

Bilag til Medicinrådets vurdering af brentuximab vetodin til behandling af avanceret Hodgkin lymfom

Vers. 1.0



Bilagsoversigt

1. Ansøgers notat til Rådet vedr. brentuximab vetodin
2. Forhandlingsnotat fra Amgros vedr. brentuximab vetodin
3. Ansøgers endelige ansøgning vedr. brentuximab vetodin

Takeda Pharma A/S Høringssvar på Medicinrådets udkast til Vurderingsrapport for brentuximab vedotin til behandling af tidligere ubehandlet avanceret Hodgkin lymfom (BrECADD)

Takeda Pharma A/S takker for muligheden for at kommentere og præcisere væsentlige elementer af beslutningsgrundlaget.

1. Fertilitetsanalyser i HD21

Medicinrådet anfører, at fertilitetsanalyserne i HD21 er uplanlagte post-hoc analyser i en selekteret population og derfor alene hypotesegenererende.

Dette er ikke korrekt. Som angivet i tabel 12 var fertilitetsanalyserne præspecificerede med analyse efter 1 år. Resultaterne for den samlede safety-population fremgår af tabel 112 og 113. Disse suppleres af post-hoc analyser blandt patienter med fertilitetspotentiale med op til 4 års opfølgning (tabel 19-20, figur 7). Analysegrundlagene er beskrevet i afsnit 7.1.1 og 7.1.3 samt i korrespondance med Medicinrådet fra december 2025.

2. Referering af time-to-event-data

Takeda bemærker flere unøjagtigheder i Medicinrådets fremstilling af time-to-event-data.

Figur 5 omtales som "7-års KM-kurver for PFS", selv om datagrundlaget er et data-cut fra oktober 2023 med median opfølgning på 48 måneder. Tilsvarende omtales figur 9 som "7-års KM-kurver for OS", selv om sådanne data ikke foreligger, og figurens datakilde ikke er refereret. Tabel 20 henviser ligeledes til 7-års OS-data. Samlet giver dette indtryk af en højere datamodenhed, end datagrundlaget understøtter.

3. Model antagelser

Vi ønsker yderligere at nuancere tre elementer i den sundhedsøkonomiske vurdering, som efter vores opfattelse bør overvejes, og som kunne belyses i følsomhedsanalyser:

- 1.** Ekstrapolering af progressionsfri overlevelse
- 2.** Den antagne behandlingsvarighed for BrECADD
- 3.** Nyttelværdier for helbredsrelateret livskvalitet

1) Ekstrapolering af progressionsfri overlevelse

Medicinrådet ændrer PFS fremskrivningen fra den samlede (joint) parametriske model til separate generaliserede gamma-modeller pr. arm med den begrundelse, at proportional hazards (PH) antagelsen ikke er opfyldt. Betydningen af denne ændring er af væsentlig karakter og vi vil derfor gerne nuancere dette

- Medicinrådets vurdering af PH er ikke forkert, dog vælger den udelukkende at fokusere på metodiske overvejelser, hvorimod det indsendte valg af fremskrivning havde ladet kliniske overvejelser veje tungest. Valget af separate fittings tillader højere følsomhed overfor den sene fase af KM-kurverne, som kun baseres på en meget lille andel (7%) af patienterne der indgik i studiet.
- Medicinrådet fremhæver også usikkerheden forbundet med den sene del af PFS-kurven, hvor kurverne konvergerer efter ca. 5,5 år. På dette tidspunkt er antallet af patienter i risiko, 52 og 53 i de to arme, svarende til ca. 7 % af den oprindelige population. Dog væger Medicinrådet udelukkende at belyse udelukkende usikkerheden ved præsentation af mere pessimistiske analyser, hvilket der rent klinisk ikke vurderes at være belæg for da recidiv af HL efter intensiv højdosis kemoterapi alt overvejende er et tidligt fænomen.

2) Behandlingsvarighed for BrECADD

Rapporten anvender HD21-studiets cyklusfordeling for interventionen (64 % modtager fire cyklusser / 36 % seks) i stedet for Takedas antagelse (81 % / 19 %), mens komparatorfordelingen i praksis er uændret (65 % / 34 %). Denne antagelse er af væsentlig betydningen for omkostningen forbundet med BrECADD og vi vil derfor gerne nuancere dette:

- BrECADD er et PET-adapteret regime: der gives to cyklusser efterfulgt af en interim PET-scanning (PET-2), hvorefter patienterne modtager i alt fire eller seks cyklusser afhængigt af respons, og behandlingen justeres eller seponeres ved toksicitet. Studiets fordeling afspejler derfor protokoldefineret praksis.
- I dansk klinisk praksis afgøres antallet af cyklusser tilsvarende af interim PET-respons og tolerabilitet, og det er på baggrund af danske data vurderet sandsynligt, at den reelle behandlingsvarighed vil afvige fra studiets faste fordeling grundet moderne PET-udstyr og moderne fortolkningspraksis. Vi er bevidste om at de danske real world-data på dette punkt endnu ikke er publiceret.
- På trods af betydningen af denne antagelse, er der ikke vurderet behov for at fremføre en følsomhedsanalyse. Vi mener det vil være retvisende at belyse betydningen af ændringer i behandlingsvarighed.
- Der bør samtidig lægges vægt på, at den samlede budget impact forventes at være begrænset, da indikationen vedrører en relativt lille patientpopulation, og behandlingen gives i et afgrænset antal cyklusser. Eventuelle forskelle i lægemiddelomkostninger skal derfor vurderes i lyset af et begrænset samlet budgetaftryk, særligt hvis dansk klinisk praksis medfører en højere andel patienter med fire cyklusser end antaget i Medicinrådets base case.

3) Nyteværdier for helbredsrelateret livskvalitet

Medicinrådet vælger at erstatte behandlingsspecifikke nytteværdier med progressionsbaserede, stadiespecifikke værdier. Vi er forstående for dette valg, grundet statistisk signifikans ikke opnåes (omend marginalt, $p=0.065$). Dog er det endnu en parameter med væsentlig betydning, hvor det har værdi at nuancere billedet.

- Det indsendte valg for behandlingsspecifik modellering af nytteværdi, var valgt i overensstemmelse med regimernes forskellige tolerabilitet. Det var vurderet at omend statistisk signifikans ikke var opnået, så var der stadig et klinisk rationale for at livskvaliteten bør være lavere hos patienter behandlet med escBEACOPP, som følge af dets høje toksicitet. Dette er reflekteret i den store og signifikante forskel i det primære endepunkt *Treatment Related Morbidity* (TRMB) mellem de to behandlingsarme.

Takeda ønsker samtidig at bemærke, at en villighed fra Medicinrådets sekretariat om tættere løbende dialog og større transparens undervejs i forløbet potentielt kunne have bidraget til at afklare flere forhold tidligere i processen.

Med venlig hilsen

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Forhandlingsnotat

11.08.2026

DBS/LSC

Dato for vurdering i Medicinrådet	02.09.2026
Leverandør	Takeda
Lægemiddel	Adcetris (brentuximab vedotin)
Ansøgt indikation	Behandling af voksne patienter med ikke tidligere behandlet CD30+ HL stadie IIB med risikofaktorer, stadie III eller stadie IV i kombination med etoposid, cyclophosphamid, doxorubicin, dacarbazin og dexamethason (BrECADD).
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Adcetris:

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (pakning)	AIP (DKK)	Forhandlet SAIP (DKK)	Forhandlet rabat ift. AIP
Adcetris	50 mg (1 stk.)	18.321,73		

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Adcetris, indkøbes lægemidlet til AIP.

Aftaleforhold

Amgros har en eksisterende aftale på Adcetris. Aftalen gælder til den 31.03.2027 med mulighed for at forlænge i 4 x 6 måneder. Der er inkluderet mulighed for prisregulering i aftalen.

[REDACTED]

Informationer fra forhandlingen

[REDACTED]

[REDACTED]

[REDACTED]

Konkurrencesituationen

Patienter med avanceret Hodgkin lymfom behandles på hæmatologiske afdelinger med intensiv kemoterapi, eventuelt suppleret med strålebehandling. Flere behandlingsregimer anvendes i klinisk praksis, og behandlingen tilpasses den enkelte patient.

Medicinrådet har i juni 2026 anbefalet Opdivo (nivolumab) i kombination med doxorubicin, vinblastin og dacarbazin (AVD) til voksne og unge på 12 år og derover med tidligere ubehandlet klassisk Hodgkins lymfom i stadie III eller IV. Denne behandling er ikke vurderet ift. Adcetris. Lægemiddeludgiften til behandling med Opdivo er [REDACTED] ved en dosering på 240 mg hver 2. uge i 6 serier af 28 dage, jf. SmPC på Opdivo.

Adcetris er tidligere vurderet af Medicinrådet til kutant T-celle lymfom (ikke anbefalet) og tidligere ubehandlet systemisk anaplastisk storcellet T-celle lymfom (delvis anbefalet).

[REDACTED]

Adcetris administreres sammen med etoposid, cyclophosphamid, doxorubicin, dacarbazin og dexamethason i en 21-dages behandlingsserie. Behandlingen gives i 4 eller 6 serier afhængigt af en PET-scanning, jf. Medicinrådets vurdering af brentuximab vedotin til behandling af tidligere ubehandlet avanceret Hodgkin lymfom.

Tabel 2 viser lægemiddeludgifter ved behandling med Adcetris for et behandlingsforløb på hhv. 4 og 6 serier. Lægemiddeludgifter til kemoterapi er ikke inkluderet i tabel 2, da de udgør en minimal del af de samlede lægemiddeludgifter.

Tabel 2: Lægemiddeludgift pr. patient

Lægemiddel	Styrke (pakning)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling (SAIP, DKK)
Adcetris	50 mg (1 stk.)	1,8 mg/kg* hver 3. uge i op til 6 serier, i.v.		4 serier: 6 serier:

*Patientvægt 76,16 kg, jf. Medicinrådets vurdering af brentuximab vedotin til behandling af tidligere ubehandlet avanceret Hodgkin lymfom.

Status fra andre lande

Tabel 2: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
Sverige	Under vurdering	Link til status
England	Anbefalet	Link til anbefaling

Opsummering

Amgros har en aftale på Adcetris, der gælder til den 31.03.2027 med mulighed for at forlænge. Den tilbudte SAIP er betinget af en anbefaling.





Application for assessment of
Adcetris (brentuximab vedotin) 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)

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information
[Other]	[Definition of color-code]



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Abbreviations

Abbreviation	Definition
ABVD	Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine
ASCT	Autologous Stem Cell Transplant
ATMP	Advanced Therapy Medicinal Products
AVD	Doxorubicin, Vinblastine, and Dacarbazine
BEGR	Dispensing Group
BrECADD	Brentuximab Vedotin, Etoposide, Cyclophosphamide, Doxorubicin, Dacarbazine, Dexamethasone
BSA	Body Surface Area
COPD	Chronic Obstructive Pulmonary Disease
CP	Cardiopulmonary
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-Cell Lymphoma
CVD	Cardiovascular Disease
DMC	Danish Medicines Council
DRG	Diagnosis-Related Group



eBEACOPP	Escalated BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone)
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EMA	European Medicines Agency
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EORTC	European Organization for Research and Treatment of Cancer
-------	--

EPAR	European Public Assessment Report
------	-----------------------------------

FAS	Foreningen af Speciallæger
-----	----------------------------

FSH	Follicle Stimulating Hormone
-----	------------------------------

G-CSF	Granulocyte Colony-Stimulating Factor
-------	---------------------------------------

GHSg	German Hodgkin Study Group
------	----------------------------

HL	Hodgkin Lymphoma
----	------------------

HRQoL	Health-Related Quality of Life
-------	--------------------------------

HSUV	Health State Utility Values
------	-----------------------------

ICER	Incremental Cost-Effectiveness Ratio
------	--------------------------------------

ILD	Interstitial Lung Disease
-----	---------------------------

IV	Intravenous
----	-------------

JNHB	Joint Nordic Assessment
------	-------------------------

NCRD	No Clinically Relevant Decrease
------	---------------------------------

NLPHL	Nodular Lymphocyte-Predominant Hodgkin Lymphoma
-------	---

NR	Not Reported
----	--------------

OS	Overall Survival
----	------------------

PET	Positron Emission Tomography
-----	------------------------------

PFS	Progression-Free Survival
-----	---------------------------



PLO	Praktiserende Lægers Organisation
PO	Per Os (by mouth)
QALY	Quality-Adjusted Life Year
R/R HL	Refractory Hodgkin Lymphoma
RLTN	Regionernes Lønnings- og Takstnævn
sALCL	Systemic anaplastic large cell lymphoma
SC	Secondary Cancer
SLR	Systematic Literature Review
TRMB	Treatment Related Morbidity



1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	Adcetris
Generic name	Brentuximab Vedotin
Therapeutic indication as defined by EMA	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)
Marketing authorization holder in Denmark	Takeda Pharma A/S
ATC code	L01FX05
Combination therapy and/or co-medication	Combination therapy with etoposide, cyclophosphamide, doxorubicin, dacarbazine and dexamethasone
(Expected) Date of EC approval	May 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes. EU/3/08/595; 15-JAN-2009: systemic Anaplastic Large Cell Lymphoma. EU/3/08/595; 21-AUG-2019: Peripheral T-Cell Lymphoma.
Other therapeutic indications approved by EMA	<u>Hodgkin lymphoma</u> 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). 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). 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. <u>Systemic anaplastic large cell lymphoma</u> ADCETRIS in combination with cyclophosphamide, doxorubicin and



Overview of the medicine	
	prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). ADCETRIS is indicated for the treatment of adult patients with relapsed or refractory sALCL. <u>Cutaneous T-cell lymphoma</u> ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy
Other indications that have been evaluated by the DMC (yes/no)	<u>Systemic anaplastic large cell lymphoma</u> ADCETRIS in combination with cyclophosphamide, doxorubicin and prednisone (CHP) is indicated for adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL). <u>Cutaneous T-cell lymphoma</u> ADCETRIS is indicated for the treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy
Joint Nordic assessment (JNHB)	Are the current treatment practices similar across the Nordic countries (DK, FI, IS, NO, SE)? No Is the product suitable for a joint Nordic assessment? No If not, why not? Reimbursed for this indication in Sweden.
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Pack of one vial containing 50 mg of powdered brentuximab vedotin for reconstitution and infusion. After reconstitution in 10 mL each mL contains 5 mg of brentuximab vedotin.



2. Summary table

Provide the summary in the table below, maximum 2 pages.

Summary	
Indication relevant for the assessment	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).
Dosage regimen and administration	21-day cycle of BrECADD: 1.8 mg/kg Adcetris by infusion on day 1 of a 21 day cycle by infusion in combination with: Cyclophosphamide: 1.250 mg/m² on day 2 of a 21 day cycle. Doxorubicin: 40mg/m² on day 2 of a 21 day cycle. Etoposide: 150 mg/m² on day 2-4 of a 21 day cycle. Dacarbazine: 250 mg/m² on day 3-4 of a 21 day cycle. Dexamethasone 40 mg on day 2-5 of 21 day cycle. Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive.
Choice of comparator	21-day cycle of eBEACOPP: Bleomycin 10 mg/m², day 8 Etoposide 200 mg/m², day 1-3 Doxorubicin 35 mg/m², day 1 Cyclophosphamide 1.250 mg/m², day 1 Vincristine 1.4 mg/m² (max 2 mg), day 8 Procarbazine 100 mg/m², day 1-7 Prednisone 40 mg/m², day 1-14 Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive.
Prognosis with current treatment (comparator)	The prognosis for patients with advanced Hodgkin Lymphoma treated with the comparator (eBEACOPP) is good, when measured solely as progression free survival and overall survival. Thus, 5-year PFS and OS rates are 91% and 98%, respectively (1). However, the treatment is associated with significant acute and long term toxicities such as life-threatening grade 4 cytopenias and organ toxicities (2), secondary cancers (AML/MDS and solid tumors) (1, 3), cardiovascular (4) and pulmonary (5) disease, persistent fatigue (6, 7), loss of gonadal function (8), infertility (9), loss of affiliation with labor market (7), permanently reduced quality of life (10), and non-HL related excess mortality (11, 12).
Type of evidence for the clinical evaluation	Investigator initiated international, randomized, active comparator, head-to-head phase 3 study.



