8)
Dose level 2	20 (2.7)	26 (3.5)
Dose level 1	1 (0.1)	13 (1.8)
Baseline	23 (3.1)	57 (7.7)

Source: Table 15.3.7.2.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.
Percentages were calculated using the safety population as denominator.

Therapy adherence

Therapy adherence was a secondary endpoint of the randomised main study. Results suggested a higher therapy adherence rate for BrECADD patients than for eBEACOPP patients. No dose adjustments were reported for 59% of BrECADD patients and 34% of eBEACOPP patients in the safety population.

Both dose reductions and treatment delays were reported for a higher proportion of eBEACOPP patients than BrECADD patients over the entire treatment period and at most treatment cycles. Over the entire treatment period, at least 1 dose reduction was reported for 243 BrECADD patients (32.5%) and 452 eBEACOPP patients (61%) and a treatment delay for 114 BrECADD patients (15.3%) and 160 eBEACOPP patients (21.6%). A shorter overall treatment duration (a median of 72 days) was reported for BrECADD patients than for eBEACOPP patients (a median of 82 days).

Adverse events

Table 30 - Study HD21: Overview of Safety Profile (Safety Population)

No. of patients (%)	BrECADD N=747	eBEACOPP N=741
Any TEAE	745 (99.7)	741 (100)
Treatment-related TEAE	743 (99.5)	738 (99.6)
Grade 3 or higher TEAE	682 (91.3)	717 (96.8)
Treatment-related Grade 3 or higher TEAE	679 (90.9)	706 (95.3)
SAE	328 (43.9)	310 (41.8)
Treatment-related SAE	294 (39.4)	270 (36.4)
SAEs leading to treatment discontinuation	15 (2.0)	15 (2.0)
AE resulting in dose modification	300 (40.2)	486 (65.6)
Dose reduction	243 (32.5)	452 (61.0)
Treatment delay	114 (15.3)	160 (21.6)
Grade 5 TEAE	4 (0.5)	3 (0.4)
Death due to treatment-related AE	3 (0.4)	3 (0.4)
On-study death	3 (0.4)	2 (0.3)
Follow-up deaths	0	1 (0.1)

Source: HD21 Table 15.3.1.1.
AE: adverse event; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; eCRF: electronic case report form; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event; TEAE: treatment-emergent adverse event.
A TEAE was defined as any AE that occurred after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Treatment related refers to causal relationship to study medication as possible, probable, or certain, per the eCRF.
On-study deaths were defined as deaths that occurred between the first dose of study drug and up to 30 days of the last dose of any study drug; follow-up deaths were defined as deaths that occurred 30 days after the last dose of therapy.

Table 31 - Study HD21: TEAEs of Any Grade Reported for at Least 10% of Patients by CTCAE Toxicity or PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
At least 1 TEAE	745 (99.7)	741 (100)
CTCAE Toxicity	744 (99.6)	741 (100)
Anaemia	712 (95.3)	725 (97.8)
Leukopenia	697 (93.3)	724 (97.7)
Thrombocytopenia	645 (86.3)	689 (93.0)
Nausea/vomiting	411 (55.0)	464 (62.6)
Infection	400 (53.5)	372 (50.2)
GI disorders (except nausea, vomiting, mucositis)	398 (53.3)	334 (45.1)
Peripheral sensory neuropathy	291 (39.0)	362 (48.9)
Skin and subcutaneous tissue disorders	286 (38.3)	317 (42.8)
Respiratory, thoracic and mediastinal disorders	283 (37.9)	356 (48.0)
Mucositis	217 (29.0)	244 (32.9)
Febrile neutropenia	198 (26.5)	145 (19.6)
Nervous system disorders (except neuropathy)	193 (25.8)	208 (28.1)
Hepatobiliary disorders	172 (23.0)	152 (20.5)
Cardiac disorders	155 (20.7)	139 (18.8)
Renal and urinary disorders	71 (9.5)	95 (12.8)
Other Toxicities (PT)	468 (62.7)	513 (69.2)
Fatigue	223 (29.9)	207 (27.9)
Neutropenia	75 (10.0)	85 (11.5)

Source: HD21 Table 15.3.1.3.2.

Treatment-related TEAEs of any grade

At least 1 treatment-related TEAE of any grade was reported for 743 BrECADD patients (99.5%) and 738 eBEACOPP patients (99.6%).

Among the most commonly reported treatment-related CTCAE toxicities of any grade, a ≥5% higher frequency of thrombocytopenia (6.9%), nausea/vomiting (7.8%), peripheral sensory neuropathy (9.4%), Skin and subcutaneous tissue disorders (5.4%), Respiratory, thoracic and mediastinal disorders (11.6%) was reported for eBEACOPP patients than BrECADD patients, whereas a ≥5% higher frequency of GI disorders (excluding nausea, vomiting, mucositis) (8.8%) and febrile neutropenia (7.1%) was reported for BrECADD patients than eBEACOPP patients.

Table 32 - Study HD21: Treatment-related TEAEs of Any Grade by CTCAE Toxicity or PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
At least 1 treatment-related TEAE of any grade	743 (99.5)	738 (99.6)
CTCAE Toxicity	742 (99.3)	738 (99.6)
Anaemia	692 (92.6)	707 (95.4)
Leukopenia	689 (92.2)	718 (96.9)
Thrombocytopenia	638 (85.4)	684 (92.3)
Nausea/vomiting	401 (53.7)	456 (61.5)
GI disorders (except nausea, vomiting, mucositis)	341 (45.6)	273 (36.8)
Infection	326 (43.6)	306 (41.3)
Peripheral sensory neuropathy	282 (37.8)	350 (47.2)
Skin and subcutaneous tissue disorders	231 (30.9)	269 (36.3)
Mucositis	211 (28.2)	232 (31.3)
Febrile neutropenia	197 (26.4)	143 (19.3)
Respiratory, thoracic and mediastinal disorders	185 (24.8)	270 (36.4)
Nervous system disorders (except neuropathy)	162 (21.7)	159 (21.5)
Hepatobiliary disorders	153 (20.5)	132 (17.8)
Cardiac disorders	97 (13.0)	92 (12.4)
Other Toxicities (PT)	415 (55.6)	443 (59.8)
Fatigue	219 (29.3)	196 (26.5)
Neutropenia	75 (10.0)	83 (11.2)

Source: Table 15.3.1.4.1.
AE: adverse event; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CTCAE: Common Terminology Criteria for Adverse Events; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GI: gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.
Percentages are calculated using the safety population as denominator.
A patient was counted once for each CTCAE toxicity or PT. Grade 3 or higher febrile neutropenia included in the summary.
BrECADD group sorted by decreasing frequency for CTCAE toxicity term or PT.
MedDRA 25.1 was applied.

Grade 3 or higher TEAEs

Grade 3 or higher TEAEs were reported for a higher proportion of eBEACOPP patients and Grade 3 or higher leukopenia was the most commonly reported Grade 3 CTCAE toxicity across treatment groups.

At least 1 Grade 3 or higher TEAE was reported for 682 BrECADD patients (91.3%) and 717 eBEACOPP patients (96.8%) and included at least 1 Grade 3 or higher CTCAE toxicity reported for 679 BrECADD patients (90.9%) and 716 eBEACOPP patients (96.6%).

Grade 3 or higher leukopenia was reported for 646 BrECADD patients (86.5%) and 698 eBEACOPP patients (94.2%). The Grade 3 or higher CTCAE toxicities reported for at least 20% of BrECADD patients were leukopenia (86.5% of patients), thrombocytopenia (55%), anaemia (29.5%), infection (28.1%), and febrile neutropenia (26.5%).

The Grade 3 or higher CTCAE toxicities reported for at least 20% of eBEACOPP patients were leukopenia (94.2% of patients), thrombocytopenia (71.9%), anaemia (58.7%), and infection (24.7%).

Treatment-related Grade 3 or higher TEAEs

At least 1 treatment-related Grade 3 or higher TEAE was reported for 679 BrECADD patients (90.9%) and 706 eBEACOPP patients (95.3%) and included at least 1 CTCAE toxicity term for 676 BrECADD patients (90.5%) and 706 eBEACOPP patients (95.3%).