Summary	
Most important efficacy endpoints (Difference/gain compared to comparator)	Treatment related morbidity: 42% vs. 59%, relative risk 0.72 (95% CI: 0.65 – 0.80), $p < 0.0001$ 4-years PFS rate: 94.3% (95% CI: 92.6 – 96.1) vs. 90.9% (95% CI: 88.7 – 93.1), HR: 0.66 (95% CI: 0.45 – 0.97), $p=0.035$ Gonadal Function Recovery: Follicle Stimulating Hormone levels returned to baseline levels after 4 years: females: 95.3% (95% CI: 92.0% – 98.8%) vs. 72.5% (95% CI: 66.1% – 79.5%); males: 86.0% (95% CI: 81.1% – 91.1%) vs 39.2% (33.2% – 46.4%). Live child births: 62 vs. 46, $p < 0.0001$.
Most important serious adverse events for the intervention and comparator	Intervention (BrECADD) <u>SAEs:</u> - Febrile Neutropenia: 20.1% - Pyrexia: 5.2% - Neutropenia: 3.1% <u>Grade 3-4 AEs:</u> -Leukopenia: 86.5% -Thrombocytopenia: 55.0% -Anemia: 29.5% -infection: 28.1% -gastrointestinal disorder (excl. Nausea, vomiting, and mucositis): 7.8% -mucocitis: 4.4% -neutropenia: 9.5% Comparator (eBEACOPP) <u>SAEs:</u> - Febrile Neutropenia: 15.9% - Pyrexia 6.2% - Neutropenia 2.8% <u>Grade 3-4 AEs:</u> -Leukopenia: 94.2.5% -Thrombocytopenia: 71.9% -Anemia: 58.7 -infection: 24.7% -gastrointestinal disorder (excl. Nausea, vomiting, and mucositis): 4.5% -mucocitis: 5.8% -neutropenia: 11.1%
Impact on health-related quality of life	Health economic model: BrECADD demonstrates improved Quality-Adjusted Life Years (QALY) compared to eBEACOPP .
Type of economic analysis that is submitted	Cost utility analysis (Partitioned survival model)
Data sources used to model the clinical effects	The HD21 study: Assessing the efficacy and tolerability of PET-guided BrECADD versus PET-guided eBEACOPP in advanced-



Summary	
	stage, classical Hodgkin lymphoma (HD21): a randomized, multicentre, parallel, open-label, phase 3 trial (13).
Data sources used to model the health-related quality of life	The HD21 study: Assessing the efficacy and tolerability of PET-guided BrECADD versus PET-guided eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomized, multicentre, parallel, open-label, phase 3 trial (13).
Life years gained	
QALYs gained	
Incremental costs	
ICER (DKK/QALY)	
Uncertainty associated with the ICER estimate	
Number of eligible patients in Denmark	Incidence: 60 Prevalence: 0
Budget impact (in year 5)	



3. The patient population, intervention, choice of comparator(s) and relevant outcomes

3.1 The medical condition

Pathophysiology and clinical presentation

Classic Hodgkin Lymphoma (HL) is a type of lymphoma characterized by large, abnormal lymphocytes (Reed-Sternberg cells).

The clinical presentation of HL is diverse, with symptoms depending on the disease stage and organ involvement. Common symptoms include lymphadenopathy, B Symptoms (fever, night sweats, and weight loss), fatigue, and pruritus. Some patients additionally experience respiratory symptoms (cough, chest pain, and shortness of breath) caused by mediastinal lymphadenopathy, as well as abdominal discomfort (bloating, early satiety) caused by splenomegaly and/or hepatomegaly. Finally, bone marrow infiltration can cause anemia, leucopenia, and thrombocytopenia. Age at HL diagnosis displays a biphasic distribution with most patients diagnosed as adolescents or young adults but with a second, smaller, incidence peak among older people, see Figure 47 Appendix Q for illustration of age-dependent incidences.

Prognosis

Advanced Hodgkin lymphoma is an aggressive life-threatening disease, which – if left untreated – is invariably fatal. However, up-front aggressive multicomponent chemotherapy leads to excellent cure-rates for the younger (< 60 years of age) and fitter patients who can sustain aggressive treatment. On the other hand, elderly and/or unfit patients, who cannot sustain aggressive treatments, face a progressively worse prognosis. See Figure 48 Appendix Q for illustration of age dependent survival.

Influence of current treatment on functioning and health related quality-of-life

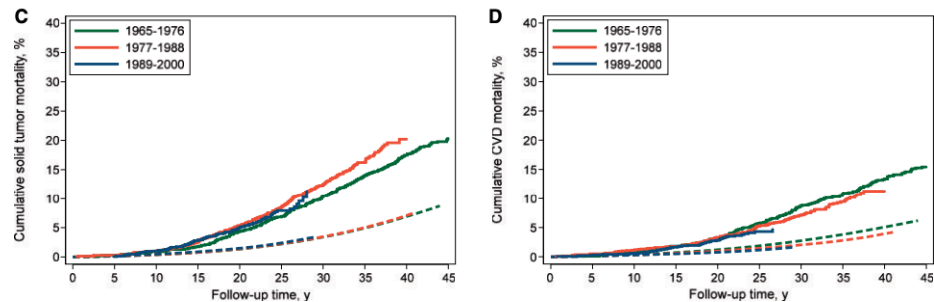
The very high cure rates of the intensive medicinal and radiotherapy treatments offered to patients with advanced HL are associated with a significant toxicity burden.

Acute toxicities include febrile neutropenia, thrombocytopenia, anemia, leukopenia, infections, pulmonary and cardiac disease, hepatobiliary, renal, gastrointestinal, and nervous system disorders including peripheral sensory and motor neuropathy (14).

Long term toxicities are significant and include persistent fatigue, dyspnea, cognitive impairment, decreased thyroid function, loss of gonadal function, premature menopause in females, and infertility for both males and females (6, 7, 10, 15, 16). Long-term toxicities also include development of pulmonary- and cardiac-disease and secondary cancers; MDS, AML and solid tumors, leading to excess mortality of otherwise cured HL patients over time, exemplified in Figure 1. (5, 12, 16-20).



Figure 1. Excess mortality among Hodgkin lymphoma survivors



Cumulative solid tumor mortality (left panel) and cardiovascular disease mortality (right panel) among Hodgkin lymphoma survivors (solid lines) as compared to the general population (dashed lines). Colors indicate the period of diagnosis. From (12).

These long-term treatment related morbidities result in delays in return-to-work after treatment (7, 21, 22), a decrease in life-income (23), and a persistent and clinically significant reduced health related quality of life for survivors of HL (7, 10).

Influence on function and health for Danish Patients

In accordance with the above international and historic data, contemporary Danish data published from 2023 to 2025 have shown that HL survivors in complete remission have significantly increased risk of sick leave and delayed return to work (21), excess non-HL mortality caused by secondary cancers, congestive heart failure, and pulmonary disease (4, 5, 11), as well as a 40% reduction of fatherhood as compared to healthy matched controls (9). Table 1 summarizes recent studies on long-term consequences of HL treatment for Danish patients.

Table 1: Summary of Danish research on long-term consequences of HL treatment on Danish HL survivors.

Finding	Patients / time period	Ref
Pulmonary disease, COPD and ILD. HR 2.93 (95% CI 2.33-3.68) for ABVD and BEACOPP treated patients vs. matched controls	18-60 years of age, Treated 2000-2018.	(5)
Higher risk of death from long-term toxicities than death from HL. Cause specific mortality 25 years following HL diagnoses: HL: 5.7% Secondary Cancers: 4.0% Cardio/Pulmonary: 2.8%	15-40 years of age. Diagnosed 1995-2015.	(11)
Loss of affiliation with labor market 30% of HL patients lose affiliation with labor market when diagnosed.	18-60 years of age, matched controls	(21)
Cardiovascular diseases HR: 1.87 (95% CI: 1.58-2.23) for HL patients vs matched controls	≥ 18 years of age. Diagnosed 2000-2022.	(24)
Reduced Quality of Life, QLQ-C30 Overall, lower QoL across length of follow-up. Lower QoL for functional domains global health, physical, role, cognitive, and social functioning across all lengths of follow-up; short and medium follow-up groups also had lower emotional	> 18 years of age. Diagnosed after 2000 1.777 HL patients and 6.166 matched controls	(16)



Finding	Patients / time period	Ref
function. More fatigue, dyspnea, and insomnia and financial problems.		
Reduced fertility 40% reduction in fatherhood for eBEACOPP treated males.	18-40 years of age. 1995-2018.	(9)
COPD: Chronic Obstructive Pulmonary Disease. ILD: Interstitial Lung Disease. HL: Hodgkin Lymphoma. CVD: coronary artery disease, acute coronary syndrome, heart failure, aortic-, mitral-or tricuspid stenosis, cardiomyopathy, restrictive pericarditis, or atrial or ventricular arrhythmias.		

Summary

HL is a life-threatening disease that is highly curable for young and fit patients using aggressive systemic chemotherapy. However, aggressive treatment results in a very high treatment burden characterized by both acute and persistent toxicities. This results in persistently decreased quality of life among survivors who suffer from decreased fertility, early menopause, loss of gonadal function (9, 15), high risk of peripheral neuropathy, chronic fatigue, cognitive impairment, and dyspnea resulting in persistent negative impacts on quality of life and life income (6, 7, 10, 23). Additionally, HL survivors are at increased risk of death from cardiovascular disease and secondary cancers such as AML/MDS (12, 17-19). As HL frequently occurs in young adults there is a need for treatments that are not associated with high rates of acute and persistent long-term toxicities while retaining the high cure rates of current treatments.

3.2 Patient population

Patient population: newly diagnosed Hodgkin lymphoma patients, age 18-60 years with advanced disease (stage IIb with bulky disease and/or lymph node involvement to stage IV).

No patient characteristics affect prognosis or relative effectiveness of the intervention compared to the control (2, 25).

Table 3 summarizes incidence and prevalence in Denmark from 2020-2025. Note that this data is not available from 2023 to 2024, NR (26).

Table 2 Incidence and prevalence of HL from 2020 to 2024. All incidences are reported pr. 100.000 inhabitants (26).

Year	2020	2021	2022	2023	2024
Incidence in Denmark	3.0	2.6	3.0	NR	NR
Prevalence in Denmark	12.5	12.2	12.3	NR	NR
Global prevalence *	10.5	10.3	10.2	NR	NR

* For small patient groups, also describe the worldwide prevalence.



Table 3 provides an estimate of the total number of patients eligible for treatment based on data from the Danish Lymphoma Database (LyFo) (27). Numbers are yearly average of numbers of advanced stage patients aged 18 – 60 from 2015 to 2023 (27) with a deduction of 5% pr year to account for rare patients not eligible for treatment due to severe morbidities.

Table 3 Estimated number of patients eligible for treatment according to the Danish Lymphoma Database (27).

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of Diagnosed patients	63	63	63	63	63
Number of patients in Denmark who are eligible for treatment in the coming years	60	60	60	60	60

3.3 Current treatment options

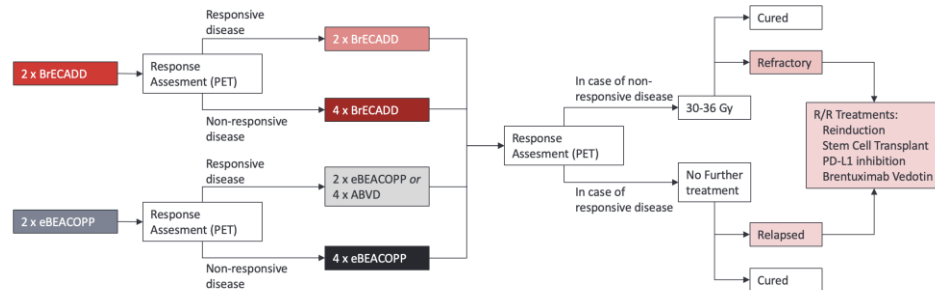
Current Danish treatment for advanced Hodgkin lymphoma

Current treatment guideline from the Danish Hodgkin group recommend response adapted BrECADD and escalated BEACOPP (eBEACOPP) as standard 1st line treatmentsFigure 2 Table 4 (28).

Following an intermittent PET-scan after two cycles of therapy both regiments allow for an additional two cycles of therapy in case of response, or escalation to an additional four cycles of therapy in case of lack of response, Figure 2. For eBEACOPP, the last four cycles can be replaced by four cycles of the less efficacious ABVD regiment, Figure 2. As of May 2026, this option is reserved for rare frail patients, Table 3. Correspondingly, it will not be further addressed. A few patients will relapse, and others harbor tumors that do not respond adequately to chemotherapy. These patients with relapsed or refractory Hodgkin lymphoma (R/R HL) are treated with second-line combination chemotherapy which is non-cross-resistant with the first-line therapy, typically with a gemcitabine and/or platinum base followed by high-dose chemotherapy with autologous stem cell support. Later relapses are treated with PD-1 inhibitors and brentuximab vedotin, Figure 2.



Figure 2: Overview of HL treatments in Denmark.



ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine. BrECADD: Brentuximab vedotin, cyclophosphamide, doxorubicin, etoposide, dacarbazine, and dexamethasone. eBEACOPP: escalated BEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone. Gy: Gray. PET: positron emission tomography. Based on (29).

Table 4: Overview of components, concentration, and infusion schedule of BrECADD and eBEACOPP.

BrECADD – 21 day cycle	eBEACOPP – 21 day cycle
1.8 mg/kg Adcetris by infusion on day 1 Cyclophosphamide: 1.250 mg/m ² on day 2. Doxorubicin: 40mg/m ² on day 2. Etoposide: 150 mg/m ² on day 2-4. Dacarbazine: 250 mg/m ² on day 3-4. Dexamethasone 40 mg on day 2-5.	Bleomycin 10 mg/m ² , day 8 Etoposide 200 mg/m ² , day 1-3 Doxorubicin 35 mg/m ² , day 1 Cyclophosphamide 1.250 mg/m ² , day 1 Vincristine 1.4 mg/m ² (max 2 mg), day 8 Procarbazine 100 mg/m ² , day 1-7 Prednisone 40 mg/m ² , day 1-14 Optional: Peg. G-CSF, 6 mg, day 4 (recommended)

Current Treatment Practice

BrECADD is not reimbursed in Denmark. eBEACOPP is therefore considered current standard of care and is the comparator in this application; BrECADD is the intervention.

Prognosis with current treatment

Table 5 summarizes the efficacy and toxicities of response guided eBEACOPP, broken down according to PET2(response)-status.

Table 5. Summary of prognoses (efficacy and toxicity) for eBEACOPP.



eBEACOPP	PET2- negative	PET2-positive	Reference
5-yr PFS, %	91.0	90.1	(1)
95% CI	86.6 – 95.1	87.2 – 92.9	
5-yr OS, %	97.5	96.7	(1)
95% CI	95.0–100.0	94.9 – 98.4	
Acute grade 3 – 4 toxicities, %	91	95	(30)
Secondary Malignancies, %	3.7	3.3	(1)
Loss of gonadal function, %			
Females	21	37	(8)
Males	58	62	

Toxicity is summarized as the percentage of patients experiencing CTCAE grade 3 and 4 toxicity.
Yr: year. CI: confidence interval.

While eBEACOPP is clearly very efficacious, it carries a risk of secondary malignancies, lung toxicity, life-long reduced gonadal function and reduced fertility despite use of reproductive assistance as well as the toxicities laid out in 3.1.

Integrated care; preservation of gonadal function and assisted reproduction techniques

eBEACOPP is gonadal toxic and is associated with significant risk of premature menopause and infertility (31).

All female patients of child bearing potential are therefore offered as individualized assessment of the indication for cryopreservation of ovarian tissue prior to initiation of treatment and/or cryopreservation of unfertilized or fertilized oocytes as part of comprehensive assisted reproduction treatment (31). Following a two-year observational period cryopreserved tissue can be reinserted to stimulate reinitiation of menstrual cycles.

Female patients can subsequently undergo in-vitro fertilization procedures.

Male patients cryopreserve spermatocytes prior to treatment initiation.

Despite these procedures, 25% and 60% of eBEACOPP treated women and men do not recover gonadal function after treatment (8), resulting in a roughly 40% reduction in fatherhood for male HL survivors in Denmark (9).

Additionally, cryopreservation of ovarian tissue and oocytes results in significant delays in treatment initiation.

Integrated care: impact on relatives

Sixty percent of male HL survivors do not recover gonadal function following curative treatment (2, 32). Partners of male patients with pregnancy-wish may therefore undergo in-vitro fertilization procedures using cryopreserved spermatocytes. Despite this, male survivors of HL and their female partners experience a roughly 40% life-time reduction in live births as compared to aged-matched controls (9).



3.4 The intervention

Adcetris, brentuximab vedotin, is an antibody-drug-conjugate of a CD30-targeted antibody brentuximab with a microtubule disrupting chemotherapeutic agent vedotin (monomethyl auristatin E, MMAE).

In this application Adcetris is incorporated into an overall update on the long-standing treatment regimen escalated BEACOPP (eBEACOPP). This update aims to address some of the recognized toxicities of eBEACOPP while retaining the established efficacy.

BrECADD was designed to result in fewer acute toxicities (infections, cytopenias, peripheral sensory neuropathy) and long-term persistent toxicities such as AML/MDS, pulmonary toxicities and peripheral sensory neuropathy.

Table 6 provides a summary overview of changes/rationale and expected outcomes; from the clinical study protocol of HD21 (13).