Table 33 - Study HD21: Treatment-related Grade 3 or Higher TEAEs Reported for at Least 1% of Patients by CTCAE Toxicity Terms or PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
At least 1 treatment-related Grade 3 or higher TEAE	679 (90.9)	706 (95.3)
CTCAE Toxicity Grade 3 or higher	676 (90.5)	706 (95.3)
Leukopenia	642 (85.9)	691 (93.3)
Thrombocytopenia	406 (54.4)	527 (71.1)
Anaemia	218 (29.2)	426 (57.5)
Infection	197 (26.4)	143 (19.3)
Febrile neutropenia	191 (25.6)	159 (21.5)
GI disorders (except nausea, vomiting, mucositis)	51 (6.8)	23 (3.1)
Hepatobiliary disorders	36 (4.8)	18 (2.4)
Mucositis	30 (4.0)	43 (5.8)
Respiratory, thoracic and mediastinal disorders	24 (3.2)	25 (3.4)
Nausea/vomiting	18 (2.4)	25 (3.4)
Cardiac disorders	13 (1.7)	9 (1.2)
Nervous system disorders (except neuropathy)	9 (1.2)	19 (2.6)
Peripheral sensory neuropathy	9 (1.2)	16 (2.2)
Skin and subcutaneous tissue disorders	7 (0.9)	8 (1.1)
Drug fever	6 (0.8)	9 (1.2)
Other Toxicities (PT) Grade 3 or higher	144 (19.3)	158 (21.3)
Neutropenia	71 (9.5)	80 (10.8)
Neutrophil count decreased	20 (2.7)	21 (2.8)
Fatigue	11 (1.5)	8 (1.1)
Lymphocyte count decreased	5 (0.7)	11 (1.5)

Source: Table 15.3.1.6.1.
AE: adverse event; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; CTCAE: Common Terminology Criteria for Adverse Events; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; GI: gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; TEAE: treatment-emergent adverse event.
Percentages are calculated using the safety population as denominator.
Grade 3 or higher neutropenia included in the summary.
A patient was counted once for each CTCAE toxicity or PT.
BrECADD group sorted by decreasing frequency for CTCAE toxicity term or PT.
MedDRA 25.1 was applied.

Serious adverse event/deaths/other significant events

Serious adverse events

At least 1 treatment-emergent SAE of any grade was reported for 328 BrECADD patients (43.9%) and 310 eBEACOPP patients (41.8%) and at least 1 Grade 3 or higher SAE for 298 BrECADD patients (39.9%) and 281 eBEACOPP patients (37.9%)

As of data cutoff 31 October 2023, one additional Grade 3 or higher SAE occurred in the eBEACOPP arm (back pain).

Table 34 - Study HD21: Treatment-emergent SAEs (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
Any treatment-emergent SAE	328 (43.9)	310 (41.8)
Grade 1	17 (2.3)	17 (2.3)
Grade 2	46 (6.2)	58 (7.8)
Grade 3 or higher	298 (39.9)	281 (37.9)
Grade 3	256 (34.3)	229 (30.9)
Grade 4	60 (8.0)	74 (10.0)
Grade 5	4 (0.5)	3 (0.4)
Any treatment-related SAE	294 (39.4)	270 (36.4)
Grade 1	11 (1.5)	15 (2.0)
Grade 2	29 (3.9)	39 (5.3)
Grade 3 or higher	271 (36.3)	250 (33.7)
Grade 3	231 (30.9)	198 (26.7)
Grade 4	54 (7.2)	70 (9.4)
Grade 5	3 (0.4)	3 (0.4)
Any treatment-emergent SAE that resulted in treatment discontinuation	15 (2.0)	15 (2.0)
Grade 1	1 (0.1)	1 (0.1)
Grade 2	2 (0.3)	2 (0.3)
Grade 3 or higher	12 (1.6)	13 (1.8)
Grade 3	6 (0.8)	7 (0.9)
Grade 4	4 (0.5)	5 (0.7)
Grade 5	2 (0.3)	1 (0.1)

Source: Table 15.3.1.2.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; SAE: serious adverse event.
Percentages are calculated using the safety population as denominator.
MedDRA 25.1 was applied.

Treatment-emergent SAEs by PT

Febrile neutropenia was the most commonly reported SAE PT across treatment groups and was reported for a higher proportion of BrECADD patients than eBEACOPP patients.

The most commonly reported treatment-emergent SAE PTs for BrECADD patients were febrile neutropenia (20.1% of patients), pyrexia (5.2%), neutropenia (3.1%), diarrhoea (2.8%), and infection (2%).

The most commonly reported SAE PTs for eBEACOPP patients were febrile neutropenia (15.9%), pyrexia (6.2%), anaemia (3%), neutropenia (2.8%), thrombocytopenia (2.6%), leukopenia (2.3%), and infection (2%).

Treatment-related SAEs

At least 1 treatment-related SAE was reported for 294 BrECADD patients (39.4%) and 270 eBEACOPP patients (36.4%). The most commonly reported treatment-related SAEs for BrECADD patients were febrile neutropenia (19.8% of patients), pyrexia (4%), neutropenia (3.1%) and diarrhoea (2.5%). For eBEACOPP patients, the most commonly reported treatment-related SAEs were febrile neutropenia (15.9% of patients), pyrexia (5.3%), neutropenia and anaemia (2.8% each), thrombocytopenia (2.6%), and leukopenia (2.3%).

Table 35 - Study HD21: Treatment-related SAEs Reported at Least 1% of Patients by PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
At least 1 treatment-related SAE	294 (39.4)	270 (36.4)
Febrile neutropenia	148 (19.8)	118 (15.9)
Pyrexia	30 (4.0)	39 (5.3)
Neutropenia	23 (3.1)	21 (2.8)
Diarrhoea	19 (2.5)	10 (1.3)
General physical health deterioration	12 (1.6)	7 (0.9)
Abdominal pain	11 (1.5)	2 (0.3)
Infection	11 (1.5)	13 (1.8)
Nausea	10 (1.3)	11 (1.5)
Pancytopenia	10 (1.3)	11 (1.5)
Pneumonia	10 (1.3)	9 (1.2)
Thrombocytopenia	10 (1.3)	19 (2.6)
Leukopenia	8 (1.1)	17 (2.3)
Neutropenic infection	8 (1.1)	7 (0.9)
Vomiting	8 (1.1)	10 (1.3)
Anaemia	7 (0.9)	21 (2.8)
Mucosal inflammation	7 (0.9)	9 (1.2)
Stomatitis	1 (0.1)	8 (1.1)

Source: Table 15.3.1.10.2.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; SAE: serious adverse event.
Percentages are calculated using the safety population as denominator.
A patient was counted once at the highest severity for each PT. Grade 3 or higher febrile neutropenia included in the summary.
BrECADD treatment group sorted by decreasing frequency of PTs.
MedDRA 25.1 was applied.

Deaths

As of the 31 December 2022 cutoff for data analysis, death was reported for 11 BrECADD patients (1.5%) and 12 eBEACOPP patients (1.6%) in the ITT population.

As of the 31 October 2023 data cutoff, death was reported for 12 BrECADD patients (1.6%) and 13 eBEACOPP patients (1.7%) in the ITT population.

Table 36 - Study HD21: Deaths (ITT Population; data cutoff 31 Oct 2023)

No of patients (%)	BrECADD N=751	eBEACOPP N=749
All deaths	12 (1.6)	13 (1.7)
Primary cause of death		
Death within 30 days of last dose of primary therapy	4 (0.5)	2 (0.3)
Other disease	2 (0.3)	0
Tox. primary chemotherapy, NOS	0	1 (0.1)
Tox. primary chemotherapy, infection	0	1 (0.1)
Unclear	2 (0.3)	0
Death after 30 days of last dose of primary therapy	8 (0.9)	11 (1.3)
Hodgkin lymphoma	3 (0.4)	1 (0.1)
Infection/sepsis, not related to treatment	2 (0.3)	1 (0.1)
Other disease	1 (0.1)	2 (0.3)
Respiratory system, not related to treatment	1 (0.1)	0
Suicide	1 (0.1)	0
Cardiovascular; not related to study treatment	0	1 (0.1)
Second neoplasia	0	2 (0.3)
Tox. allogenic SCT, infection	0	1 (0.1)
Tox. primary chemotherapy, infection	0	1 (0.1)
Unclear	0	2 (0.3)

Source: Table 15.3.2.5. Data cut 31 October 2023.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone; ITT: intent-to-treat; NOS: not otherwise specified; SCT: stem cell transplantation.
Percentages are calculated using the ITT population as denominator.