Table 6 Changes to the eBEACOPP regimen resulting in BrECADD

Drug	Change	Rationale
Bleomycin	Remove	Eliminate risk of bleomycin induced pulmonary toxicities
Vincristine	Replace with Adcetris (brentuximab vedotin)	Targeted delivery of a microtubule disrupting agent (brentuximab vedotin) to the tumor cells makes the broad administration of a non-targeted microtubule agent (vincristine) unnecessary. Expected to increase the efficacy while reducing vincristine associated grade 3-4 polyneuropathies
Etoposide	Reduce dose to 150 mg/m ² (from 200 mg/m ²)	Reduce risk of secondary AML/MDS as etoposide is a major driver of secondary AML/MDS
Doxorubicin	Increase dose from 35mg to 40mg	Maintain cumulative dose of chemotherapy
Prednisone	Replace 14 days of prednisone with 4 days of dexamethasone	Reduce risk of serious infections and cytopenias during the aplasia phase (usually commencing between day 6 and 10 of each chemotherapy cycle)
Procarbazine	Replace 7 days of oral administration of procarbazine with 2	Reduce risk of secondary AML/MDS as procarbazine is a major driver of secondary AML/MDS.Reduce risk of



	days of IV dacarbazine.	gonadal toxicity/infertility as procarbazine is a major driver of gonadal toxicity
Cyclophosphamide	No changes	

One cycle of BrECADD is completed in four days as opposed to the 10-day regimen of BEACOPP, making BrECADD easier to schedule and manage for both clinics and patients (note: the EMA indication stipulates administration of dexamethasone on days 2-5 resulting in BrECADD being a five-day schedule. In Real-World practice dexamethasone is administered on day 1-4).

Below gives an overview of the various components of BrECADD (the intervention).

Overview of intervention	
Indication relevant for the assessment	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).
ATMP	No.
Method of administration	Infusion.
Dosing	1.8 mg/kg on day 1 of a 21-day cycle. Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive.
Dosing in the health economic model (including relative dose intensity)	1.8 mg/kg on day 1 of a 21-day cycle (RDI 99%). Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive.
Should the medicine be administered with other medicines?	Cyclophosphamide: 1.250 mg/m ² on day 2 of a 21-day cycle. Doxorubicin: 40mg/m ² on day 2 of a 21-day cycle. Etoposide: 150 mg/m ² on day 2-4 of a 21-day cycle. Dacarbazine: 250 mg/m ² on day 3-4 of a 21-day cycle. Dexamethasone 40 mg on day 2-5 of 21-day cycle. Additional: Peg. G-CSF, 6 mg on day 5 of a 21-day cycle. An antibiotic prophylaxis must be given 3 x/week during the whole duration of chemotherapy. Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive.
Treatment duration / criteria for end of treatment	In case of chemo-responsive disease (negative interim PET2): four infusions over 77 days



Overview of intervention	
	In case of lack of interim response (positive interim PET2): six infusions over 119 days.
Necessary monitoring, both during administration and during the treatment period	Complete blood counts should be monitored prior to administration of each dose of treatment. Patients should be monitored during and after infusion
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Response to therapy must be monitored by PET-scanning after two cycles of treatment in accordance with current Danish practice for response adapted treatments for HL (29). The costs for PET and CT scans are included in the model during the pre-oncologic phase for monitoring and in the post-oncologic phase for follow-up.
Package size(s)	1 pack of one 50 mg vial.
Dosage assumption used in the model	Body weight: 76.16 kg, HD-21 study BSA: 1.91 m², HD21-study

3.4.1 Description of ATMP

N/A.

3.4.2 The intervention in relation to Danish clinical practice

The intervention is expected to replace the use of escalated BEACOPP (eBEACOPP) for response adapted 1st line treatment of Hodgkin lymphoma for patients 18 to 60 years of age.

It is expected that replacement of eBEACOPP with BrECADD will result in a decreased need for integrated care at fertility clinics such as fertility preserving procedures and assisted reproductive treatments.

Replacement of eBEACOPP with BrECADD in 1st line treatment is expected to result in fewer Relapsed/Refractory HL patients yearly.

Replacement of eBEACOPP with BrECADD in 1st line treatment is not expected to change subsequent treatment choice for Relapsed/Refractory patients significantly as choice of re-induction regimens, stem-cell transplant, and PD-1 inhibition is mostly agnostic to the 1st line treatment choice and 3rd - 4th line retreatment with single agent Adcetris is a well-established treatment choice with good chance of response following prior exposure to Adcetris. Finally, use of Adcetris in the Relapsed/Refractory setting for 18–60-year-old individuals is already an infrequent event, as most HL patients < 60 typically are cured in the 1st line setting.



Replacement of eBEACOPP with BrECADD will not require any changes to diagnostic test or patient selection currently employed in Denmark.

3.5 Choice of comparator(s)

Danish clinical guidelines recommend response adapted BrECADD or response adapted escalated BEACOPP as equal treatment options (29).

As of May 2026, BrECADD is not approved by the Danish Medicines Council for treatment of fit 18–60-year-old patients.

The comparator is therefore response adapted escalated BEACOPP (eBEACOPP, Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone).

An overview of the individual components of eBEACOPP (the comparator) is provided in appendix O.

3.6 Cost-effectiveness of the comparator(s)

There has not been a DMC evaluation of the cost-effectiveness of eBEACOPP. Possible because the regimen is 20 years old, have strong progression-free-survival (PFS) and overall survival (OS) rates (29), and is composed of low-cost components.

Given the established nature of eBEACOPP in Danish treatment of HL, impressive efficacy, and low cost of the current treatment, placebo is considered irrelevant as comparator in this application.

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Table 7 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall Survival	Continuously	Time from enrolment until death from any cause	Death was evaluated by investigators at every study visit in the ITT population.
Progression Free Survival	Continuously	Time from enrolment until disease progression, relapse or death from any cause	Progression and/or death was evaluated by investigators at every study visit in the ITT population.



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
TRMB, Treatment Related Morbidity	During primary chemotherapy administration; including a period of 30 days after the last chemotherapy dose.	Any acute non-hematological organ toxicity of CTCAE grade 3 or 4 of the following system organ classes: Cardiac Disorders, Gastrointestinal Disorders (excluding vomiting, nausea and mucositis), Hepatobiliary Disorders, Nervous System Disorders, Renal and Urinary Disorders, Respiratory, Thoracic and Mediastinal Disorders. Acute hematological toxicity: Grade 4 Anemia, Grade 4 Thrombocytopenia, Grade 4 Infections	TRMB was measured by investigators at study visits and in case of hospitalizations outside of study visits in the ITT population.
Gonadal Function Recovery, GHSG	Before start of treatment.	Ovarian recovery was defined as return of FSH levels to < 25 U/L.	Blood samples in the population <i>Patients of Child Bearing Potential</i> : females < 40 years of age and males < 50 years of age, with baseline FSH levels < 25 U/L and < 15U/L, respectively.
Levels of Follicle Stimulating Hormone	At end of treatment (chemotherapy)	Testicular recovery was defined as return to FSH levels to < 15 U/L.	
Study: HD21	Every 12 months after end of treatment for five years.		
Gonadal Function Recovery, Takeda	Before start of treatment.	Ovarian recovery was defined as return of FSH levels to < 21.5 U/L.	Blood samples in the population <i>Patients of Child Bearing Potential</i> : females < 40 years of age and males < 50 years of age, with baseline FSH levels < 25 U/L and < 15U/L, respectively.
Levels of Follicle Stimulating Hormone	At end of treatment (chemotherapy)	Testicular recovery was defined as return to FSH levels to < 12.4U/L.	
Study: HD21	Every 12 months after end of treatment for five years.		



Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Live Births Fraction of live births in each arm. Fraction of live births among study subjects who declared a wish to have children in the future	Assessed following study end at follow-up. Every 12 months after end of treatment for five years.	Live birth is defined as any birth resulting in a live child.	Pregnancies, spontaneous and provoked abortions, still births and live births was collected in the ITT population and among ITT population members who declared a wish to have children in the future.
Failure Free Survival	Median follow-up was 11 months.	Time from treatment to the first occurrence of either disease progression, relapse, treatment stop, or death from any cause.	Data was collected directly from electronic health records at Odense University Hospital.

* Time point for data collection used in analysis (follow up time for time-to-event measures). GSGH; German Hodgkin Lymphoma Group.

Validity of outcomes

Progression Free Survival

In oncological studies, OS is considered the gold standard outcome for clinical efficacy. However, in Hodgkin lymphoma OS is not a practical outcome as current 1st line treatment has an extraordinarily high cure rate of $\geq 90\%$ and several subsequent treatment options exist. Together, this makes OS events rare and late occurring. Using OS as primary outcome would thus require very large patient populations and unrealistic long follow-up time (33). Consequently, the German Hodgkin Lymphoma Group, does not incorporate OS as a primary outcome in their studies (2, 13, 30, 33).

In 1st line HL studies PFS therefore is used as proxy for OS. This is based on a study of nine 1st line HL studies conducted by the German Hodgkin Lymphoma Group between 1995 and 2018. This study analyzed a total patient population of 10.605 individuals and found a strong correlation ($r = 0.72$, $R^2 = 0.54$, $P = 0.001$) between PFS events in 1st line treatment and OS over time (33).

PFS is thus a recognized and valid clinical outcome in treatment of Hodgkin lymphoma and replaces the less feasible OS as the predominant outcome of 1st line studies (2, 13, 33).

TRMB – Treatment Related Morbidity

TRMB is not an established endpoint in HL; it was created specifically to capture significant toxicities associated with treatment with eBEACOPP.

The rationale for developing TRMB as a composite endpoint is laid out below.



Virtually all patients treated with eBEACOPP will experience severe treatment related toxicity. However, the majority of these toxicities are transient and easily managed by experienced hematologist and are thus not considered significant, despite their severity. To capture significant acute and potentially long-term treatment related toxicities associated with eBEACOPP, the German Hodgkin Study Group defined a composite outcome that comprises clinically relevant toxicities of eBEACOPP. The chosen toxicities (and their grades) are based on extensive experience with eBEACOPP toxicities from the HD15 and HD18 clinical studies that developed eBEACOPP as a treatment option for HL.

The chosen toxicities are grade 4 anemia, grade 4 thrombocytopenia, and grade 4 infection, as well as grade 3-4 organ toxicity.

The reasoning for the chosen toxicities is laid out in Appendix N.

Gonadal Function Recovery

Measure of gonadal function recovery through serum measures of follicle stimulating hormone in male and females is a well-established and frequently used outcome of gonadal function recovery in Hodgkin lymphoma studies. Thus, the outcome has historically been utilized by the EORTC, the Italian, German and UK Hodgkin study groups (2, 30, 34-36).

In the HD21 study, ovarian and testicular recovery was considered achieved by the GHSG when FSH values were <25 U/L and <15 U/L, respectively. Following consultation with EMA, Takeda performed a supportive analysis using the more conservative cut-offs of <21.4 U/L and <12.4 U/L.

Live births

Live births is an intuitive measure of fertility that does not require formal validation.

Failure Free Survival

Failure Free Survival captures treatment success; not only being alive and free from disease progression, but also without need for secondary therapies and having completed the primary therapy. As such it captures not only disease control but also toxicity of treatment.

Overall Survival

In oncological studies, OS is considered the gold standard outcome for clinical efficacy. However, in Hodgkin lymphoma the high cure rates and young age of patients make OS an impractical endpoint (see above, PFS).

OS is therefore only included to ensure lack of detrimental effects of the intervention.



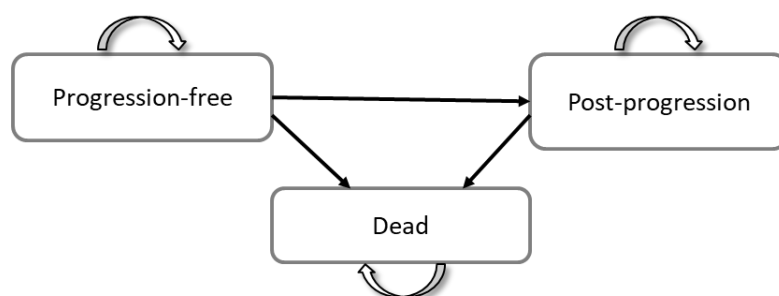
4. Health economic analysis

The choice of model is a cost-utility analysis using a partitioned survival model (PSM) comparing the two alternatives from the HD-21 study: BrECADD and eBEACOPP.

4.1 Model structure

The health state membership over time is determined by modeling and extrapolating two survival curves, PFS and OS. The model includes three mutually exclusive health states which reflects the treatment pathway, progression free, post-progression and dead. At any timepoint the proportion of patients falling under the PFS curve are in the “progression-free” health state, the proportion of patients falling above the OS curve are in the “dead” health state, and the difference (i.e., relapse and refractory patients who are alive but who have experienced progressed disease; OS - PFS) are in the “post-progression” health state. Long-term OS estimates are constrained by general population mortality informed by Danish life tables. PFS and OS curves are modeled using joint fits. Costs and QALYs were accrued according to the proportion of patients in the “progression-free” and “post-progression” states over time.

Figure 3 PSM health states; progression-free, post-progression, and dead.



Model features

Base-case analyses were based on patient-level data from the HD21 trial for patients aged 18-60 years at diagnosis (ITT population, data cutoff: October 31, 2023) which is further described in section 6.1.3. Table 8 describes all relevant model features in accordance with the Danish Medicines Council’s guidelines.

Table 8 Features of the economic model

Model features	Description	Justification
Patient population	ITT population from the HD21 study.	Head-to-head study comparison and described in section 3.
Perspective	Restricted societal perspective	According to DMC guidelines



Model features	Description	Justification
Time horizon	Lifetime (70 years)	To capture all health benefits and costs in line with DMC guidelines because of the high likelihood of cure and the relatively young trial population. Median age at diagnosis in the study which is in line with the Danish population treated with BrECADD.
Cycle length	1 week	To capture the possibility of progression and death events that occur within a short timeframe.
Half-cycle correction	Yes	Life-table method
Discount rate	3.5 % (costs and effects)	In accordance with the DMC guidelines.
Intervention	BrECADD	HD-21 intervention
Comparator(s)	eBEACOPP	HD-21 comparator
Outcomes	QALY (EQ-5D-3L)	In accordance with the DMC guidelines. Justification for using the 3L-version is found in section 10
	PFS and OS	To inform the PSM.

5. Overview of literature

5.1 Literature used for clinical assessment

The clinical assessment is exclusively informed by the HD-21 head-to-head study with the most relevant comparator in Danish clinical practice.

An additional Danish real-world study describing ██████ treated with BrECADD at a single center is included as validation of patient characteristics of a relevant Danish patient population.



Table 9 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut- offs)	Used in comparison of*
Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Borchmann, Ferdinandus, Schneider <i>et al.</i> The Lancet, Volume 404, Issue 10450, pp. 341 – 352. (2)	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.	NCT02661503	Start: 22/07/16 Completion: Follow-up for survival is ongoing Data cut-off: Primary Analysis 31/12/22 Secondary Analysis: 31/10/23 Future data cut-offs : NA	PET-guided BrECADD vs PET-guided eBEACOPP in patients with treatment-naïve, advanced HL in patients between 18 and 60 years of age.
Gonadal Function Recovery and fertility in patients with advanced-stage classical Hodgkin Lymphoma: comparison of BrECADD and eBEACOPP in the phase 3 German Hodgkin Study Group HD21 trial. Ferdinus, Schneider, Moccia <i>et al.</i> <i>Lancet Oncology Volumen 26, Issue 8, pp 1081-1090, 2025.</i> (8).				



Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut- offs)	Used in comparison of*
Jacob Haaber Christensen, 2025. Unpublished data. (37)	Real-World Study of BrECADD in Denmark	NA	Start: 01/04/25 Completion: 21/05/25 Data Cut-off: 21/05/25	Study summarizing patient characteristics and response among Danish HL patients treated with BrECADD.

* If there are several publications connected to a trial, include all publications used.

5.2 Literature used for the assessment of health-related quality of life

The utility scores in the health economic analysis are exclusively informed by the HD-21 head-to-head study with the relevant comparator in Danish clinical practice, thus literature search is omitted. Disutility for adverse events and infertility are informed by an TLR (see Appendix J) and the disutility for loss of gonadal function and Danish health state preferences are identified by a non-structured literature search, which was considered as a practical approach to identify a single input. The utility values can be found in the CEM under “**HRQoL**”, cell; **D3704** and **D3705** and Table 52.

Table 10 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
GHSG HD21 EudraCT: 2014-005130-55 NCT02661503 Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma	Progression-free and post-progression	Section 6, 8, and 10



Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
(HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024 Jul 27;404(10450):341-352 (2).		
Krol, M., Nap, A., Michels, R., Veraart, C., & Goossens, L. (2019). Health state utilities for infertility and subfertility. <i>Reproductive Health</i> , 16 doi: https://doi.org/10.1186/s12978-019-0706-9 (38).	Disutility for infertility	Applied in the model as utility decrements for infertility Appendix J
Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. <i>Health Qual Life Outcomes</i> . 2010;8:50 (39).	Disutility for Anemia	Applied in the model as utility decrements for adverse events 3+ Appendix J
Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. <i>Leuk Lymphoma</i> . 2015;56(6):1839-45 (40).	Disutility for Febrile neutropenia and Neutropenia	Applied in the model as utility decrements for adverse events 3+ Appendix J
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. <i>Health Qual Life Outcomes</i> . 2008;6:84 (41).	Disutility for Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis) and Mucositis	Applied in the model as utility decrements for adverse events 3+ Appendix J



Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ, et al. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1):193 (42)	Disutility for Infection	Applied in the model as utility decrements for adverse events 3+ Appendix J
Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90 (43).	Disutility for Leukopenia	Applied in the model as utility decrements for adverse events 3+ Appendix J
Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ. 2013;14(3):507-14 (44).	Disutility for Thrombocytopenia	Applied in the model as utility decrements for adverse events 3+ Appendix J

5.3 Literature used for inputs for the health economic model



Table 11 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
GHSG HD21 EudraCT: 2014-005130-55 NCT02661503 Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024 Jul 27;404(10450):341-352 (2).	PFS, OS, and HRQoL	HD-21 study	Section 6, 8 and 10
Wittrup-Jensen KU, Lauridsen J, Gudex C, Pedersen KM. Generation of a Danish TTO value set for EQ-5D health states. Scand J Public Health. 2009 Jul;37(5):459-66. doi: 10.1177/1403494809105287. Epub 2009 May 1. PMID: 19411320. (38)	Danish health state preferences	Non-structured literature search	Section 10
Young TA, Mukuria C, Rowen D, Brazier JE, Longworth L. Mapping Functions in Health-Related Quality of Life: Mapping from Two Cancer-Specific Health-Related Quality-of-Life Instruments to EQ-5D-3L. Med Decis Making. 2015 Oct;35(7):912-26. doi: 10.1177/0272989X15587497. Epub 2015 May 21. PMID: 25997920; PMCID: PMC4574084 (45).	Mapping algorithm from EORTC-QLQ-C30 to EQ-5D-3L	TLR	Section 10



Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Krol, M., Nap, A., Michels, R., Veraart, C., & Goossens, L. (2019). Health state utilities for infertility and subfertility. <i>Reproductive Health</i> , 16 doi:https://doi.org/10.1186/s12978-019-0706-9 (38).	Disutility for infertility: - 0.0020	TLR	Appendix J
Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. <i>Health Qual Life Outcomes</i> . 2010;8:50 (39).	Disutility for Anemia: - 0.09	TLR	Appendix J
Swinburn P, Shingler S, Acaster S, Lloyd A, Bonthapally V. Health utilities in relation to treatment response and adverse events in relapsed/refractory Hodgkin lymphoma and systemic anaplastic large cell lymphoma. <i>Leuk Lymphoma</i> . 2015;56(6):1839-45 (40).	Disutility for Febrile neutropenia: - 0.09 Neutropenia: - 0.09	TLR	Appendix J
Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. <i>Health Qual Life Outcomes</i> . 2008;6:8 (41).	Disutility for Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis): - 0,05 Mucositis: - 0.05	TLR	Appendix J



Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Stein EM, Yang M, Guerin A, Gao W, Galebach P, Xiang CQ, et al. Assessing utility values for treatment-related health states of acute myeloid leukemia in the United States. Health Qual Life Outcomes. 2018;16(1):193 (42).	Disutility for Infection: - 0.22	TLR	Appendix J
Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90 (43).	Disutility for Leukopenia: - 0.15	TLR	Appendix J
Brown RE, Stern S, Dhanasiri S, Schey S. Lenalidomide for multiple myeloma: cost-effectiveness in patients with one prior therapy in England and Wales. Eur J Health Econ. 2013;14(3):507-14 (44).	Disutility for Thrombocytopenia: - 0.31	TLR	Appendix J



6. Efficacy

6.1 Efficacy of BrECADD for previously untreated advanced stage Hodgkin lymphoma patients aged 18 to 60.

6.1.1 Relevant studies

Table 12 Overview of study design for studies included in the comparison

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
GHSG HD21 EudraCT: 2014-005130-55 NCT02661503 Borchmann P, Ferdinandus J, Schneider G, et al. Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin	Randomized, international, phase III, open-label, active comparator-control. Academically sponsored by the German Hodgkin Lymphoma Group. Conducted independently of Takeda.	12 or 18 weeks active treatment followed by 30 Gy radiotherapy in presence of residual tumor activity	Previously untreated advanced stage Hodgkin lymphoma patients aged 18 to 60. Definition of advanced stages included Ann Arbor stage III/IV as well as stage II with B symptoms and one or both risk factors of large mediastinal mass or	Four or six 21-day cycles of: Brentuximab vedotin, 1.8 mg/kg up to a maximum of 180 mg absolute dose intravenously on day 0. Etoposide, 150 mg/m ² intravenously on days 1–3. Cyclophosphamide, 1250 mg/m ² intravenously on day 1 Doxorubicin, 40	Four or six 21-day cycles (21 days) of: Etoposide, 200 mg/m ² intravenously on days 1–3 Doxorubicin, 35 mg/m ² intravenously on day 1 Cyclophosphamide 1250 mg/m ² intravenously on day 1 Bleomycin, 10 mg/m ² intravenously on	<u>Co-Primary outcomes:</u> 1) PFS-rate, 4-years follow-up 2) Rate of serious treatment-related morbidity (TRMB) during treatment, 30 days follow-up <u>Secondary outcomes:</u> 1) CR rates after completion of chemotherapy 2) Overall Survival, 4-years follow-up 3) Infertility rate at 1 year, one year follow-up 4) Second malignancies, 4-years follow up 5) Number of SAEs within 30 days after end of treatment 6) Therapy adherence – until end of therapy. 7) Quality of life before, during and after therapy, with FU to 5 years. All follow-up times were predefined.



Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial. Lancet. 2024 Jul 27;404(10450):341-352. (2)			extranodal lesions. ECOG PS 0-2.	mg/m ² intravenously on day 1. Dacarbazine, 250 mg/m ² intravenously on days 2–3, and Dexamethasone, 40 mg orally on days 1–4.	day 8 Vincristine (1.4 mg/m ² intravenously on day 8 procarbazine (100 mg/m ² orally on days 1–7), and Prednisone, 40 mg/m ² orally on days 1–14). In addition Peg. G-CSF, 6 mg on day 4 was recommended.	
GHSG HD21 EudraCT: 2014-005130-55 NCT02661503 Ferdinandus J, Schneider, Moccia <i>et al.</i> Gonadal Function Recovery and fertility in patients	Randomized, international, phase III, open-label, active comparator-control. Academically sponsored by the German Hodgkin Lymphoma Group.	12 or 18 weeks active treatment followed by 30 Gy radiotherapy in presence of residual tumor activity	Previously untreated advanced stage Hodgkin lymphoma patients with potential for parenthood: aged 18 to 40 (females) or 18 to 50 (males). Definition of	Four or six 21-day cycles of: Brentuximab vedotin, 1.8 mg/kg up to a maximum of 180 mg absolute dose intravenously on day 0. Etoposide, 150 mg/m ² intravenously on days 1–3.	Four or six 21-day cycles (21 days) of: Etoposide, 200 mg/m ² intravenously on days 1–3 Doxorubicin, 35 mg/m ² intravenously on day 1 Cyclophosphamide 1250 mg/m ²	1) Gonadal function recovery rate 48 months following termination of treatment. 2) Live births at 48 months following termination of treatment.



Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
with advanced-stage classical Hodgkin Lymphoma: comparison of BrECADD and eBEACOPP in the phase 3 German Hodgkin Study Group HD21 trial. Lancet Oncology, Vol 26 (8), PP 1081-1090 (8).	Conducted independently of Takeda.		advanced stages included Ann Arbor stage III/IV as well as stage II with B symptoms and one or both risk factors of large mediastinal mass or extranodal lesions. ECOG PS 0-2.	Cyclophosphamide, 1250 mg/m ² intravenously on day 1 Doxorubicin, 40 mg/m ² intravenously on day 1. Dacarbazine, 250 mg/m ² intravenously on days 2–3, and Dexamethasone, 40 mg orally on days 1–4.	intravenously on day 1 Bleomycin, 10 mg/m ² intravenously on day 8 Vincristine (1.4 mg/m ² intravenously on day 8 procarbazine (100 mg/m ² orally on days 1–7), and Prednisone, 40 mg/m ² orally on days 1–14). In addition Peg. G-CSF, 6 mg on day 4 was recommended.	
Real-World Study of BrECADD in Denmark NCT: NA	Summary of health records from treating hospital (OUH)	July 2023 to May 2025	Previously untreated advanced HL patients at OUH.	BrECADD	NA	PET2 response Failure Free Survival Use of radiotherapy Baseline demographics Median FU: 11 months



Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
Jacob Haaber Christensen, 2025. Unpublished data.						

(37)

Figure 49 and Figure 50 in Appendix R illustrates design and patient flow (CONSORT) of the HD21 study.



6.1.2 Comparability of studies

Not applicable; the application is based on a large randomized, international, head-to-head study.

A single, small, Danish RW study of BrECADD treated patients serve as supplement to describe the Danish BrECADD population and the Real-World experience with the BrECADD regiment in Denmark.

6.1.2.1 Comparability of patients across studies

This application is based on a randomized head-to-head study; the HD21 study. Table 13 therefore summarizes the baseline characteristics of the two study arms from the HD21 study.

Table 13 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

GHSG HD21		
	Comparator, eBEACOPP n = 740	Intervention BrECADD n = 742
Age median (IQR)	31 (24-42)	31 (24-42)
Male, n/N (%)	419/740 (56)	56
Female, n/N (%)	321/740 (44)	44
Race, n/N (%)		
White		
Asian	672/740 (91)	680/742 (92)
Black	12/740 (2)	11/742 (1)
Other/Unkn	2/740 (<1)	0/742 (0)
	53/740 (7)	51/742 (7)
Ann Arbor Stage, n/N (%)		
IIa	0/739 (0)	2/742 (< 1)
IIb	117/739 (16)	115/742 (16)
IIIa	132/739 (18)	129/742 (17)
IIIb	156/739 (21)	164/742 (22)
Iva	112/739 (15)	104/742 (14)
Ivb	222/739 (30)	228/742 (31)
ECOG PS, n/N (%)		
0	517/735 (70)	508/739 (69)
1	200/735 (27)	220/739 (30)
2	18/735 (2)	11/739 (1)
Risk Factors, n/N (%)		
Large Mediastinal Mass	235/735 (32)	253/739 (35)
Extranodal Involvement	175/735 (24)	202/739 (27)



Involvement of ≥ 3 nodal areas	655/735 (89)	667/739 (90)
High erythrocyte sedimentation rate	470/709 (66)	481/708 (68)
IPS, n/N (%)		
0-1	175/740 (24)	195/742 (26)
2-3	395/740 (53)	390/742 (53)
4-7	170/740 (23)	157/742 (21)

6.1.3 Comparability of the study population(s) with Danish patients eligible for treatment

Takeda Denmark has not been able to find published peer-reviewed data describing Danish patients exclusively treated with eBEACOPP. However, Takeda Denmark has been provided summary data of 16 HL patients treated with BrECADD at a single Danish site, Odense University Hospital (OUH) (37) and have identified one publication summarizing patient data for patients treated with both ABVD and eBEACOPP (5).

Both data sources are sub-optimal; the single center data only describes 16 patients, while the national data predominantly describes ABVD treated patients due to preferred treatment practices early in the period 2000-2018. Thus, the inclusion of ABVD treated patients in the national register study results in a higher median age than what is expected for BrECADD treated patients as 22.3% of the patients were older than 60 years of age.

Nonetheless, the two data sources combined describe the relevant population in Denmark. Accordingly, the relevant Danish population is described using these two sources, Table 14.

It is noteworthy that the median age of the 16 Danish patients treated with BrECADD is [REDACTED]; the median age of the patients in the HD21 study is 31.0 years.

Table 14 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population OUH and Dk (5, 37)	Value used in health economic model (reference if relevant)
N		
OUH	16	
DK	1474	
Age, OUH		
Median (IQR)	[REDACTED]	31.0 (24.0 – 42.0)
Min		18.0
Max	40 (28 – 57)	60.0
Age, DK	725/1474 (49.2)	
Median (IQR)		
18-39 n/N (%)		



40-59, n/N (%)	421/1474 (28.6)
≥ 60, n/N (%)	328/1474 (22.3)
Gender, OUH	
Male, n/N (%)	
Female, n/N (%)	
Gender, DK	
Male, n/N (%)	861/1474 (58.4)
Female, n/N (%)	613/1474 (41.6)
Ann Arbor Stage, OUH	
II, n/N (%)	
III - IV, n/N (%)	869/1474 (59)
Ann Arbor Stage, Dk	598/1474 (41)
I - II, n/N (%)	
III - IV, n/N (%)	
ECOG PS, Dk	
0, n/N (%)	1085/1474 (73.6)
1-4, n/N (%)	382/1474 (25.9)
Missing, n/N (%)	7/1474 (0.5)
CCI, Dk	
0-1, n/N (%)	1439/1474 (97.6)
≥ 2, n/N (%)	35/1474 (2.4)
B-symptoms, Dk	
No, n/N (%)	767/1474 (52.0)
Yes, n/N (%)	685/1474 (46.5)
Missing, n/N (%)	22/1474 (1.5)
IPS, Dk	
1-2, n/N (%)	685/1474 (46.5)
3-4, n/N (%)	134/1474 (9.1)
Missing, n/N (%)	655/1474 (44.4)
Bulky Disease, Dk	
No, n/N (%)	1175/1474 (79.7)
Yes, n/N (%)	119/1474 (8.1)
Missing, n/N (%)	180/1474 (12.2)
Renal Function (eGFR), Dk	104.36 (91.16 – 118.16)
Median (IQR)	39/1474 (2.6)
< 60, n/N (%)	1124/1474 (76.3)
≥ 60, n/N (%)	311/1474 (21.1)
Missing, n/N (%)	
Albumin levels (g/L), Dk	39 (35.0 -43.0)
Median (IQR)	760/1474 (51.6)
< 40, n/N (%)	



≥ 40, n/N (%)	638/1474 (43.3)
Missing, n/N (%)	311 (5.1)

Abbreviations: CCI: Charlson Comorbidity Index, IQR: Interquartile Range, ECOG: Eastern Cooperative Oncology Group, eGFR: estimated Glomerular Filtration Rate, IPS: International Prognostic Score. OUH: data from RW-study performed at Odense University Hospital. DK: data from a national register study summarizing HL patients treated with ABVD and BEACOPP between 2000 and 2018.

6.1.4 Efficacy – results of GHSG HD21

The randomized head-to-head study upon which this application is based is published (2). However, the study sponsor (the German Hodgkin Study Group) did not design or analyze the study results aiming for a regulatory approval. Takeda has therefore conducted supportive analyses of the data following dialogue with the EMA.

Both the publication by the GHSG and the regulatory analyses conducted by Takeda are based on two data cut offs. The primary data cut-off date was 31st December 2022 (40 months of median follow-up); the supportive data cut-off date was 31st October 2023 (median follow-up: 48 months).

All data as published by the study sponsor (German Hodgkin Study Group) is presented below.

The supportive analyses from Takeda reflecting the outcomes and wordings in the Summary of Product Characteristics (SPC) and the Scientific Discussion of European Public Assessment Report (EPAR) are presented in Appendix M. Similarities and differences in patient populations, analyses methods and data cut-off dates are presented in Table 25, section 7.

Treatment Related Morbidity

The primary endpoint of the study, Treatment Related Morbidity (TRMB), was analyzed in the part of the population that received at least one full cycle of chemotherapy at the time of the primary data cut-off date. TRMB was found to be statistically and clinically significantly diminished in the BrECADD arm as compared to the BEACOPP arm,

Table 15 (2).