On-study deaths

On-study deaths were defined as deaths that occurred within 30 days after the last dose of primary therapy. On-study death was reported for 4 BrECADD patients and 2 eBEACOPP patients. The causes of on study death for BrECADD patients were reported as Cardiac disorders for 3 patients, and febrile neutropenia and infection for 1 patient. Death was considered treatment related for 3 BrECADD patients. No investigator assessment was provided regarding relationship to study treatment for 1 patient whose cause of death was reported as Cardiac disorders.

The cause of on study death was reported as GI disorders (excluding nausea, vomiting, mucositis) for 1 eBEACOPP patient; and anal haemorrhage, circulatory collapse, diarrhoea, pancytopenia, and respiratory arrest were the reported causes of on study death for 1 eBEACOPP patient. Death was considered treatment related for both eBEACOPP patients.

Deaths During PTFU

Follow-up death was defined as death that occurred after 30 days of the last dose of primary therapy. The death of 8 BrECADD patients (0.9%) and 11 eBEACOPP patients (1.3%) was reported during PTFU.

The cause of death for BrECADD patients during PTFU was reported as HL for 3 patients, infection and sepsis, not treatment related for 2 patients, suicide, NSCLC, and GI haemorrhage (1 patient each). All of these patients received either 4 or 6 cycles of BrECADD.

The cause of death for eBEACOPP patients during PTFU was reported as T cell lymphoma, HL, septic organ failure, complications associated with second neoplasia (AML), toxic side effects of allogeneic stem cell transplantation (alloSCT) (graft vs host disease after alloSCT), complications of lymphoma, including mucormycosis, cytomegalovirus (CMV) pneumonia, ARDS (acute respiratory distress syndrome), AML, and aneurysm of the vertebral artery with subarachnoid cerebral haemorrhage (1 patient each). Collectively, the causes of death ranged from disease progression (HL), second malignancy with AML reported for 2 patients, and infection as a sequel of the disease under study

Selected AEs of clinical interest

Peripheral neuropathy

At least 1 PN event (sensory or motor) of any grade was reported for 296 BrECADD patients (39.6%) and 372 eBEACOPP patients (50.2%) in the safety population.

Peripheral sensory neuropathy of any grade was reported for 291 BrECADD patients (39%) and 362 eBEACOPP patients (48.9%), and Grade 3 peripheral sensory neuropathy for 10 BrECADD patients (1.3%) and 17 eBEACOPP patients (2.3%).

Peripheral motor neuropathy of any grade was reported for 28 BrECADD patients (3.7%) and 35 eBEACOPP patients (4.7%) and Grade 3 peripheral motor neuropathy for 3 BrECADD patients (0.4%) and 1 eBEACOPP patient (0.1%). Grade 3 PN was the highest severity reported across treatment groups.

Peripheral sensory neuropathy led to a dose reduction for 35 BrECADD patients (4.7%) and 129 eBEACOPP patients (17.4%), and a treatment delay for 11 BrECADD patients (1.5%) and 3 eBEACOPP patients (0.4%). Peripheral motor neuropathy led to a dose reduction for 5 patients each (0.7%) across treatment groups and in treatment delay for 1 BrECADD patient.

A PN event was reported as an SAE for 2 BrECADD patients and 1 eBEACOPP patient.

Haematological toxicity

Anaemia, thrombocytopenia, febrile neutropenia, and infection were included in the 19 prespecified CTCAE toxicity terms.

Among the hematologic toxicities, a 21.3% higher frequency of Grade 4 thrombocytopenia was reported for eBEACOPP patients than BrECADD patients whereas a 6.9% higher frequency of Grade 3 or higher febrile neutropenia was reported for BrECADD patients than eBEACOPP patients.

Table 37 - Study HD21: TEAEs of Clinical Interest by CTCAE Toxicity or PT; Hematologic Toxicities (Safety Population) (Excerpt)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
CTCAE Toxicities	734 (98.3)	735 (99.2)
Anaemia; any grade	712 (95.3)	725 (97.8)
Grade 1	156 (20.9)	50 (6.7)
Grade 2	336 (45.0)	240 (32.4)
Grade 3	217 (29.0)	432 (58.3)
Grade 4	3 (0.4)	3 (0.4)
Thrombocytopenia; any grade	645 (86.3)	689 (93.0)
Grade 1	115 (15.4)	74 (10.0)
Grade 2	118 (15.8)	82 (11.1)
Grade 3	184 (24.6)	150 (20.2)
Grade 4	227 (30.4)	383 (51.7)
Infection; any grade	400 (53.5)	372 (50.2)
Grade 1	100 (13.4)	83 (11.2)
Grade 2	88 (11.8)	102 (13.8)
Grade 3	195 (26.1)	168 (22.7)
Grade 4	14 (1.9)	14 (1.9)
Grade 5	1 (0.1)	1 (0.1)

Source: HD21 Table 15.3.1.18.
Percentages are calculated using the safety population as denominator.
A patient was counted once at the highest severity for each CTCAE term or PT.
Grade 3 or higher febrile neutropenia included in the summary.
BrECADD treatment group sorted by decreasing frequency of CTCAE toxicity term or PTs.
MedDRA 25.1 was applied.

Febrile neutropenia and G-CSF use

Grade 3 or Grade 4 febrile neutropenia was reported for 198 BrECADD patients (26.5%) and 144 eBEACOPP patients (19.4%) in the safety population.

Table 38 - Study HD21: Treatment-emergent Grade 3 and Grade 4 Febrile Neutropenia (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
With Grade 3 or 4 febrile neutropenia		
Grade 3 or 4	198 (26.5)	144 (19.4)
Grade 3	186 (24.9)	132 (17.8)
Grade 4	15 (2.0)	17 (2.3)
Treatment-related		
Grade 3 or 4	197 (26.4)	142 (19.2)
Grade 3	185 (24.8)	130 (17.5)
Grade 4	15 (2.0)	17 (2.3)
SAEs		
Grade 3 or 4	149 (19.9)	118 (15.9)
Grade 3	137 (18.3)	97 (13.1)
Grade 4	17 (2.3)	26 (3.5)

Source: Table 15.3.1.16.

Table 39 - Study HD21: Febrile Neutropenia, Neutropenia, Infection With G-CSF Use (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
Any G-CSF use during treatment	747 (100)	741 (100)
Febrile neutropenia	199 (26.6)	145 (19.6)
Febrile neutropenia in Cycle 1	135 (18.1)	86 (11.6)
Neutropenia	75 (10.0)	85 (11.5)
Grade 3 or higher neutropenia	71 (9.5)	82 (11.1)
Grade 4 or higher neutropenia	67 (9.0)	79 (10.7)
Grade 3 or higher TEAEs	682 (91.3)	717 (96.8)
Infection	400 (53.5)	372 (50.2)
Grade 3 or higher infection	211 (28.2)	183 (24.7)

Source: Table 15.3.1.17.

Cardiac disorders

Cardiac disorders were reported as a TRMB event for 18 BrECADD patients (2.4%) and 10 eBEACOPP patients (1.3%) and considered treatment related for 11 BrECADD patients (1.5%) and 9 eBEACOPP patients (1.2%).

Cardiac disorders of any grade were reported for 155 BrECADD patients (20.7%) and 139 eBEACOPP patients (18.8%), and considered treatment related for 97 BrECADD patients (13%) and 92 eBEACOPP patients (12.4%).

Grade 3 or higher Cardiac disorders were reported for 21 BrECADD patients (2.8%) and 10 eBEACOPP patients (1.3%) and considered treatment related for 13 BrECADD patients (1.7%) and 9 eBEACOPP patients (1.2%).

Cardiac disorders were reported as the cause of on-study death for 3 BrECADD patients and considered treatment related for 2 BrECADD patients. No investigator assessment of relationship to study treatment was provided for 1 BrECADD patient whose cause of on-study death was reported as cardiac failure.