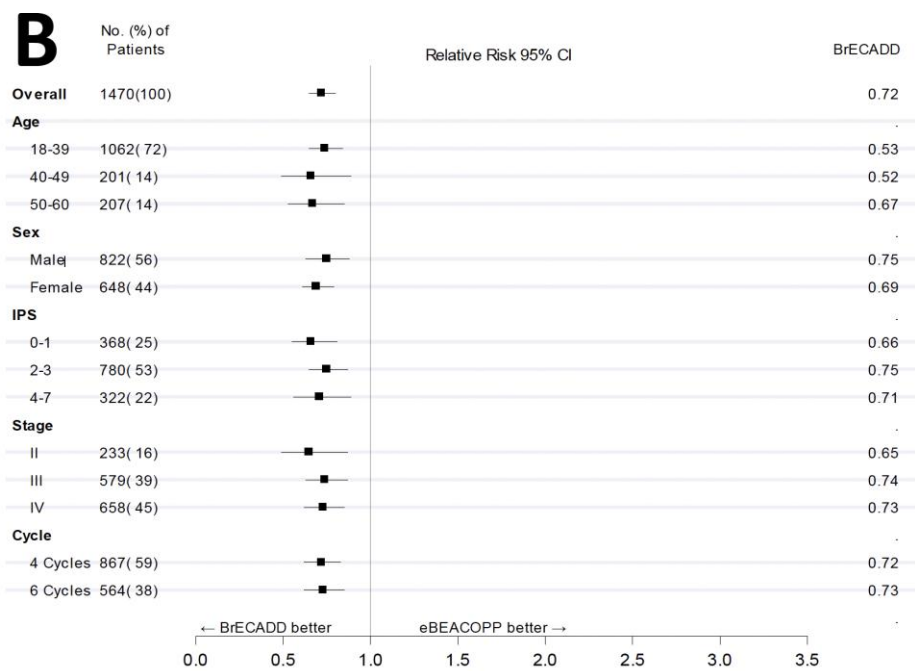
Table 15: Rate of treatment related morbidity, TRMB according to GHSG.

	Occurrence of at least one TRMB n/N	Occurrence of at least one TRMB %	Relative Risk, 95% CI P-value
BrECADD	312/738	42	0.72 0.65 – 0.80
BEACOPP	430/732	59	< 0.0001



Similarly, RRs of all predefined subgroups favored BrECADD over BEACOPP, Figure 4 (2).

Figure 4: Forrest plot of RR for TRMB across predefined subgroups.



The decrease in TRMB translated into fewer transfusions and less sensory peripheral neuropathy, Table 16.

Table 16 Clinical implications of reduced TRMB.

Toxicity	BEACOPP	BrECADD
N	732	737



Transfusion*		
Red cell transfusion, n/N (%)	384/732 (52)	78/737 (24)
Platelet transfusion, n/N (%)	248/732 (34)	125/732 (17)
Sensory PNP		
All Grades, n/N (%)	360/732 (49)	287/737 (38)
Grade 2, n/N (%)	99/732 (14)	46/737 (6)
Grade 3, n/N (%)	17/732 (2)	10/737 (1)

*: patients with at least one transfusion

Treatment related morbidity was a composite endpoint composed of grade 4 anemia, grade 4 thrombocytopenia, or grade 4 infection, as well as grade 3-4 organ toxicity. Table 17 reports the incidences of the various components of TRMB.

In accordance with the aim of the study, the largest impact on individual components of TRMB is observed in the rate of life-threatening acute grade 4 thrombocytopenia.

Table 17. Rate of the components of TRMB.

	BrECADD	eBEACOPP
No of patients (%)	N=747	N=741
Number of patients with TRMB	315 (42.2)	435 (58.7)
Acute Hematologic Toxicity Grade 4	233 (31.2)	386 (52.1)
Anemia	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	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	< 0.0001	
RR (Unstratified BrECADD/eBEACOPP) ^b	0.718	



	BrECADD	eBEACOPP
95% CI	(0.648, 0.797)	
RR (Stratified BrECADD/eBEACOPP) ^c	0.715	
95% CI	(0.645, 0.792)	
% Difference (BrECADD-eBEACOPP)	-16.5	
Exact 95% CI	(-21.6, -11.4)	

CMH: Cochran-Mantel-Haenszel; GI: gastrointestinal. Percentages are calculated using the safety population as denominator. a: 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 using unstratified CMH test. c: RR calculated using stratified CMH test.

Progression Free Survival

The Co-primary endpoint PFS was analyzed for non-inferiority at time of the primary data cut-off (31st December 2022). As this interim analysis showed non-inferiority, the sponsors could test for superiority in the final data cut (31st October 2023) in the ITT population (2).

PFS was statistically and clinically relevant prolonged in the BrECADD arm as compared to BEACOPP, Table 18, Figure 5 (2).

Similarly, an HR favoring BrECADD was observed across all prespecified subgroups except one,

Figure 6 (2).

Table 18: 4-yr PFS rates from HD21.

	4-yr PFS %	95% CI %	Hazard Ratio, 95% CI P-value
BrECADD	94.3	92.6-96.1	0.66 0.45 – 0.97
BEACOPP	90.9	88.7-93.1	0.035



Figure 5: 4-yr KM curves of PFS from HD21.

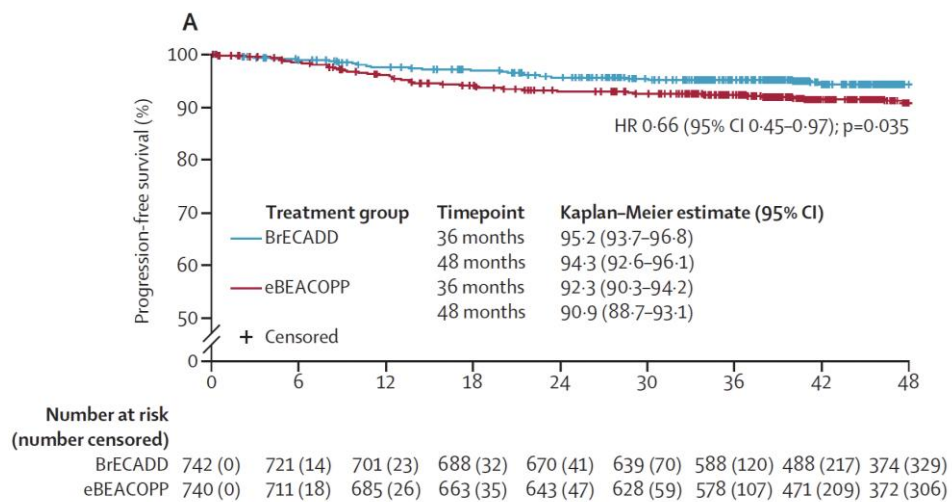
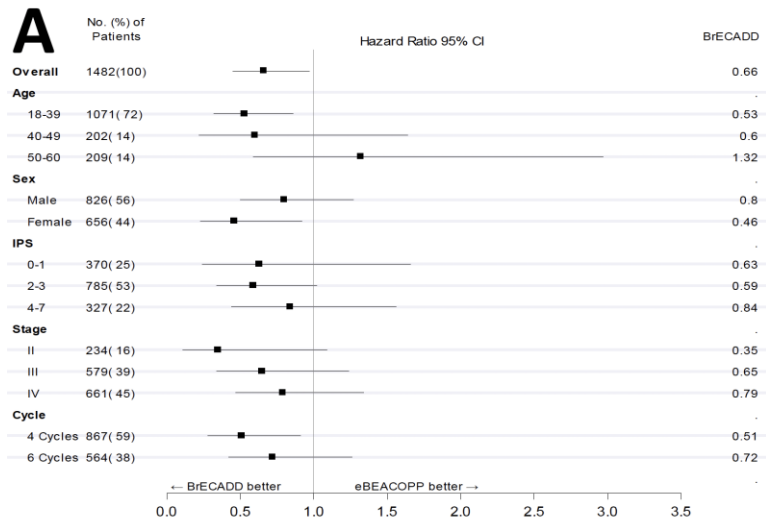




Figure 6: Forest plot of 4-yr PFS from HD21.



Gonadal recovery and live births

Gonadal recovery was measured in the cohort of patients with child bearing potential: males < 51 years and females < 41 years with baseline FSH levels < 15 U/L and < 25 U/L, respectively (32). Of the 1138 patients in this cohort, FSH levels during follow-up was available for 767 patients (347 females; 420 males).

For both males and females BrECADD significantly improved the rate of gonadal function recovery post-treatment, time to gonadal function recovery, and time to first parenthood, respectively (32).

Table 19 summarizes 4-yr female gonadal function recovery rates; corresponding male rates are summarized in Table 20.

Table 19: Female gonadal function recovery rates.

Females	4-yr gonadal function recovery rate, %	95% CI %	Hazard Ratio, 95% CI
BrECADD	95.3	92.0 – 98.8	1.69
BEACOPP	73.3	66.9 – 80.4	1.34 – 2.14

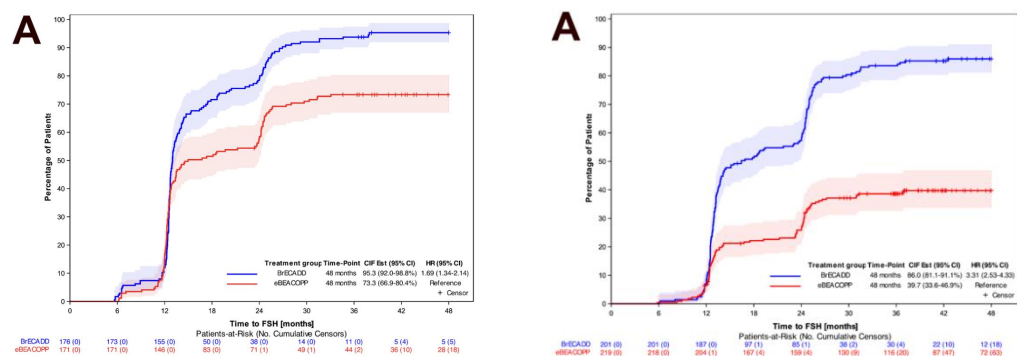


Table 20: Male gonadal function recovery rates.

Males	4-yr gonadal function recovery rate, %	95% CI %	Hazard Ratio, 95% CI
BrECADD	86.0	81.1 – 91.1	3.31 2.53 – 4.33
BEACOPP	39.7	33.6 – 46.9	

Figure 7 display gonadal function recovery rates over time for females and males (32).

Figure 7 Gonadal function recovery rates



Gonadal function recovery rates for females (left) and males (right) respectively, see Appendix S for enlarged figures.

With median 48 months of follow-up, incidence of live births per women following BrECADD and eBEACOPP was not statistically different, Table 21, but a marked delay in time to first motherhood was observed in the eBEACOPP arm, Figure 8A. In men, the incidence of patients fathering at least one child was statistically higher in the BrECADD than in the eBEACOPP group, Table 21. Male participants similarly experienced a marked delay in time to first fatherhood, Figure 8B. Among patients with a stated desire to have children at study start (N=465) , a near doubling of parenthood was observed in the BrECADD arm, Table 21 (32).

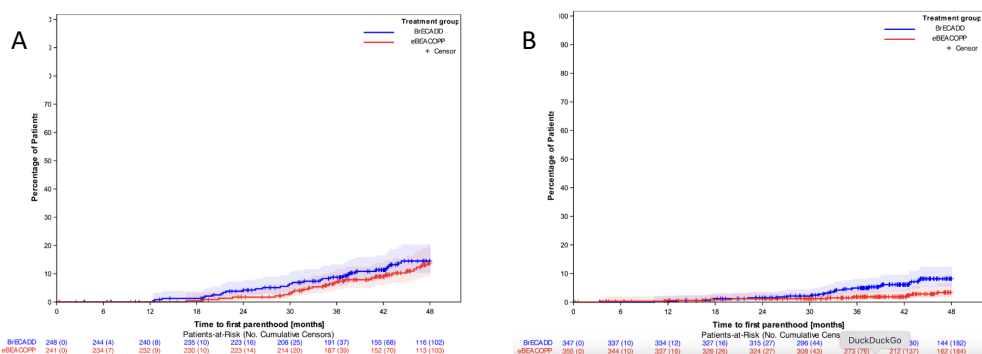
Table 21: Rate of live births. NR: Not Reported. 48-months follow-up.

	Live Births n/N (%)	P
BrECADD, females	35/248 (14)	0.531
eBEACOPP, females	29/243 (12)	



	Live Births n/N (%)	P
BrECADD, males	24/343 (7)	0.014
eBEACOPP, males	10/349 (3)	
Desire to have children; BrECADD	39/246 (16)	NR
Desire to have children; eBEACOPP	19/219 (9)	

Figure 8 Time to first parenthood.



Time to first motherhood (A) and fatherhood (B) among participants in HD21, see Appendix S for enlarged figures.

Overall Survival

Overall survival was included as a secondary endpoint to ensure no detrimental effects of BrECADD.

Overall survival was similar between the BrECADD and eBEACOPP arms, Table 22, Figure 9. Hazard Rate was not reported.

Cause of death in the two arms are summarized in Table 23. Notably, no patients died from toxicity related to HL treatment in the BrECADD arm in accordance with the positive finding of the primary endpoint: Treatment Related Morbidity, TRMB.

Table 22. Overall Survival rates from HD21

	4-yr OS %	95% CI %	Hazard Ratio, 95% CI P-value
BrECADD	98.6	97.7 – 99.5	NR
BEACOPP	98.2	97.2 – 99.3	



Figure 9. 4-yr KM curves for OS from HD21.

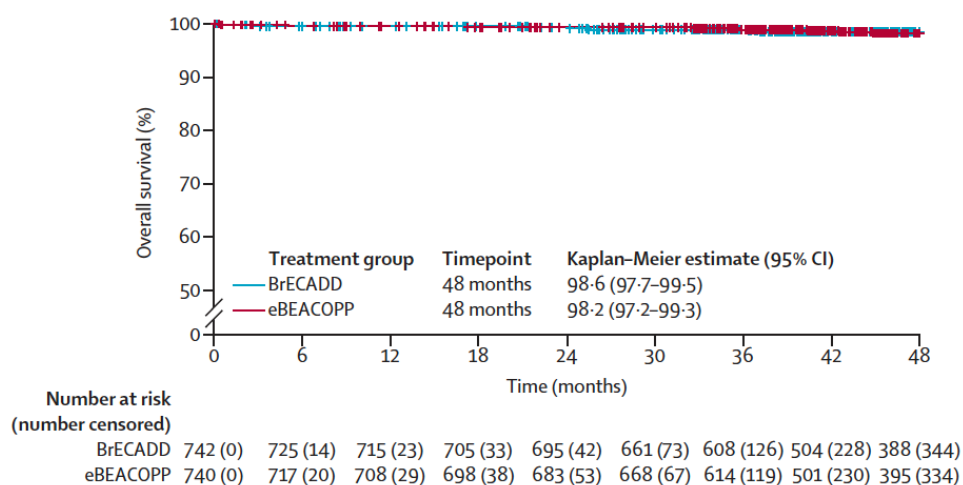


Table 23. Cause of death in HD21.

Cause of Death	eBEACOPP n = 740	BrECADD n= 742
Hodgkin Lymphoma, n (%)	1 (< 1)	3 (< 1)
Toxicity of study treatment, n (%)	3 (< 1)	0
Toxicity of salvage treatment, n (%)	1 (< 1)	0
Second neoplasia, n (%)	2 (< 1)	0
Cardiovascular, n (%)	1 (< 1)	0
Respiratory, n (%)	0	1 (< 1)
Infection, n (%)	0	2 (< 1)
Suicide, n (%)	0	1 (< 1)
Other disease, n (%)	1 (< 1)	3 (< 1)
Unclear, n (%)	2 (< 1)	2 (< 1)
Total, n (%)	12 (2)	12 (2)



6.1.5 Efficacy – results of Real-World study of Danish BrECADD patients

It has been possible to treat newly diagnosed advanced HL patients with BrECADD following individual patient requests in Region South since July 2023. Dr. Jacob Haaber-Christensen has graciously provided Takeda Denmark with the below unpublished data describing the real-world experience with BrECADD at a Danish center. All data are descriptive and have been collected manually through individual patient hospital records. Baseline demographics of patients are presented in Table 14. Total number of patients is [REDACTED]. Data is intended published independently of Takeda Denmark.

Failure Free Survival

At data lock on May 21st 2025, the median follow-up time was 0.9 years (11 months) and the failure free survival was [REDACTED], (37).

Figure 10 [REDACTED]



In March 2026, the cohort was increased to [REDACTED] patients; failure free survival remained at 100%. No patients have needed unplanned hospitalization during or after treatment.

PET2-negativity

The number of infusions of the BrECADD regiment is guided by an interim PET-scan following 2 cycles of chemotherapy (PET2). If the interim PET-scan is negative, the disease has responded to treatment and the patient will have another two cycles of BrECADD administered. If the interim PET-scan is positive, the patient will have an additional four cycles of BrECADD administered. Table 24 summarizes PET2 status for the Danish real-world patients (37).

Table 24 PET2 status of Danish real-world patients.

PET2 Negative	PET2 Positive
n/N	n/N
%	%





7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

One head-to-head study forms the basis of this application. However, the study data was analyzed separately by the academic sponsor (the German Hodgkin Study Group) and the Marketing Authorization Holder (Takeda) as per guidance of EMA. Table 25 gives an overview of the analyses used as well as definitions from the supportive Danish Real-World study.

Table 25 Differences in definitions of outcomes between analyses

Parameter	Comment
Failure Free Survival	Time from treatment to the first occurrence of either disease progression, relapse, treatment stop, or death from any cause. Only used in Danish Real-World study.
Gonadal toxicity	The GHSG reported the impact of treatment on gonadal function through assessments of rates gonadal function recovery four years post treatment in patients deemed of potential to parent children; women < 41 years of age, and men < 51 year of age. Gonadal function recovery was defined as FSH < 15 U/L in men, and 25 U/L in women. Takeda reported the impact of treatment on gonadal function through assessments of rates of infertility one year post treatment in the safety population (all patients enrolled in the study). Infertility was defined as FSH levels > 12.4 IU/L and 21.5 IU/L for men and women, respectively. Takeda conducted a supportive analysis in participants considered fertile at baseline (FSH levels between 3.5 to 21.5 IU/L for women and 1.5 to 12.4 IU/L for men).
Live births	No difference in definition. GHSG used a four-year follow-up; Takeda a three-year follow-up.
Overall Survival	No difference in definition: death due to any cause following randomization.
PET2 Status	Deauville score > 3 was considered positive. Deauville score < 4 was considered negative. Only used in Danish Real-World study.
Progression Free Survival	No difference in definition: time from randomization to the first occurrence of either disease progression or relapse, or death from any



cause. PFS was assessed by local investigator with confirmation by a central committee.

Treatment Related Morbidity	No difference in definition; a composite endpoint composed of grade 4 anemia, grade 4 thrombocytopenia, or grade 4 infection, as well as grade 3-4 organ toxicity.
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7.1.2 Method of synthesis

N/A.

7.1.3 Results from the comparative analyses

Results from the comparative analysis are presented below in Table 26. Supportive comparative analyses performed by Takeda are presented in Appendix M.

A summary of the efficacy data from the Danish Real-World Study is presented in Table 27.

The below data is from (2, 32).

Table 26 Outcome of comparative analyses by German Hodgkin Study Group.

Outcome measure	BrECADD (N=742)	eBEACOPP (N=740)	Result
Progression Free Survival, 4-yr	94.3% 95 CI: 92.6 - 96.1	90.9 95% CI: 88.7 – 93.1	HR: 0.66 95% CI: 0.45 – 0.97 P = 0.035
Treatment Related Morbidity, TRMB, 4-yr	312/738 42%	439/732 59%	RR: 0.72 95% CI: 0.65 – 0.80 P < 0.0001
Gonadal recovery, 4-yr Women, %	95.3 95% CI: 92.0 -98.8 N=176	73.3 95% CI: 66.9 – 80.4 N=171	HR: 1.69 95% CI: 1.34 – 2.14
Gonadal recovery, 4-yr Men, %	86.0 95% CI: 81.1 – 91.1 N = 201	39.7 95% CI: 33.6 – 46.9 N = 219	HR: 3.31 95% CI: 2.53 – 4.33
Live Births, % Female participants	14	12	P = 0.531
Live Births, % Partners of male participants	7	3	P < 0.014



Outcome measure	BrECADD (N=742)	eBEACOPP (N=740)	Result
Live births among participants with stated desire to have children, %	16	9	NR
Overall Survival, 4-yr, %	98.6 95% CI: 97.7 – 99.5	98.2 95% CI: 97.2 – 99.3	NR

Table 27 Summary of outcome of treatment of █████ BrECADD patients treated in standard clinical practice at OUH (37).

Outcome measure	BrECADD
Failure Free Survival	100%
PET2-status	
Negative, n/N - %	13/16 - 81.3
Positive, n/N - %	3/16 - 18.7

7.1.4 Efficacy – results per outcome measure

N/A

8. Modelling of efficacy in the health economic analysis

8.1 Presentation of efficacy data from the clinical documentation used in the model

The efficacy outcomes OS and PFS from the HD21 study (data cut:31Oct2023) was directly used in the health economic model. More specifically, the following analyses were conducted: Extrapolation of long-term OS, PFS, post-progression survival (PPS), time to progression (TTP) and time-to-death (TTD) outcomes with following methods: Standard parametric survival models and Mixture cure models (MCM). The standard parametric model was chosen because it provided more reliable OS and PFS analyses compared to the MCM. The standard parametric survival analysis was conducted by fitting exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalized gamma distributions to the data from the HD-21 study. The properties of these distributions are described in Ishak et al. 2013 (46) and all analyses followed the approach outlined in the NICE Decision Support Unit Technical Services Document 14 (flowchart in Appendix P), as referred in the DMC online appendix. When choosing between independent and joint fits, joint fits were considered more appropriate because independent fits lacked clinical validity as they suggested higher projected survival for



eBEACOPP than BrECADD. Joint fits leverage more power from higher number of events and the drop at month 65 in the BrECADD arm (outlier) was therefore less influential. Different distributions could not be used across treatment arms because the joint model included treatment as a predictor. Therefore, for each selected distribution, a single fitted set of parameters was applied to both arms as a group. Specifically, Weibull and Gompertz distributions were used for OS and PFS, respectively.

The assumption of proportional hazards (PH) was evaluated graphically in three ways. Visual inspection of the log cumulative hazard, plots of the Schoenfeld residuals, and quantile-quantile (Q-Q) plot was checked to assess the assumption of Accelerated Failure Time (AFT).

The parametric survival approach consists of initially fitting exponential, Weibull, Gompertz, log-logistic, log-normal, gamma and generalized gamma distributions to the observed data collected from the trial. The goodness-of-fit for each parametric model was evaluated using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) metrics, with lower values signifying a better alignment with the observed data.

8.1.1.1 Extrapolation of OS

All fitted distributions projected high long-term survival rates, suggesting that long-term OS needs to be capped by general mortality in the model for all fitted distributions. Based on AIC and BIC values and clinical opinion, Weibull was selected for BrECADD and eBEACOPP.

Table 28 Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	HD-21 study
Model	Standard parametric model (joint)
Assumption of proportional hazards between intervention and comparator	Yes
Function with best AIC fit	Intervention: Weibull function Comparator: Weibull function
Function with best BIC fit	Intervention: Weibull function Comparator: Weibull function
Function with best visual fit	Intervention: Weibull function Comparator: Weibull function
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Weibull function Comparator: Weibull function



Method/approach	Description/assumption
Validation of selected extrapolated curves (external evidence)	Graphical Assessment of Fits, Fitting of Models (independent or joint), clinical plausibility
Function with the best fit according to external evidence	Intervention: Weibull function Comparator: Weibull function
Selected parametric function in base case analysis	Intervention: Weibull function Comparator: Weibull function
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	60 months

The empirical time-to-event plot for OS with the number of patients at risk over time is shown in Appendix P. The OS curve for each arm is very immature, with heavy censoring along the entire observed period. The median OS was not reached; only 12 (1.6%) and 13 (1.7%) patients in the BrECADD and eBEACOPP arms, respectively, experienced an event by the end of follow-up (figure to be found in Appendix P).

Extrapolation of PFS

For PFS, based on standard parametric models, joint parametric models (Weibull, log-normal, log-logistic, exponential, Gompertz, and generalized gamma) were fit to the KM curves on the basis of the proportional hazard assumption. Gompertz was the best fitting distribution based on visual fit. Gompertz was also the only distribution that plateaued early enough and captured the tail end of the observed PFS curves. This selection was also supported by clinical opinion.

Table 29 Summary of assumptions associated with extrapolation of PFS

Method/approach	Description/assumption
Data input	HD-21 study
Model	Standard parametric model (joint)
Assumption of proportional hazards between intervention and comparator	Yes



Method/approach	Description/assumption
Function with best AIC fit	Intervention: Gompertz function Comparator: Gompertz function
Function with best BIC fit	Intervention: Gompertz function Comparator: Gompertz function
Function with best visual fit	Intervention: Gompertz function Comparator: Gompertz function
Function with best fit according to evaluation of smoothed hazard assumptions	Intervention: Gompertz function Comparator: Gompertz function
Validation of selected extrapolated curves (external evidence)	Graphical Assessment of Fits, Fitting of Models (independent or joint), clinical plausibility
Function with the best fit according to external evidence	Intervention: Gompertz function Comparator: Gompertz function
Selected parametric function in base case analysis	Intervention: Gompertz function Comparator: Gompertz function
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	60 months

The empirical time-to-event plot for PFS, with the number of patients at risk over time, is shown in Appendix P. The PFS curve for each arm is immature, with heavy censoring after 30 months. The median PFS was not reached; only 44 (5.9%) and 65 (8.7%) patients in the BrECADD and eBEACOPP arms, respectively, experienced an event by the end of follow-up.

8.1.2 Calculation of transition probabilities

N/A

Table 30 Transitions in the health economic model

Health state (from)	Health state (to)	Description of method	Reference
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N/A

8.2 Presentation of efficacy data from [additional documentation]

N/A

8.3 Modelling effects of subsequent treatments

N/A

8.4 Other assumptions regarding efficacy in the model

N/A

8.5 Overview of modelled average treatment length and time in model health state

This parameter as Time on Treatment for the model was addressed based on IPD from the HD21 trial and can be called back to the CSR for treatment duration. It was additionally tested under the PSA to address uncertainty (sampling with replacement) among other parameters.

Table 31 Estimates in the model

	Modelled average OS (years)	Modelled median OS (years)	Observed median from relevant study
BrECADD	40.89	42.99	N/A
eBEACOPP	40.80	42.95	N/A

Table 32 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length [years]	PFS [years]	PPS [years]
BrECADD	0.22	38.8	2.1
eBEACOPP	0.23	37.3	3.5



9. Safety

9.1 Safety data from the clinical documentation

The publication reports safety data for all patients completing one cycle of chemotherapy (2), while the clinical study report summarizes safety from all patients receiving at least one dose of one study drug (25).

The following section is therefore based on the clinical study report.

Adverse events and reactions are treatment emergent.

All definitions of adverse events and adverse reactions are standard definitions; e.g. events are considered not related to the treatment; reactions are considered related to the treatment.

Not all requested information is available. Relevant fields are marked as NR; Not Reported.

Table 33 Overview of safety events. All safety events were captured up to 30 days after last treatment.

	BrECADD (N = 738) (2, 47)	eBEACOPP (N= 732) (2, 47)	Difference, % (95 % CI)
Number of adverse events, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse events, n (%)	745/747 (99.7)	741/741 (100)	NR
Number of serious adverse events*, n	NR	NR	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	328/747 (43.9)	311/741 (42.0)	NR
Number of CTCAE grade ≥ 3 events, n	NR	NR	NR
Number and proportion of patients	682/747 (91.3)	717/741 (96.8)	NR



	BrECADD (N = 738) (2, 47)	eBEACOPP (N= 732) (2, 47)	Difference, % (95 % CI)
with ≥ 1 CTCAE grade ≥ 3 events [§] , n (%)			
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	743 (99.5)	738 (99.6)	NR
Number and proportion of patients who had a dose reduction, n (%)	243/747 (32.5)	452 (61.0)	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	NR	NR	NR
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	15 (2)	15 (2)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the [ICH's complete definition](#)).

§ CTCAE v. 5.0 must be used if available.

Table 34 Serious adverse events collected until 30 days after last treatment.

Adverse events	BrECADD (N=747)		Comparator (N=741)	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Adverse event, n (%)				
Febrile neutropenia	150 (20.1)	NR	118 (15.9)	NR
Pyrexia	39 (5.2)	NR	46 (6.2)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the [ICH's complete definition](#)).



Most of the toxicity induced by BrECADD and eBEACOPP does not fit the definitions of SAEs, Table 34, despite being extensive. For instance, both regimens induce deep cytopenias, which are managed clinically by transfusions in day clinics and thus do require hospitalizations despite being potentially life-threatening if not managed.

To adequately report the toxicity profile of each drug regiment Table 35 and Table 36 therefore summarizes Treatment Emergent Adverse Events (TEAEs) of any grade and grade 3 and higher for 10% and 1% of the patients respectively (25).

Table 37 summarizes occurrence of AML/MDS following treatment as modifications of eBEACOPP to BrECADD was partly motivated by a desire to reduce these life-threatening late occurring events.

Table 35. TEAEs of Any Grade Reported for at Least 10% of Patients by CTCAE Toxicity or PT (Safety Population).

	BrECADD	eBEACOPP
No of patients (%)	N=747	N=741
At least 1 TEAE	745 (99.7)	741 (100)
CTCAE Toxicity	744 (99.6)	741 (100)
Anemia	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)



	BrECADD	eBEACOPP
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)

Table 36. Grade 3 or Higher TEAEs Reported for at Least 1% of Patients by CTCAE Toxicity Terms or PT (Safety Population).

	BrECADD N=747 n (%)	BEACOPP N=741 n (%)
At least 1 Grade 3 or higher TEAE	682 (91.3)	717 (96.8)
CTCAE Toxicity Grade 3 or higher	679 (90.9)	716 (96.6)
Leukopenia	646 (86.5)	698 (94.2)
Thrombocytopenia	411 (55.0)	533 (71.9)
Anemia		
Infection	210 (28.1)	183 (24.7)
GI disorders (except nausea, vomiting, mucositis)		
Hepatobiliary disorders	37 (5.0)	22 (3.0)



	BrECADD N=747 n (%)	BEACOPP N=741 n (%)
Mucositis	33 (4.4)	43 (5.8)
Respiratory, thoracic and mediastinal disorders	25 (3.3)	35 (4.7)
Nausea/vomiting	24 (3.2)	26 (3.5)
Cardiac disorders	21 (2.8)	10 (1.3)
Nervous system disorders (except neuropathy)	12 (1.6)	24 (3.2)
Peripheral sensory neuropathy	10 (1.3)	17 (2.3)
Skin and subcutaneous tissue disorders	10 (1.3)	14 (1.9)
Drug fever	7 (0.9)	10 (1.3)
Renal and urinary disorders	7 (0.9)	10 (1.3)
Other Toxicities (PT)	160 (21.4)	188 (25.4)
Neutropenia	71 (9.5)	82 (11.1)

Table 37 Occurrences of secondary AML/MDS

	BrECADD	eBEACOPP
Acute myeloid leukemia or myelodysplastic syndrome, n/N (%)	2/747 (<1%)	6/742 (1%)

Treatment-related adverse events (TRAEs) of grade ≥ 3 that occurred in $\geq 5\%$ of patients who received BrECADD or eBEACOPP in the HD21 trial are included in the model. The model provides an option to consider only TRMB adverse events or to include “all” adverse events (defined as grade ≥ 3 TRAEs occurring in $\geq 5\%$ of patients in the respective trials). TRMB inclusion criteria are grade 4 for hematologic events and grade 3 or 4 for non-hematologic events. These criteria are deemed appropriate and sufficient to capture adverse events that require hospital resources or significantly impacts HRQoL. All rates



were sourced from the HD21 clinical trial study report and are presented in Table 38 and Table 39.

Table 38 TRMBs used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic model for intervention	Frequency used in economic model for comparator	Source	Justification
Anemia	0%	0%	HD-21	grade ≥4 occurring in ≥5%
Thrombocytopenia	30%	52%	HD-21	grade ≥4 occurring in ≥5%
Infection	2%	1%	HD-21	grade ≥4 occurring in ≥5%
Cardiac disorders	2%	1%	HD-21	grade ≥3 occurring in ≥5%
Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)	8%	4%	HD-21	grade ≥3 occurring in ≥5%
Hepatobiliary disorders	5%	3%	HD-21	grade ≥3 occurring in ≥5%
Nervous system disorders (sensory, motor, and other)	3%	5%	HD-21	grade ≥3 occurring in ≥5%
Renal or urinary disorders	1%	1%	HD-21	grade ≥3 occurring in ≥5%
Respiratory, thoracic or mediastinal disorders	3%	5%	HD-21	grade ≥3 occurring in ≥5%

Table 39 TRAEs events used in the health economic model

Adverse events	Intervention	Comparator		
	Frequency used in economic	Frequency used in economic	Source	Justification



Adverse events	Intervention	Comparator		
	model for intervention	model for comparator		
Anemia	30%	59%	HD-21	grade ≥3 occurring in ≥5%
Febrile neutropenia	27%	20%	HD-21	grade ≥3 occurring in ≥5%
Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)	8%	5%	HD-21	grade ≥3 occurring in ≥5%
Infection	29%	25%	HD-21	grade ≥3 occurring in ≥5%
Leukopenia	119%	133%	HD-21	grade ≥3 occurring in ≥5%
Mucositis	5%	6%	HD-21	grade ≥3 occurring in ≥5%
Neutropenia	11%	13%	HD-21	grade ≥3 occurring in ≥5%
Thrombocytopenia	75%	108%	HD-21	grade ≥3 occurring in ≥5%

9.2 Safety data from external literature applied in the health economic model

N/A



Table 40 Adverse events that appear in more than X % of patients

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for intervention	Number of patients with adverse events	Number of adverse events	Frequency used in economic model for comparator	Number of patients with adverse events	Number of adverse events
Adverse event, n	N/A							



10. Documentation of health-related quality of life (HRQoL)

The model was informed by a mapping analysis of the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) to EQ-5D-3L, and application of the Danish TTO population weights (48). All HRQoL data from the EORTC QLQ-C30 were collected in the HD21 study and mapped (indirect) to EQ-5D-3L utility scores using the algorithm reported by Young et al. The algorithm was identified through a targeted literature search, as described in Appendix I.