With data cutoff 31 Oct 2023 at least 1 treatment-emergent SAE in the SOC Cardiac disorders was reported for 25 BrECADD patients (3.3%) and 9 eBEACOPP patients (1.2%). The most commonly reported SAE PTs for BrECADD patients were tachycardia (1.1% of patients), cardiac failure (0.5% of patients), and bradycardia (0.4%). The most commonly reported SAE PTs for eBEACOPP patients was atrial fibrillation (0.3% of patients). An SAE resulted in study treatment discontinuation for 4 patients in the BrECADD group (0.5%) vs 1 in the eBEACOPP group (0.1%). Cardiac failure was reported to have led to treatment discontinuation for 2 BrECADD patients (0.3%). Other PTs that resulted in treatment discontinuation were pericardial effusion (0.1%) and atrial fibrillation (0.1%). Atrial fibrillation was reported to have led to treatment discontinuation for 1 eBEACOPP patient (0.1%).

No cardiac SAEs were reported >1 year after the first dose, nor did any event have a fatal outcome.

Table 40 - Study HD21: Treatment-Emergent Serious Cardiac Adverse Events by MedDRA System Organ Class, High Level Term, and Preferred Term (Safety Population; data cutoff 31 Oct 2023)

MedDRA Primary System Organ Class High Level Term Preferred Term	BrECADD N=747 n (%)	eBEACOPP N=741 n (%)
Cardiac disorders	25 (3.3)	9 (1.2)
Rate and rhythm disorders NEC	12 (1.6)	0
Tachycardia	8 (1.1)	0
Bradycardia	3 (0.4)	0
Arrhythmia	1 (0.1)	0
Heart failures NEC	4 (0.5)	0
Cardiac failure	4 (0.5)	0
Cardiac disorders NEC	2 (0.3)	0
Cardiovascular disorder	2 (0.3)	0
Atrial thrombosis	1 (0.1)	0
Ischaemic coronary artery disorders	2 (0.3)	0
Acute myocardial infarction	2 (0.3)	0
Cardiac signs and symptoms NEC	1 (0.1)	0
Palpitations	1 (0.1)	0
Coronary artery disorders NEC	1 (0.1)	0
Coronary artery disease	1 (0.1)	0
Heart failure signs and symptoms	1 (0.1)	0
Cardiac asthma	1 (0.1)	0
Pericardial disorders NEC	1 (0.1)	1 (0.1)
Pericardial effusion	1 (0.1)	1 (0.1)
Supraventricular arrhythmias	1 (0.1)	5 (0.7)
Atrial fibrillation	1 (0.1)	2 (0.3)
Atrial tachycardia	0	1 (0.1)
Sinus bradycardia	0	1 (0.1)
Supraventricular tachycardia	0	1 (0.1)
Ventricular arrhythmias and cardiac arrest	1 (0.1)	1 (0.1)
Ventricular tachycardia	1 (0.1)	0
Ventricular extrasystoles	0	1 (0.1)
Cardiomyopathies	0	1 (0.1)
Cardiomyopathy	0	1 (0.1)
Noninfectious pericarditis	0	1 (0.1)
Pericarditis	0	1 (0.1)

Source: Table 15.3.1.10, data cutoff date 31 October 2023.
a Treatment-emergent adverse events are defined as any AE that occurs after administration of the first dose of any study drug and through 30 days after the last dose of any study drug.
Patient incidence: a patient counts once for each preferred term, high level term, and system organ class.
The BrECADD group is sorted in descending frequency by primary system organ class, high level term, and preferred term.
Percentages use the number of treated patients as the denominator.
Grade 3 or higher febrile neutropenia adverse events are counted.
MedDRA Version 25.1 was applied.

Table 41 - Study HD21: Cardiac Events Reported as SAEs (Safety Population; BrECADD Patients)

Cycle Onset	MedDRA PT [Verbatim Text]	CTCAE Grade	Treatment Related	Outcome
2	Tachycardia [febrile neutropenia associated with tachycardia]	Grade 4	Probable	Recovered; resolved
2	Tachycardia [tachycardia]	Grade 3	Possible	Recovered; resolved
2	Supraventricular tachycardia [supraventricular tachycardia (AVNRT)]	Grade 2	None	Recovered; resolved
2	Tachycardia [fevers, neutropenia]	Grade 3	Certain	Recovered; resolved
3	Tachycardia [weakness; tachycardia due to pancytopenia]	Grade 4	Certain	Recovered; resolved
3	Tachycardia [tachycardia; SIRS]	Grade 3	Certain	Recovered; resolved
3	Tachycardia [hypotonia, tachycardia, dizziness]	Grade 3	None	Recovered; resolved
3	Tachycardia [febrile neutropenia, circulation problems, tachycardia]	Grade 3	Possible	Recovered resolved
3	Atrial tachycardia [paroxysmal atrium tachycardia]	Grade 3	Probable	Recovered; resolved
4	Cardiac failure [heart failure; information from patient's mother]	Grade 5	Not evaluable	Fatal
4	Cardiac failure [cardiac decompensation, multiple pulmonary emboli]	Grade 3	Possible	Recovered; resolved
5	Cardiac failure [heart failure]	Grade 4	Possible	Unknown
6	Acute myocardial infarction [suspected NSTEMI]	Grade 3	Possible	Recovered resolved
9	Tachycardia [dyspnea, tachycardia]	Grade 3	Probable	Lasting damage

Source: Table 15.3.2.2. Data cut 31 October 2023.
AVNRT: atrioventricular nodal reentrant tachycardia; BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; MedDRA: Medical Dictionary for Regulatory Activities; NSTEMI: non-ST-segment elevation myocardial infarction; NYHA: New York Heart Association; PPCI: primary percutaneous coronary intervention; PT: Preferred Term; RCA: right coronary artery; SAE: serious adverse event; SIRS: systemic inflammatory response syndrome.

Second malignancy

As of the 31 October 2023 cutoff for data analysis, a second malignancy was reported for 18 BrECADD patients (2.41%) and 16 eBEACOPP patients (2.16%) in the safety population. The malignancies were reported for 1 patient each across the 2 treatment groups. A variety of hematologic malignancies seemed to predominate among the second malignancies reported for patients across the 2 treatment groups.

The death of 1 BrECADD patient and 4 eBEACOPP patients during PTFU was attributed to a second malignancy.

Table 42 - Summary of Second Malignancies by Tumor Type (Safety Population) (data cutoff 31 Oct 2023)

	BrECADD N=747	eBEACOPP N=741
Patients with second malignancies, n (%)	18 (2.41)	16 (2.16)
Patients with Second malignancy tumor types*, n (%)		
MDS/CMML/AML	2 (0.27)	8 (1.08)
MDS/CMML	0	2 (0.27)
AML**	2 (0.27)	6 (0.81)
Lymphoma	8 (1.07)	2 (0.27)
B-cell Lymphoma	3 (0.40)	0
T-cell Lymphoma	5 (0.67)	2 (0.27)
Solid Tumor	8 (1.07)	6 (0.81)
Deaths among patients with Second malignancy tumor types*, n (%)		
MDS/CMML/AML	0	3 (0.40)
MDS/CMML	0	1 (0.13)
AML**	0	2 (0.27)
Lymphoma	1 (0.13)	0
B-cell Lymphoma	0	0
T-cell Lymphoma	1 (0.13)	0
Solid Tumor	0	2 (0.27)

Source: Table 15.3.2.6.2, data cutoff 31 October 2023, run time 06 September 2024 16:01.
AML = Acute Myeloid/Myelogenous Leukemia; MDS = Myelodysplastic Syndrome; CMML= Chronic Myelomonocytic Leukemia.
* Second malignancy tumor types were based on the World Health Organization (WHO) International Classification of Diseases Version 10 (ICD-10); deaths were due to any cause.
** One patient who had CMML and AML was classified as AML.
Percentages use the number of treated patients as the denominator.

Infertility

The infertility rate at 1 year was assessed by measurement of hormone levels before the start of study treatment, at restaging after completion of primary therapy, and at the 12-month PTFU visit.

The infertility rate was defined in this study as the proportion of patients with follicle-stimulating hormone (FSH) values above the upper limit of normal (ULN) among the patients for whom FSH values were available at 1-year follow-up. The normal FSH ranges were considered 3.5 to 21.5 IU/L for women and 1.5 to 12.4 IU/L for men.

Among the study participants with an FSH value at the 1-year PTFU visit, the infertility rate was 26.5% (43 of 162 patients) for female BrECADD patients, and 46.1% (77 of 167 patients) for female eBEACOPP patients, and 53.7% (94 of 175 patients) for male BrECADD patients and 80.5% (140 of 174 patients) for male eBEACOPP patients.

Another fertility analysis was performed to assess the proportion of patients in the safety population who were categorized as fertile at baseline and at 1-year PTFU. For this analysis, the infertility rate at 1 year was defined as the percentage of fertile patients with FSH values >ULN among the number of fertile patients both at baseline and at 1-year PTFU. At baseline, the fertile age range was defined as 18 years to 39 years for women and 18 years to 49 years for men and normal FSH ranged from 3.5 to 21.5 IU/L for women and 1.5 to 12.4 IU/L for men.

Results of the analysis showed that 56.6% of BrECADD patients and 54.7% of eBEACOPP patients who were categorized as fertile on the basis of FSH values at randomisation continued to be categorised as

fertile at 1-year PTFU. At 1-year PTFU, the infertility rate was 11.8% for female BrECADD patients and 35.4% for female eBEACOPP patients, and 50% for male BrECADD patients and 78.3% for male eBEACOPP patients.

Laboratory findings

At least 1 SAE of any grade was reported as a result of a clinical laboratory result for 247 BrECADD patients (33.1%) and 221 eBEACOPP patients (29.8%). This included at least 1 Grade 3 SAE for 184 BrECADD patients (24.6%) and 137 eBEACOPP patients (18.5%), and at least 1 Grade 4 SAE for 48 BrECADD patients (6.4%) and 65 eBEACOPP patients (8.8%).

Febrile neutropenia was the most commonly reported PT across the 2 treatment groups and included Grade 3 febrile neutropenia for 15.1% of BrECADD patients and 12.9% of eBEACOPP patients.

Safety in special populations

Age

Adult patients aged between 18 years and 60 years were enrolled in the randomised main HD21 study. Age at randomisation was one of the stratification factors used for randomisation of study participants. A subgroup analysis of TRMB dichotomized by the age groups 18 to 44 years and 45 to 60 years. In both age groups, a lower TRMB rate was reported for BrECADD patients than eBEACOPP patients. The RR was 0.747 (95% CI, 0.662-0.843), corresponding to a 25.3% reduced risk of TRMB event for BrECADD patients than eBEACOPP patients in the age group 18 years to 44 years, and 0.639 (95% CI, 0.524-0.78), corresponding to 36.1% reduced risk of a TRMB event for BrECADD patients than eBEACOPP patients in the age group of 45 to 60 years. An HR of <1 favored BrECADD.

The conduct of the HD21 study was modified to add an independent, nonrandomised, older cohort of patients aged between 61 years and 75 years. Results for this cohort are to be presented in an addendum when they become available, as per a recommendation of the CHMP.

Safety related to drug-drug interactions and other interactions

No drug-drug or drug-disease interactions were assessed in the HD21 study.

Discontinuation due to adverse events

Table 43 - Overview of Action on Study Drugs by Cycle (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
All Cycles	747	741
No action taken [a]	441 (59.0)	252 (34.0)
Action on study drug		
Dose reduced	243 (32.5)	452 (61.0)
Treatment delayed	114 (15.3)	160 (21.6)
Discontinuation of treatment	16 (2.1)	15 (2.0)
First dose reduction		
Cycle 1	81 (10.8)	163 (22.0)
Cycle 2	39 (5.2)	91 (12.3)
Cycle 3	69 (9.2)	111 (15.0)
Cycle 4	34 (4.6)	59 (8.0)
Cycle 5	15 (2.0)	25 (3.4)
Cycle 6	5 (0.7)	3 (0.4)
Treatment delayed		
Cycle 1	34 (4.6)	32 (4.3)
Cycle 2	37 (5.0)	37 (5.0)
Cycle 3	37 (5.0)	60 (8.1)
Cycle 4	18 (2.4)	30 (4.0)
Cycle 5	15 (2.0)	38 (5.1)
Cycle 6	3 (0.4)	3 (0.4)

Source: Table 15.3.7.2; Listing 16.2.5.2.
BrECADD: brentuximab vedotin, etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone; eBEACOPP: escalated doses of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone.
Percentages were calculated using the safety population as denominator.
a: Patient recorded same action on study drug multiple times in all cycles and each cycle was counted only once respectively. Patient recorded more than one action in all cycles and each cycle was counted once in each category.

TEAEs That Resulted in Premature Treatment Discontinuation

Given the importance of maintaining treatment intensity in the frontline treatment setting, sites were instructed to report adverse events that led to permanent treatment discontinuation as SAEs.

An SAE resulted in study treatment discontinuation for 15 patients each (2%) across the 2 treatment groups. Febrile neutropenia was the most commonly reported SAE that resulted in premature treatment discontinuation across treatment groups. Febrile neutropenia was reported to have led to premature treatment discontinuation for 4 patients each (0.5%), and cardiac failure led to premature treatment discontinuation for 2 BrECADD patients (0.3%). Other PTs that resulted in premature treatment discontinuation were reported for 1 patient each across the 2 treatment groups.

TEAEs That Resulted in Dose Reduction

A TEAE that resulted in dose reduction was reported for 243 BrECADD patients (32.5%) and 452 eBEACOPP patients (61%).

Table 44 - Study HD21: TEAEs Resulting in Dose Reduction by CTCAE Toxicity Terms or PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
TEAEs resulting in dose reduction	243 (32.5)	452 (61.0)
CTCAE Toxicity	238 (31.9)	445 (60.1)
Thrombocytopenia	148 (19.8)	257 (34.7)
Leukopenia	106 (14.2)	243 (32.8)
Peripheral sensory neuropathy	35 (4.7)	129 (17.4)
Febrile neutropenia	34 (4.6)	46 (6.2)
Anaemia	25 (3.3)	51 (6.9)
Infection	20 (2.7)	43 (5.8)
Cardiac disorders	7 (0.9)	5 (0.7)
Respiratory, thoracic and mediastinal disorders	5 (0.7)	68 (9.2)
Mucositis	4 (0.5)	10 (1.3)
Renal and urinary disorders	1 (0.1)	5 (0.7)
Skin and subcutaneous tissue disorders	1 (0.1)	7 (0.9)
Avascular necrosis	0	2 (0.3)
Other Toxicities (PT)	19 (2.5)	44 (5.9)
Neutropenia	8 (1.1)	18 (2.4)
Neutrophil count decreased	2 (0.3)	7 (0.9)

Source: Table 15.3.1.7.1.

Avascular necrosis was reported to have led to dose reduction for 2 eBEACOPP patients. Avascular necrosis of any grade was reported for 9 eBEACOPP patients (1.2%) and Grade 3 or higher avascular necrosis for 1 eBEACOPP patient (0.1%). Avascular necrosis was not reported for any BrECADD patient.

TEAEs That Resulted in Treatment Delay

A TEAE was reported to have resulted in treatment delay for 114 BrECADD patients (15.3%) and 160 eBEACOPP patients (21.6%)

The CTCAE toxicities that resulted in treatment delay for at least 2% of patients in either treatment group were infection (5.5% of BrECADD patients and 7.3% of eBEACOPP patients), leukopenia (5% of BrECADD patients and 7.6% of eBEACOPP patients), thrombocytopenia (1.9% of BrECADD patients and 4.5% of eBEACOPP patients), and anaemia (1.2% of BrECADD patients and 2.6% of eBEACOPP patients).

Table 45 - Study HD21: TEAEs Resulting in Treatment Delay for at Least 2 Patients by CTCAE Toxicity Terms or PT (Safety Population)

No of patients (%)	BrECADD N=747	eBEACOPP N=741
TEAEs resulting in treatment delay	114 (15.3)	160 (21.6)
CTCAE Toxicity	103 (13.8)	140 (18.9)
Infection	41 (5.5)	54 (7.3)
Leukopenia	37 (5.0)	56 (7.6)
Thrombocytopenia	14 (1.9)	33 (4.5)
Peripheral sensory neuropathy	11 (1.5)	3 (0.4)
Febrile neutropenia	10 (1.3)	11 (1.5)
Anaemia	9 (1.2)	19 (2.6)
Nausea/vomiting	2 (0.3)	4 (0.5)
Skin and subcutaneous tissue disorders	2 (0.3)	5 (0.7)
Cardiac disorders	1 (0.1)	2 (0.3)
Other Toxicities (PT)	21 (2.8)	34 (4.6)
Neutropenia	4 (0.5)	7 (0.9)
Neutrophil count decreased	0	3 (0.4)
Pyrexia	0	6 (0.8)

Post marketing experience

As of January 2024, brentuximab vedotin has been approved in 80 countries and regions. As of the 18 August 2023 data-lock point for the currently approved PBRER (Periodic Benefit-Risk Evaluation Report), the cumulative estimated patient exposure to brentuximab vedotin was 143,252 patients, including 3468 patients from company-sponsored clinical studies, 4444 patients from investigator-sponsored studies, 3073 patients from various compassionate use programs, and approximately 132,271 patients from the postmarketing setting (Periodic Benefit-Risk Evaluation Report for Brentuximab Vedotin 03 October 2023).