The Medicine council's preferred mapping instrument is the EQ-5D-5L. Although EQ-5D-5L mapping is not applied in the base-case analysis, the application also includes mapping from the EQ-5D-3L to the EQ-5D-5L, enabling direct comparison of results across mapping approaches. This comparison is important because it indicates the extent to which the results are sensitive to the choice of mapping tool. However, based on the available information, it is not possible to determine whether the two-step ("double") mapping approach is more valid than the base-case approach

Table 41 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EORTC-QLQ-C30	HD 21	Comparative analysis of Core Quality of Life Questionnaire
EQ-5D-3L	Young et al.	Comparative analysis of HRQoL

10.1 Presentation of the health-related quality of life for EORTC-QLQ-C30 and EQ-5D-3/5L

10.1.1 Study design and measuring instruments

The investigators of the HD-21 study selected cancer patient specific questionnaires to assess HRQoL. The EORTC QLQ-C30 is a standardized tool for HRQoL, and it contains 30 questions covering: functioning domains, symptom scales, global health status/QoL, and other single-item measures. The questionnaire is commonly used in clinical studies and can be mapped to EQ-5D-3L using validated algorithms. The EORTC-QLQ-C30 questionnaire is used in the HD-21 study in the manner it is validated for. The EQ-5D-3L questionnaire is used in health economic evaluations to measure HRQoL. It captures health across five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and assigns a utility score which is used to calculate QALYs, the key metric in the cost-utility analyses. The EQ-5D-3L and EQ-5D-5L have the same five dimensions and both include a 0–100 VAS for self-rated health, but they differ in the number of response levels and in sensitivity. The EQ-5D-3L has three levels per



dimension (no, some, extreme problems), while the EQ-5D-5L has five levels (no, slight, moderate, severe, extreme problems), making the 5L more sensitive and better at discriminating between health states with fewer ceiling effects. Each version has its own country-specific value sets, so the resulting utility scores are not directly numerically comparable between 3L and 5L.

The chosen study design is not expected to introduce bias that can differ between the two comparators. However, Using the EQ-5D-3L instead of the EQ-5D-5L can introduce several types of bias. The 3L has stronger ceiling effects, tending to over-cluster patients at in the “no problems” item which can overestimate health status and underestimate mild impairment. Its reduced sensitivity means it captures changes and between-group differences less precisely, especially for small improvements. Because mild problems must be classified as either “no” or “some/moderate” problems, misclassification of true health states can occur. The EQ-5D-3L value sets can bias utility scores and QALY estimates compared with 5L, often leading to smaller apparent gains. This is also what can be seen when comparing the EQ-5D-3L and EQ-5D-5L utility scores per health state in Table 46.

10.1.2 Data collection

All data was collected in the HD-21 study. The number of completed questionnaires were found to be much lower than number of patients as participation in this part of the trial was not compulsory. For patients that did elect to participate in HRQoL data collection EORTC QLQ-C30 data were completed by patients before the start of chemotherapy (screening day -28 to 0), after the 2nd cycle, during restaging after completion of chemotherapy, and during restaging after completion of radiotherapy (if indicated). During the follow-up period, the assessments are completed at months 3, 6, 12, 18 and 24 after chemotherapy, and annually thereafter. Compliance rates ranged from 32% to 55% for BrECADD, and 33% to 54% for eBEACOPP. The total compliance rate was similar in the 2 treatment groups (56% for BrECADD and 55% for eBEACOPP. For missing data, guidelines by EORTC were followed when calculating the subscale scores: a scale score is calculated if at least 50% of the items of a scale are completed (i.e., non-missing), see Appendix P (Table 21 in the MC guideline). All patients who completed the questionnaire gave consent for its use.

10.1.3 HRQoL results

In Table 42 XXXXXXXXXXXXXXXXXXXX, results are given at baseline and at all relevant time points for data collection. No domain specific data is presented. Figure 11 presents a graph showing the mean changes (with 95% confidence intervals) from baseline and at the different follow-up time points for both the intervention and the comparator.



Figure 11 [REDACTED]



Results show no notable differences between treatment groups in mean EORTC QLQ-C30 scores during the treatment period. During post-treatment follow-up (PTFU) scores increased (improved) in both treatment groups compared with baseline; [REDACTED] patients at 12, 18, and 24 months. Analysis of the change from baseline generally showed a similar change in scores during treatment and a change to higher scores in BrECADD patients compared with eBEACOPP patients at 12 months PTFU (p-value=0.0031), 18 months PTFU (p-value=0.0418), and 24 months PTFU (p-value=0.0271). The estimated mean change from baseline in the BrECADD treatment group at 6, 12, 18, 24, and 36 months PTFU was considered clinically meaningful using the published minimally important difference (MID) of 10 (49). The estimated mean change from baseline in the eBEACOPP treatment group did not reach the MID of 10 at any of the PTFU time points.

Table 42 [REDACTED]

Intervention		Comparator		Intervention vs. comparator	
N	Mean (SE)	N	Mean (SE)	Difference (95% CI)	p-value
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]



Intervention	Comparator	Intervention vs. comparator

10.2 Health state utility values (HSUVs) used in the health economic model

10.2.1 HSUV

calculation

Mapping was used to provide HRQoL inputs for cost-utility analyses and it was done with a validated algorithm. Specifically, utility values were mapped from HD-21 EORTC-QLQ-C30 data to EQ-5D-3L health utilities based on the DK TTO value set by Wittrup et al. (48). In the base case, the model estimates pre-“cured” utility using either a repeated measures model or the age-based general population utility, selecting the lower value. After the cure point, the model applies the age-based general population utility for Denmark, as required by the DMC guidelines.

For patients with Hodgkin lymphoma it is assumed that they will achieve the same utility as the background population since most are relatively young and otherwise healthy at the time of diagnosis, and they are cured in the early lines of treatment. Therefore, a pragmatic and somewhat conservative assumption is applied that patients who are cured of Hodgkin lymphoma have a health-related quality of life equivalent to that of the age-matched Danish population, while temporary decreases in quality of life during treatment are explicitly captured in the treatment-related health states. The base-case applies the results from the EQ-5D-3L but the double-mapping to EQ-5D-5L is also presented for transparency and to allow for comparison and assessment of the impact on the QALY estimations from each approach.

The TTO (time trade-off) EQ-5D-3L Danish value set by Wittrup-Jensen et al. is a country-specific tariff that converts EQ-5D-3L health states into a single utility index based on time trade-off preferences elicited from a Danish general population sample. This study developed a Danish EQ-5D-3L value set based on time trade-off (TTO) valuations from 1,332 adults drawn from the Danish general population. Using computer-assisted, interviewer-administered TTO interviews, respondents directly valued 46 EQ-5D health states, selected via a split-sample design to cover a broad range of severity. Several regression approaches (OLS, fixed effects, random effects, random coefficients, Tobit) and multiple model specifications were compared. An additive random effects model (TTO3), including main effects and separate parameters for moves from level 1→2 and 2→3 for each dimension, was identified as the preferred specification because it had high explanatory power ($R^2 \approx 0.65$) and produced logically consistent and statistically significant coefficients. The resulting Danish TTO tariff provides utility weights on the –1 to 1 scale and is recommended for use in Danish cost-utility analyses using EQ-5D, instead of relying on UK value sets (48).



10.2.1.1 Missing data

After deriving EQ-5D utility scores from QLQ-C30 scores, the extent of missing EQ-5D health utility data across visits by treatment arm was assessed. The Setting International Standards in Analyzing Patient- Reported Outcomes and Quality of Life Endpoints Data Consortium recommends that the extent of missing data over time be quantified using two measures: the completion rate (also known as the variable denominator rate) and the available data rate (also known as the fixed denominator rate):

- The completion rate was defined as the number of patients in the ITT analysis set with an evaluable EQ-5D health utility value (after mapping from the QLQ-C30) at a given timepoint divided by the number of patients in the ITT analysis set who were still expected to provide HRQoL assessments at that timepoint.
- Additionally, since patients in the HD21 trial were asked to provide consent to participate in the HRQoL questionnaires, the completion rate was calculated among the ITT analysis set who provided consent to the HRQoL questionnaires.
- The available data rate was defined as the number of patients in the ITT analysis set with an evaluable EQ-5D health utility value (after mapping from the QLQ-C30) at a given timepoint divided by the number of patients in the ITT analysis set.

An evaluable assessment for the EQ-5D health utility at a given assessment visit (i.e., the numerator) was defined as having a non-missing EQ-5D health utility score derived from QLQ-C30 scores. Specifically, to have a non-missing EQ-5D health utility score at a given assessment visit, a patient needed to have non-missing scores for all QLQ-C30 domains used in the mapping. The denominator of the available data rate was defined as the number of patients in the ITT analysis set, whereas the denominator for the completion rate (i.e., variable denominator rate) was defined as the number of patients who were still in the study at that visit.

For both the numerator and denominator, the absolute number and percentage of patients at each assessment visit were calculated and summarized per treatment arm.

Table 43 Description of the QLQ-c30 item scale

Scale	Included items	Range	Number of items needed to calculate the score
Functional scale			
Physical functioning	1, 2, 3, 4, 5	3	3



Role functioning	6, 7	3	1
Emotional functioning	21, 22, 23, 24	3	2
Cognitive functioning	20, 25	3	1
Social functioning	26, 27	3	1
Global health status / QoL	29, 30	6	1
Symptom scale/single-item			
Fatigue	10, 12, 18	3	2
Nausea and vomiting	14, 15	3	1
Pain	9, 19	3	1
Dyspnea	8	3	1
Insomnia	11	3	1
Appetite loss	13	3	1
Constipation	16	3	1
Diarrhea	17	3	1
Financial difficulties	28	3	1

Table 44 Pattern of missing data and completion for the EORTC-QLQ-C30 (CSR Table 15.2.10.3)

Time point	HRQoL population	Missing	Expected to complete	Completion
	N	N (%)	N	N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients “at risk” at time point X	Number of patients who completed (% of patients expected to complete)



Baseline	1500	734 (49%)	1500	776 (52%)
Restaging after treatment (2 cycles)	1500	727 (48%)	1460	773 (53%)
Interim Restaging after treatment	1500	854 (57%)	1443	646 (45%)
Restaging after Radiotherapy (if indicated)	1500	1435 (96%)	209	65 (31%)
3 months	1500	1038 (69%)	1336	462 (35%)
6 months	1500	1057 (70%)	1375	443 (32%)
12 months	1500	1032 (67%)	1336	468 (35%)
18 months	1500	1217 (81%)	1285	283 (22%)
24 months	1500	1072 (71%)	1263	428 (34%)
36 months	1500	1139 (76%)	1126	361 (32%)
48 months	1500	1257 (84%)	739	243 (33%)
60 months	1500	1368 (91%)	329	132 (40%)
72 months	1500	1476 (98%)	66	24 (36%)

10.2.1.2 Descriptive analyses

Summary statistics of absolute EQ-5D health utility values by scheduled visit (i.e., n, mean, SD, median, 95% CI, Q1, Q3, minimum, maximum, and SE) and plots of mean (95% CI) EQ-5D health utility values over time (at each visit) were generated for the following health states:

- Overall (i.e., across all health states)
- Baseline
- Progression-free (overall; i.e., regardless of on- or off-treatment)
- Progression-free on-treatment with BrECADD
- Progression-free on-treatment with eBEACOPP
- Progression-free off-treatment with BrECADD
- Progression-free off-treatment with eBEACOPP
- Progressed (overall)

Model based analysis



This analysis was conducted in the EQ-5D-evaluable set. A mixed-effects model with repeated measures (MMRM) was used to estimate least-square (LS) mean (95% CI) health utility values. The model included EQ-5D health utility values at all post-baseline visits as the dependent variable. It used a restricted maximum likelihood estimation method and included intercept as a random effect to account for autocorrelation of utility scores due to multiple observations recorded for any given patient. An unstructured covariance matrix was applied to obtain the random effects variance components.

The model included the following as covariates:

- Treatment arm (BrECADD vs. eBEACOPP)
- On treatment (yes vs. no)
- BrECADD on treatment (interaction effect) (yes vs. no)
- Progressive disease (yes vs. no)
- Mean-centered baseline age (continuous); the mean age of the EQ-5D-evaluable population was subtracted from each patient's baseline age to facilitate interpretation of the coefficients.
- Mean-centered baseline utility (continuous); the mean utility of the EQ-5D-evaluable population was subtracted from each patient's baseline utility to facilitate interpretation of the coefficients.

The intercept and coefficient estimates (SE, p-value, and 95% CI) from the multivariable model and LS mean (95% CI) utility estimates for the health states were estimated. For each predictor and for each treatment arm, the predicted and observed mean utility value (95% CI) were also plotted across visits for comparison.

10.2.1.3 Sensitivity analysis

The mapping model indicates that utilities are primarily driven by baseline HRQoL and treatment status: higher baseline utility is associated with higher mapped EQ-5D-3L values (coefficient 0.306, $p < 0.001$), while being on treatment is associated with utility decrement (coefficient -0.091, $p < 0.001$). Progressive disease is also associated with lower utility (coefficient -0.060, $p = 0.005$), although the CI suggests greater uncertainty around the magnitude. Age has a small but statistically significant negative association with utility (coefficient -0.002 per year, $p < 0.001$). In contrast, there is no clear independent treatment-arm effect (BrECADD vs eBEACOPP), see **Error! Reference source not found.**

Table 45 Utility model coefficients (sensitivity analysis)

Covariate	Coefficient (95% CI), P-value
Intercept	
Treatment Arm (BrECADD vs. eBEACOPP)	
On/Off Treatment (On-treatment vs. Off- treatment)	
Treatment Arm * On-/Off-treatment Interaction Term	
Progressive Disease (Yes vs. No)	



Centered Age (Mean = 33.8)

Centered Baseline Score (Mean = 0.726)

Figure 12 Observed and Predicted Mean Utility Values at Each Visit (BrECADD arm;)

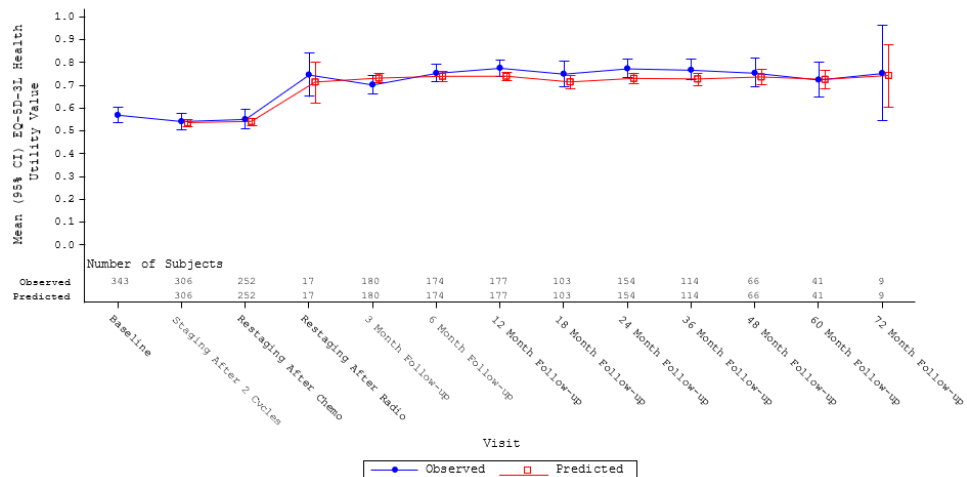
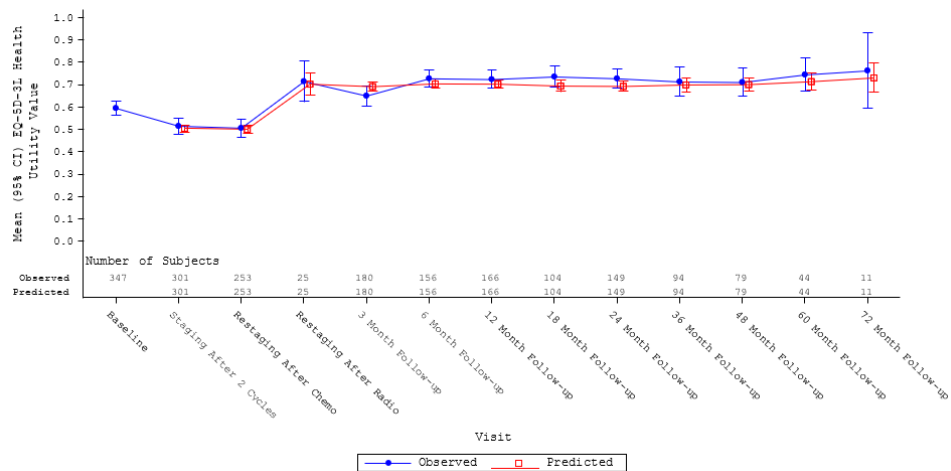


Figure 13 Observed and Predicted Mean Utility Values at Each Visit (eBEACOPP)



In the HD21 trial of first-line therapy for patients with advanced-stage classical Hodgkin lymphoma, although the sample with valid EQ-5D utility values after mapping was limited mostly to patients in Germany, baseline demographic and disease characteristics were generally comparable between both the EQ-5D evaluable and non-evaluable populations. After the on-treatment period, observed EQ-5D health utility values increased and remained stable across subsequent visits.