2.5.1. Discussion on clinical safety

Safety data with cutoff 31 December 2022 and update with data cutoff 31 October 2023 were derived from the pivotal HD21 study, an investigator-initiated, randomised, open-label phase 3 study that measured the toxicity of BrECADD versus that of eBEACOPP in terms of a novel coprimary endpoint, treatment-related morbidity (TRMB) in treatment-naïve patients with advanced-stage cHL. TRMB was defined by Grade 4 haematological toxicity and Grade 3 and 4 non-hematological organ toxicity on PT and SOC levels, which, to some extent, hinders comparison with the established safety profile of brentuximab vedotin on a PT level.

The study is ongoing and safety assessments are conducted throughout the PTFU until the end of study.

Exposure

The safety population consisted of all randomised patients who received at least 1 dose of any of the study medications. This population included 747 patients in the BrECADD arm and 741 patients in the eBEACOPP arm. The median number in treatment cycles was comparable between the treatment groups. Therapy adherence, which was a secondary endpoint, was higher in the BrECADD arm with distinctly fewer patients having dose modifications (32.5% versus 61% for eBEACOPP). Moreover, the overall treatment duration was shorter for BrECADD patients.

AEs

The overall incidence of TEAEs was similar between the treatment arms. Almost all patients experienced at least 1 treatment-related TEAE of any grade in both treatment arms (99.5% BrECADD vs 99.6% eBEACOPP).

The safety profiles of BrECADD and eBEACOPP deviated to some extent as differences in certain treatment-related TEAEs were noted. A ≥5% higher frequency difference was observed for GI disorders (excluding nausea, vomiting, mucositis) and febrile neutropenia in the BrECADD arm while for the eBEACOPP arm these toxicities were thrombocytopenia, nausea/vomiting, peripheral sensory neuropathy, skin and subcutaneous tissue disorders and respiratory as well as thoracic and mediastinal disorders.

Considering that nausea and vomiting are very common adverse reactions with brentuximab vedotin (as per section 4.8 of the Adcetris SmPC), the reduction of nausea and vomiting might also be attributed to the use of dexamethasone instead of prednisone. The same applies to other TEAEs such as anemia and thrombocytopenia (associated with etoposide) as well as peripheral neuropathy, all of which are discussed in detail below.

More patients experienced (treatment-related) Grade ≥3 TEAEs in the eBEACOPP arm compared to BrECADD (95.3% vs 90.9%) with a lower incidence in all CTCAE toxicity terms or PT except for infection, febrile neutropenia, GI and hepatobiliary disorders, cardiac disorders and fatigue.

SAEs

The slight increase in the overall number of SAEs in the BrECADD arm (39.4% vs 36.4% eBEACOPP) is solely driven by Grade 3 SAEs as the number of patients with Grade 1 and 5 SAE was comparable and the number of Grade 2 and 4 SAEs was even lower compared to eBEACOPP. Altogether, SAEs including those with higher grade of seriousness appear to have been manageable as there was no difference in the number of patients who discontinued treatment due to SAEs. In addition, the most common treatment-related SAEs were the dominated by the same PTs in both treatment arms: febrile neutropenia, pyrexia, neutropenia and infection. These are common toxicities in the frontline treatment of HL patients and as such not primarily associated with BrECADD.

Deaths

As expected in this clinical setting the number of overall deaths on-study and during PTFU is low and comparable between the treatment arms (1.6% BrECADD vs 1.7% eBEACOPP).

AEs of clinical interest

Peripheral neuropathy - The incidence of peripheral neuropathy, which is a known risk associated with brentuximab vedotin, was lower in the BrECADD arm compared to eBEACOPP (39.6% vs 50.2%). Events were mainly Grade 1 and 2 in both treatment arms. Grade 3 was the highest Grade observed with only few events each. The majority of events were peripheral sensory neuropathy with a 9.9% difference in numbers in favour of BreCADD. Consistent with this finding, more patients in the eBEACOPP arm had a dose reduction due to peripheral sensory neuropathy (17.4% versus 4.7% in BrECADD). Contrary to this, treatment delays occurred slightly more often in the BrECADD arm.

Haematological toxicity - While the overall incidence of anaemia was similar between the treatment arms, distinctly fewer Grade 4 toxicities were observed in the BrECADD arm (29.0% vs 58.3% in eBEACOPP). For thrombocytopenia the same is observed with Grade 4 events occurring in 30.4% of patients in the BrECADD arm and 51.7% in the eBEACOPP arm. Instead, for both anemia and thrombocytopenia the number of Grade 3 events is higher in the BrECADD arm thereby indicating a trend in favour of the BrECADD regimen as it appears to lead to a reduced toxicity, i.e. a downgrade from Grade 4 to Grade 3

toxicities which is of relevance in clinical practice with regards to treatment, outcome and necessity of blood product transfusions.

The slightly higher number of infections in the BrECADD arm is also driven by Grade 3 events and likely attributed to the higher incidence of febrile neutropenia.

Febrile neutropenia was observed more frequently in the BrECADD arm compared to eBEACOPP. Similar to the finding for haematological toxicities the difference is mainly driven by Grade 3 events while Grade 4 toxicity (treatment-related and SAE) was slightly lower. Interestingly, the higher frequency did not result in a higher rate of dose reductions or dose delays. Neutropenia and febrile neutropenia are known risks associated with BV. The SmPC has been updated to also reflect the risk of neutropenia and febrile neutropenia with the BrECADD regimen. Specific dose modification guidance has been added to Section 4.2 and section 4.2 was amended to clarify that febrile neutropenia also occurs with BrECADD and G-CSF prophylaxis is mandatory. These measures are considered sufficient to address the potential risks.

G-CSF administration was mandated per protocol on Day 5 for BrECADD patients and on Day 4 for eBEACOPP patients of each 21-day treatment cycle. Use of G-CSF is intended to reduce severity and intensity of neutropenia, febrile neutropenia and infections. Even with G-CSF use the incidence of febrile neutropenia is increased in the BrECADD arm.

Cardiac disorders amongst others was selected as adverse event of clinical interest due to an increased risk of late toxicity in treated HL patients. It is reassuring that no dose reduction occurred in patients with cardiac SAEs and no SAEs appear to have been reported later than 1 year after the first dose of study drug. Nevertheless, there is a distinct difference in cardiac SAEs with a nearly 3-times higher incidence in the BrECADD arm (3.3%) compared to eBEACOPP (1.2%). Moreover, the majority of these events were considered treatment related. This imbalance, although not as distinct, is also noted for cardiac disorders of any grade (20.7% vs 18.8%), treatment-related events (13% vs 12.4%), Grade 3 or higher events (2.8% vs 1.3%) and treatment related Grade 3 or higher events (1.7% vs 1.2%) suggesting an inferior safety profile of BrECADD in terms of cardiac toxicity compared to eBEACOPP. The overall incidence is also higher compared to results from other studies (ECHELON-1, AETHERA).

An impact of other backbone components cannot be excluded. The dose of doxorubicin has only been slightly increased from 35 to 40 mg/m² which leads to the assumption that brentuximab contributes to some extent to the observed cardiac toxicity. This is also supported by an analysis of the FDA Adverse Event Reporting System (FAERS) database that investigated cardiac toxicities associated with brentuximab vedotin.[5]

Taking all this into account, it is concluded that cardiac toxicity is a risk associated with the BrECADD regimen – which brentuximab vedotin is a relevant part of. Information on cardiac toxicity was included in section 4.8 of the SmPC.

Regarding the risk of long-term cardiac toxicity, it is agreed that the current study does not allow for monitoring of these events, as they often occur later than 5 years after treatment and are also depending on subsequent therapies. Late toxicities will be monitored through routine pharmacovigilance activities.

There were slightly more patients with a reported second malignancy in the BrECADD arm compared to eBEACOPP (N=18 [2.41%] vs N=16 [2.16%]). Second malignancies are a known risk of frontline HL treatment.

Fertility analyses were conducted throughout the trial. One analysis was defined by the proportion of patients with FSH values above ULN among those with available FSH values at 1-year PTFU. The second

[5] Ke C, Chen M, Huang Y, Chen Y, Lin C, Huang P. Cardiac toxicity of brentuximab vedotin: a real-word disproportionality analysis of the FDA Adverse Event Reporting System (FAERS) database. Naunyn Schmiedebergs Arch Pharmacol. 2024 Jul;397(7):5253-5264. doi: 10.1007/s00210-024-02955-6. Epub 2024 Jan 25. PMID: 38270617.

analysis was defined as proportion of fertile patients at baseline and at 1-year PTFU. In both analyses infertility rates were distinctly lower in the BreCADD arm for female and male patients. At 1-year PTFU infertility rates for women were 26.5% and 11.8% (BrECADD) compared to 46.1% and 35.7% (eBEACOPP) in the first and second analysis, respectively. Male infertility rates at 1-year PTFU were 53.7% and 50.0% (BrECADD) compared to 80.5% and 78.3% (eBEACOPP).

All AEs that led to treatment discontinuation were reported as SAEs. These presented with a comparable number of events between the treatment arms. Dose reductions occurred almost twice as frequent in the eBEACOPP arm (61.0% vs 32.5% BrECADD) with thrombocytopenia, leukopenia, peripheral sensory neuropathy and respiratory, thoracic and mediastinal disorders being the most common reason for dose reduction. These toxicities are commonly associated with the chemotherapy components etoposide, vincristine and bleomycin. The latter two have been replaced by brentuximab vedotin thereby indicating a valid exchange option that reduces relevant toxicities. The omission of bleomycin was attributed to the contraindication of co-administration with brentuximab vedotin which appears to also positively impact the safety profile of BrECADD. Dose delays were observed in more patients in the eBEACOPP arm but with a lower frequency (18.9% vs. 13.8% BrECADD). This finding coincides with the shorter treatment duration in the BrECADD arm mentioned above.

Compared to other trials with brentuximab vedotin such as the ECHELON trials, TEAEs were not documented by MedDRA exclusively. Instead, the 19 prespecified TRMB toxicities were documented by CTCAE toxicity terms while all other TEAEs were documented by MedDRA. As the former included to some extent only SOCs, pooling of safety data from those of other trials is not deemed feasible at the PT level. Due to the fact that the safety profile of brentuximab vedotin in the HD21 trial was consistent with the known safety profile, the MAH proposed to keep the ADR table in section 4.8. of the Adcetris SmPC unchanged and add commonly reported serious ADRs in text format to section 4.8. This approach is deemed reasonable.

At the cutoff date 31 October 2023, 5-year follow up data are available for N=783 patients. The study closed in December 2024 with an expected descriptive analysis of PFS approximately 6 months afterwards (depending on the timepoint of data transfer from GHSG to Takeda).

In general, the chosen period of 5 years has been supported by data from the literature (Shbib Dabaja et al. 2022) which conclude that the majority of secondary haematological malignacies occur within 5 years of follow-up whereas solid tumours as secondary malignancies often occur later. So far at the time of updated partially cleaned data (cut-off 02 December 2024), 3-year follow-up data were available for approximately 90% of patients in both treatment arms.

2.5.2. Conclusions on clinical safety

The safety profile for patients treated with brentuximab vedotin as part of the BrECADD regimen was generally consistent with the known AE profile of brentuximab vedotin in combination with chemotherapy.

Following a recommendation from the CHMP, the MAH committed to submit the final results of study HD-21 as a post-authorisation measure once available.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC

and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted/was requested to submit an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 20.0 is acceptable.

The CHMP endorsed this advice without changes.

Safety concerns

No changes were made to the Safety concerns in RMP v20.0

Summary of safety concerns

Summary of safety concerns	
Important identified risks	1. Peripheral neuropathy (sensory and motor) 2. Myelosuppression (including Neutropenia, Febrile neutropenia, Thrombocytopenia and Anaemia) 3. Infections (including bacteraemia, sepsis, septic shock and opportunistic infections) 4. Infusion-related reactions 5. Hyperglycaemia
Important potential risks	1. Severe hepatotoxicity 2. Pulmonary toxicity
Missing information	1. Long term safety

Pharmacovigilance plan

Not applicable

Risk minimisation measures

N/A for this procedure. An update to routine risk minimization measures for important potential risks of "severe hepatotoxicity" and "pulmonary toxicity" per PRAC recommendation during procedure EMEA/H/C/002455/II/0107 was included.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet (PL) is updated accordingly.

In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the SmPC.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet was submitted by the MAH and has been found acceptable for the following reasons:

The variation contains no changes that may affect the readability of the package leaflet.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The proposed target indication for this extension of indication is the treatment of adult patients with **previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with** etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (**BrECADD**).

3.1.2. Available therapies and unmet medical need

Patients with early-stage disease are typically treated with 2 to 4 cycles of ABVD, with or without focal radiotherapy to sites of disease. Patients diagnosed with Stage III/IV cHL are usually treated with 6 to 8 cycles of ABVD, with some physicians adding limited field consolidative radiotherapy for bulky mediastinal involvement. In an effort to improve frontline disease control in patients with advanced cHL, more aggressive multiagent chemotherapy regimens have been developed, such as standard-dose and escalated-dose versions of BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone).

More aggressive treatment regimens yield better initial disease control but do not demonstrate an OS advantage for the BEACOPP regimen, which is also associated with higher rates of acute toxicities such as febrile neutropenia and long-term morbidities, including infertility and secondary malignancies. Moreover, treatment-related mortality for BEACOPP is unacceptably high in patients 60 years of age and older.

About half of patients undergoing ASCT can be cured. However, a significant percentage of patients with relapsed or refractory HL never make it to ASCT because their disease does not respond adequately to salvage therapies or their clinical status, including age, precludes them from undergoing the procedure

3.1.3. Main clinical studies

Main evidence to support this extension of the indication is obtained from the pivotal Phase 3 trial HD21, an investigator-initiated, multicenter, randomised, open-label phase 3 study that measured the toxicity of BrECADD versus that of eBEACOPP in terms of a novel coprimary endpoint, treatment-related morbidity

(TRMB) (randomised main cohort) in treatment-naïve patients with histologically confirmed advanced-stage cHL.

The study was designed with the 2 coprimary endpoints that were to be tested hierarchically to account for multiplicity. First, superiority in terms of lower TRMB for BrECADD patients was to be tested by using the CMH test. The noninferiority test for PFS was to be performed only if the superiority of TRMB was confirmed for BrECADD.

3.2. Favourable effects

The study met its co-primary endpoints. TRMB showed a statistically significant superiority of BreCADD compared to eBEACOPP. The number of patients with a TRMB was 42.0% in the BreCADD arm and 58.7% in the eBEACOPP arm with a relative risk of 0.712 (95% CI, 0.643-0.789).

The reduction in hematological toxicties, was accompanied by a reduction of red cell transfusions and platelet infusions (29.5% BrECADD versus 57.2% eBEACOPP).

For PFS non-inferiority was significantly shown. Superiority could not be formally derived but a numerical benefit was observed. With data cutoff 31 October 2023 8 additional PFS events (BrECADD N=5, eBEACOPP N=3) were reported (PFS HR 0.664 (95% CI: 0.453, 0.973)) showing a consistent effect over time.

Sensitivity and subgroup analyses of TRMB and PFS were predominantly in favour of BrECADD thereby supporting the primary analyses.

3.3. Uncertainties and limitations about favourable effects

The TRMB endpoint has been met but results are driven by a notable reduction of haematological toxicities (31.2% BrECADD, 52.1% eBEACOPP) while organ toxicities are slightly increased (18.6% BrECADD, 17.4% eBEACOPP) with GI and hepatobiliary disorders being the predominant toxicities (7.8% vs 4.3% and 5.0% vs 3.0%, respectively). For the latter, the number of patients requiring dose modification or treatment delay was low and similar between the treatment arms.

The contribution of brentuximab vedotin to some effects observed in TRMB cannot be clearly defined and are likely rather attributed to the backbone regimen, eg. reduction of haematological toxicity due to replacement of procarbazine with dacarbazine and dose reduction of etoposide.

The final results as an addendum to the CSR from study HD21 will be provided as per a recommendation of the CHMP.

3.4. Unfavourable effects

The safety profile for patients treated with brentuximab vedotin as part of the BrECADD regimen was generally consistent with the known AE profile of brentuximab vedotin in combination with chemotherapy.

The overall incidence of treatment-related TEAEs was comparable between the treatment arms (BrECADD 99.5%, eBEACOPP 99.6%). The most commonly observed TEAS (overall and related) were anemia, leukopenia, thrombocytopenia, nausea/vomiting, infections and GI disorders.

SAEs occurred more frequently in the BrECADD arm (39.4% versus 36.4%) compared to eBEACOPP. These were driven by Grade 3 events (treatment emergent 39.9% versus 37.9%, treatment-related 30.9% versus 26.7%). Grade 4 events were even slightly lower in the BrECADD arm (treatment-emergent 8.0% versus 10.0%, treatment-related 7.2% versus 9.4%).

Compared to eBEACOPP febrile neutropenia occurred more often in the BrECADD arm overall (26.5% versus 19.6%) and as treatment-related Grade 3 or higher (25.6% versus 19.3%) despite the mandatory use of G-CSF in both arms. Consequently, a higher number of hospitalisations due to febrile neutropenia was also noted for patients in the BrECADD arm. However, the duration of hospitalisation was similar in both treatment arms with a median stay of 6.0 days (BrECADD range 1-41 days, eBEACOPP range 1-51 days). The SmPC adequately addresses the risk of neutropenia and febrile neutropenia with the BrECADD regimen.

Infections were also reported in more patients in the BrECADD arm overall (53.5% versus 50.2%), treatment-related (43.6% versus 41.3%) and defined as TRMB (1.7% versus 1.3%).

Slightly more patients presented with cardiac toxicities in the BrECADD arm overall (20.7% versus 18.8%), as grade 3 or higher (2.8% versus 1.7%) and as TRMB (2.4% versus 1.3%). There is also a distinct difference in cardiac SAEs with a nearly 3-times higher incidence in the BrECADD arm compared to eBEACOPP (3.3% vs 1.2%). Second malignancies occurred slightly more frequent in the BrECADD arm (N=18 (2.41%)) compared to eBEACOPP (N=16 (2.16%))

3.5. Uncertainties and limitations about unfavourable effects

Regarding the risk of long-term cardiac toxicity, it is agreed that the current study does not allow for monitoring of these events, as they often occur later than 5 years after treatment and are also depending on subsequent therapies.

3.6. Effects Table

Table 46 - Effects Table for Adcetris in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD) for the treatment of adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL (data cutoff: 31 December 2022)

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
PFS	Number of patients with event of progression Time from randomisation to disease progression/relapse/death	N (%)	44 (5.9%)	65 (8.7%)	PFS non-inferiority was significantly shown (PFS HR 0.664 (95% CI: 0.453, 0.973))	Study HD21
TRMB	Incidence of treatment related	Events	314 (42.0%)	435 (58.7%)	Absolute risk reduction -16.7% (% difference BrECADD-	Study HD21

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	morbidity up to 30 days after the last dose	N (%)			eBEACOPP) Driven by notably reduced hematological toxicity N=233 (31.2%, eBEACOPP 52.1%) But slightly higher organ toxicity N=129 (18.6%, eBEACOPP 17.4%) Organ tox driven by GI and heptaoboliary events that are transient and manageable in clinical practice.	
Unfavourable Effects						
FN	Number of patients with Febrile neutropenia	N (%)	197 (26.4%)	143 (19.3%)	Associated with higher number of hospitalisations but not prolonged duration of stay compared to eBEACOPP	Section 4.5
Cardiac toxicity	Number of patients with cardiac toxicities	N (%)	155 (20.7%)	139 (18.8%)	Contribution of individual components unknown	Section 4.5
Secondary malignancy	Number of patients with secondary malignancy	N (%)	18 (2.41%)	16 (2.16%)	Follow-up not sufficient to fully characterise the risk	Section 4.5

Abbreviations: AE=adverse event, CI=confidence interval, CR=complete response, FN=febrile neutropenia, GI=gastrointestinal, HR=hazard ratio, PFS=progression-free survival, PN=peripheral neuropathy, RBC=red blood cells, SAE=serious adverse events, TEAE=treatment-emergent adverse events, TRMB=treatment-related morbidity

Notes: Data cutoff interim analysis: 31 Dec 2022, Data cutoff updated dataset: 31 October 2023

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Improvement of outcomes in patients with newly diagnosed advanced HL is challenging as cure rates are already high in the frontline setting. The combination of approved regimens with additional treatments often leads to higher or even unacceptable toxicity without a substantial impact on efficacy. Thus, the development of alternative treatment regimens that potentially offer an improved safety profile while maintaining the established cure rates, is deemed of clinical importance.

Brentuximab vedotin in combination with chemotherapy (BrECADD) resulted in a statistically significant non-inferior and a numerical superior PFS with subgroup analyses of PFS, all in favour of the BrECADD regimen. The observed efficacy of the BrECADD regimen is considered sufficiently demonstrated and clinically relevant.

The second co-primary endpoint TRMB showed a relevant reduction of toxicity in the BrECADD arm compared to eBEACOPP. Subgroup analyses were all overall supportive of the results in the overall population.

Notably fewer haematological toxicities were the driver of the observed TRMB difference (31.2% BrECADD, 52.2% eBEACOPP). Consequently, considerably fewer platelet infusions and RBC transfusions were required by patients in the BrECADD arm (29.5% versus 57.2% eBEACOPP). As hematological toxicities are frequently observed in the HL population, a reduction of these toxicities is deemed of high clinical importance as it also avoids adverse events caused by these interventions. Taken together, organ toxicities seem to be manageable in clinical practice. Hence, the slightly higher incidence of organ toxicity appears to be acceptable in light of an overall distinctly improved safety profile.

Brentuximab vedotin is deemed to have a relevant part in the efficacy of the BrECADD regimen as alterations of the chemotherapy backbone were mainly targeting an improved safety profile, eg. by exchanging components of the same therapeutic group. Other components were either omitted or reduced. Hence, no increase in efficacy was to be expected from these changes. The slight increase of doxorubicin is very likely not the sole driver of the observed improvement in PFS for BrECADD compared to eBEACOPP, thus supporting a relevant impact of brentuximab vedotin on the efficacy of the regimen.

Infertility rates were considerably lower with the BrECADD regimen compared to eBEACOPP for both female and male patients. The reduction of gonadal toxicity is likely not to be attributed to brentuximab vedotin but rather to the replacement of procarbazine with dacarbazine and prednisone with dexamethasone, respectively. Nevertheless, Hodgkin lymphoma mainly occurs in young adults aged 20–40 years and preservation of fertility is of high clinical relevance.

Slightly more patients reported second malignancies. However, the most serious of these, AML (a known late toxicity in HL) occurred distinctly less often in the BrECADD arm (N=2 patients versus N=8 patients in eBECAOPP). Moreover, with the updated partially cleaned data (cutoff 02 Dec 2024) the initially observed difference between the treatment arms was further reduced with nearly similar incidences of second malignancies.

3.7.2. Balance of benefits and risks

Non-inferiority in PFS of the BrECADD regimen over eBEACOPP was clearly demonstrated. TRMB events occurred less frequently in the BrECADD arm with a distinct reduction of clinically relevant haematological toxicities. Overall, the availability of an additional therapeutic option in frontline treatment of HL, with a different, though manageable safety profile is considered of substantial clinical relevance. BrECADD may offer such an alternative treatment option with at least equivalent efficacy.

3.8. Conclusions

The overall B/R of Adcetris for this extension of indication is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication for ADCETRIS to include treatment for adult patients with previously untreated CD30+ Stage IIB with risk factors, Stage III or Stage IV HL in combination with etoposide, cyclophosphamide, doxorubicin, dacarbazine, dexamethasone (BrECADD), based on final results from phase 3 study HD21 (NCT02661503). This study is titled 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.
As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 20.0 of the RMP has also been submitted.
In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet and to implement editorial changes to the SmPC.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular, the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion ‘Product Name-H-C-Product Number-II-Var.No’