In the linear MMRM, on-/off-treatment, centered age, and centered baseline utility were significant predictors of utility. Treatment arm, the interaction between treatment arm



and on-/off-treatment, and progressive disease were all not significant predictors of utility. This is consistent with observed EQ-5D utility data which showed an overlap at some time points between BrECADD and eBEACOPP arms within each health state. The significance of progressive disease as a predictor was likely limited by the sample size (only 31 of the 3,845 total health utility value records included in the MMRM were while patients were in the progressed health state). Predicted values were consistent with observed, indicating that the model appropriately fits the data. When including patients in the non-randomized cohort, model coefficients and utility estimates were consistent with the base case.

This study demonstrated that mapping algorithm published by Young et al. (see section 10.2.1.4 for full description of the study and study selection) can be used to successfully derive EQ-5D health utility values from EORTC QLQ-C30 data. While patients remained progression-free, utility estimates were higher off-treatment (i.e., after chemotherapy was completed) vs. on-treatment (i.e., while chemotherapy was ongoing).

10.2.1.4 Mapping

A targeted literature search identified Young et al (45) as the most appropriate algorithm for mapping EORTC QLQ-C30 to EQ-5D utilities which is further described in Appendix J. The study explores various models to map EORTC-QLQ-C30 to EQ-5D-3L to determine the best one. The study used 3 data sets combined for the mapping analysis which are a randomized controlled trial of 572 patients with multiple myeloma, 100 patients with breast cancer and 99 patients with lung cancer. Young et al. was the only study using an indirect approach, which calculates probabilities for each response to the EQ-5D-3L questions. These probabilities can be matched with a selected value set to derive health state utility values. The mapping algorithm by Young et al. was selected because this method allows value sets from different countries to be applied. Comparison of the study populations used in Young et al. and the HD-21 study are provided in Table 46.

Table 46 Comparison of mapping study population with HD21

Author, Year	Condition	Age Mean (SD)	% Male	Country (%)	EQ-5D Mean (SD)
Young, 2015 [6]	Multiple myeloma, breast cancer, lung cancer	68.3 (9.6)	44.1	NR	0.58 (0.342) (UK)
HD21	Hodgkin's lymphoma	33.5 (11.8)	55.9	Germany: 71.5% Switzerland: 8.8% Australia: 7.1% Other: 12.6%	N/A



Methods in Young et al.

The model is validated internally using bootstrapping techniques to estimate a shrinkage factor that allows for overoptimism of the predictive ability of the fitted model. To estimate the shrinkage factors, 5000 bootstrap estimates are run, and for each bootstrap sample the EQ-5D predicted score (linear prediction) is calculated. The slope of the EQ-5D predicted score in relation to the observed score is then calculated for each sample, and the mean slope across the 5000 samples denotes the shrinkage coefficient.

The study did not involve recruiting patients or collecting patient data; instead, the analysis was based on three datasets used to analyze QLQ-C30 and EQ-5D and are combined to produce a reliable mapping function. The 3 data sets combined for the QLQ-C30 mapping analysis are a randomized controlled trial of 572 patients with multiple myeloma, 100 patients with breast cancer and 99 patients with lung cancer having consultations at a Canadian cancer clinic (Vancouver Cancer Clinic data). This gives a total of 771 cases for the mapping study; 44% of responders are male, and the mean age of patients is 68 years (45).

The authors developed mapping models using the OLS, tobit, 2-part models, splining, and response modeling (i.e., a series of multinomial logistic regression models predicting the probability of response to each level of each dimension of the EQ-5D-3L) using backward elimination. The best-fitting model included all domains of the EORTC QLQ-C30 as predictors, except for the global health status/QoL domain. Age was a predictor for mobility, self-care, and anxiety/depression, while sex was a predictor for mobility only. The model coefficients (Table 47) were used to calculate the probability of level 2 ("some problems") or 3 ("extreme problems") for the five dimensions of EQ-5D-3L (45). No imputations were made for these utility analyses.

The expected value of the EQ-5D-3L utility was calculated by multiplying the probability of being in each response level by the UK tariff (Appendix P):

$$\begin{aligned} \text{Expected (EQ-5D)} = & 1 - \text{PrMO2} * 0.069 - \text{PrMO3} * 0.314 - \text{PrSC2} * 0.104 - \text{PrSC3} * 0.214 - \\ & \text{PrUA2} * 0.036 - \text{PrUA3} * 0.094 - \text{PrPA2} * 0.123 - \text{PrPA3} * 0.386 - \text{PrAD2} * 0.071 - \\ & \text{PrAD3} * 0.236 - (1 - \\ & \text{PrPerfect}) * 0.081 - \text{PrN3} * 0.269 \end{aligned}$$

Pr indicates the probability of response level 2 ("some problems") or 3 ("extreme problems"), as calculated using the respective coefficients for each level in 253 Appendix P:

$$\text{Pr} = \text{EXP}(\text{PF} * \beta_{\text{PF}} + \text{RF} * \beta_{\text{RF}} + \text{EF} * \beta_{\text{EF}} + \text{CF} * \beta_{\text{CF}} + \text{SF} * \beta_{\text{SF}} + \text{FA} * \beta_{\text{FA}} + \text{NV} * \beta_{\text{NV}} + \text{PA} * \beta_{\text{PA}} + \text{DY} * \beta_{\text{DY}} + \text{SD} * \beta_{\text{SD}} +$$

$$\text{AL} * \beta_{\text{AL}} + \text{CO} * \beta_{\text{CO}} + \text{DI} * \beta_{\text{DI}} + \text{FI} * \beta_{\text{FI}} + \text{Age} * \beta_{\text{Age}} + \text{Female} * \beta_{\text{female}} + \text{Constant})$$

PrPerfect is the probability of being in perfect health while "PrN3" is the probability of being in level 3 of any dimension. Each will be calculated using the following equations:



$$\text{PrPerfect} = (1 - \text{PrMO2} - \text{PrMO3}) * (1 - \text{PrSC2} - \text{PrSC3}) * (1 - \text{PrUA2} - \text{PrUA3}) * (1 - \text{PrPA2} - \text{PrPA3}) * (1 - \text{PrAD2} - \text{PrAD3})$$

$$\text{PrN3} = 1 - (1 - \text{PrMO3}) * (1 - \text{PrSC3}) * (1 - \text{PrUA3}) * (1 - \text{PrPA3}) * (1 - \text{PrAD3})$$

The repeated measures model was used in the base case, model predictions for both arms were generally aligned with observed utility values at each visit Figure 14 and Figure 15, provide results at baseline and at all relevant data collection timepoints instrument. Results for observed EQ-5D-3L utility values by time point are presented in Figure 14 and Figure 15. Results show no notable differences between treatment groups in mean EORTC QLQ-C30 scores during the treatment period. During post-treatment follow-up (PTFU) scores increased (improved) in both treatment groups compared with baseline; XXXXXXXXXXXXXXXXXXXX patients at 12, 18, and 24 months. Analysis of the change from baseline generally showed a similar change in scores during treatment and a change to higher scores in BrECADD patients compared with eBEACOPP patients at 12 months PTFU (p-value=0.0031), 18 months PTFU (p-value=0.0418), and 24 months PTFU (p-value=0.0271). The estimated mean change from baseline in the BrECADD treatment group at 6, 12, 18, 24, and 36 months PTFU was considered clinically meaningful using the published minimally important difference (MID) of 10 (49). The estimated mean change from baseline in the eBEACOPP treatment group did not reach the MID of 10 at any of the PTFU time points.

Table 42 Coefficients for Response Model Mapping from the EORTC QLQ-C30 to the EQ-5D-3L can be found in Table 47

Table 47 Coefficients for Response Model Mapping from the EORTC QLQ-C30 to the EQ-5D-3L

Coefficient	MO2	MO3	SC2	SC3	UA2	UA3	PA2	PA3	AD2	AD3
PF	- 0.0715 2	- 0.1666 5	- 0.0492 1	- 0.0989 9	- 0.0358 5	- 0.08515	- 0.0008 5	- 0.0128	- 0.0143 1	- 0.0442
RF	- 0.0109 8	- 0.0066 2	- 0.0165 5	- 0.0295 8	- 0.0321 9	- 0.0550 8	0.0012 2	- 0.0013 8	0.00497 3	0.0187 78
EF	0.0104 31	0.0237 46	0.0078 67	0.0082 22	0.0205 53	0.02798 8	0.0086 09	0.0112 92	- 0.07811	- 0.1475 7
CF	- 0.0108 7	- 0.0059 7	- 0.0098 7	- 0.0088 7	0.0035 5	- 0.00071	0.0027 02	0.0150 75	- 0.00659	0.0056 51
SF	0.0030 96	0.0109 56	- 0.0093 5	- 0.0054 7	- 0.0213 4	- 0.03437	0.0052 08	- 0.0006 4	0.00550 4	0.0084 16
FA	0.0059 73	0.0022 79	- 0.0220 3	- 0.0250 5	0.0278 38	0.03300 1	0.0071 31	0.0063 54	- 0.00634	0.0072 86
NV	0.0005 88	0.0157 5	0.0068 15	0.0186 91	0.0218 26	0.02156 9	0.0054 72	- 0.0035 4	- 0.00741	- 0.0088 8
PA	0.0228	0.0430	0.0158	0.0244	0.0200	0.02291	0.1004	0.1643	0.00202	-



	16	39	18	97	72		41	61	4	0.01189
DY	0.001602	0.004479	– 0.00461	– 0.01534	– 0.00535	– 0.01544	0.01011	0.007721	0.000166	– 0.01779
SD	0.002049	0.010413	0.001558	– 0.00019	– 0.00107	– 0.00218	0.012575	0.02121	– 0.00292	0.011685
AL	– 0.00929	0.004167	– 0.00017	0.009572	– 0.01012	– 0.01092	– 0.01272	– 0.00819	0.006152	0.01609
CO	– 0.00422	– 0.01152	– 0.00412	– 0.00896	– 0.00046	0.004172	0.005891	0.0099	0.004256	0.000673
DI	–0.005	0.009786	0.003027	0.00513	– 0.00889	– 0.01112	–0.0037	– 0.00768	0.001803	0.001991
FI	– 0.0012	– 0.0033	0.004999	0.014695	0.007706	0.006497	0.009976	0.011657	0.012372	0.014618
Age	0.028467	– 0.02062	0.048086	0.131205					0.025968	0.008105
Female	– 0.34865	– 1.3967								
Intercept	3.168647	3.54151	0.498039	– 6.61854	3.49354	5.675094	– 3.25498	– 9.81874	4.561572	6.023862

Figure 14





Figure 15 [REDACTED]



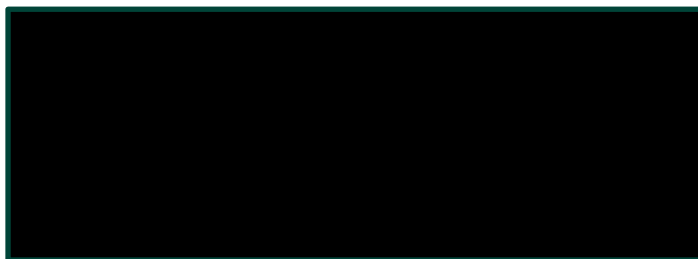
Sensitivity analysis showed that when including patients from a non-randomized cohort (n=27) in the utility model, the same predictors were significant as in the base case, and the 95% CIs for the coefficients were widely overlapping and showing robustness to the variations tested.

Model predictions for the EQ-5D-evaluable population were generally aligned with observed utility values at each visit in both treatment arms (Figure 16 and Figure 17).

Figure 16 [REDACTED]



Figure 17 [REDACTED]



Health State	LS Mean	95% CI
Progression-free, On treatment, BrECADD	0.728	0.714, 0.741
Progression-free, On treatment, eBEACOPP	0.720	0.707, 0.734
Progression-free, Off treatment, BrECADD	0.827	0.814, 0.840



Progression-free, Off treatment, eBEACOPP	0.811	0.798, 0.824
Progressed, Off treatment	0.759	0.717, 0.801

Table 48 Observed Mean EQ-5D-3L Health Utility Value for the base-case analysis

Health State	N	Mean	SD	Median	95% CI	Q1, Q3	Min, Max	SE
Overall	3845							
Overall (BrECADD)	1936							
Overall (eBEACOPP)	1909							
Baseline	690							
Baseline (BrECADD)	343							
Baseline (eBEACOPP)	347							
Progression-free (Overall)	3814							
Progression-free on treatment BrECADD	900							
Progression-free on treatment eBEACOPP	901							
Progression-free off treatment BrECADD	1022							
Progression-free off treatment eBEACOPP	991							
Progressed (Overall)	31							

Table 49 Least Square Mean from MMRM in EQ-5D-3L Health Utility for the base-case analysis

Progression-free, On treatment, BrECADD		
Progression-free, On treatment, eBEACOPP		
Progression-free, Off treatment, BrECADD		
Progression-free, Off treatment, eBEACOPP		
Progressed, Off treatment		

Table 50 Coefficients of the covariates from the MMRM used in the base-case analysis

Effect	Coefficient	95% CI	P-value	SE
Intercept				



Treatment Arm (BrECADD vs. eBEACOPP)	████	████	████	████
On/Off Treatment (On Treatment vs. Off Treatment)	████	████	████	████
Treatment Arm * On/Off Treatment: BrECADD * On Treatment	████	████	████	████
Progressive Disease (Yes vs. No)	████	████	████	████
Centered Age (Mean=33.8)	████	████	████	████
Centered Baseline Score (Mean=0.726)	████	████	████	████

Figure 18 Utility model coefficients (sensitivity analysis)

Covariate	Coefficient (95% CI), P-value
	████
Intercept	████
Treatment Arm (BrECADD vs. eBEACOPP)	████
On/Off Treatment (On-treatment vs. Off- treatment)	████
Treatment Arm * On-/Off-treatment Interaction Term	████
Progressive Disease (Yes vs. No)	████
Centered Age (Mean = 33.8)	████
Centered Baseline Score (Mean = 0.726)	████

10.2.1.4.1 Mapping from EQ-5D-3L (UK) to EQ-5D-5L (DK)

The mapping study by Torkildseng (50) was to develop to address the specific DMC request for using EQ-5D-5L in the reimbursement submission (50). The study presents a validated algorithm that can accurately predict mean Danish EQ-5D-5L utilities based on published mean UK EQ-5D-3L utilities. The study incorporated a secondary analysis of patient-level UK EQ-5D-3L utility index scores from 11 oncology clinical trials. The EQ-5D-3L responses were mapped to EQ-5D-5L responses with the van Hout and Shaw preferred mapping algorithm. Model fitting and internal cross-validation were completed on a pooled dataset formed from eight trials including a total of 30,755 EQ-5D-3L responses. Three other trials were used for external validation (21,587 EQ-5D-3L observations). From the model fitting phase, a simple linear model for mean utility scores exhibited good fit and was selected as the optimal prediction algorithm. External validation using the algorithm to predict mean Danish EQ-5D-5L utilities was excellent, with the largest absolute prediction error being 0.020 (observed UK EQ-5D-3L means: 0.628–0.835). The base case uses the ‘repeated measures model’ which generates



estimated values in terms of UK EQ-5D-3L utilities. Each of the of the estimated EQ-5D-3L utility values is further transformed to Danish EQ-5D-5L utilities using the following equation:

Mean Danish EQ-5D-5L (predicted) = $0.231 + 0.773 * \text{mean UK EQ-5D-3L (observed)}$.

The equation for conversion of EQ-5D-3L to EQ-5D-5L is applied in the model for each health state.

Figure 19 



10.2.2 Disutility calculation

Concerns about loss of fertility are particularly critical for younger cancer patients and survivors, as treatments such as chemotherapy, radiation, or surgery can significantly impact reproductive health. For patients with concerns about fertility preservation or infertility, complementary assessments are essential to provide a comprehensive understanding of their well-being. This is supported by the development of fertility-specific tools like FertiQoL, which captures dimensions such as general health, self-perceptions, emotions, partnership, family and social relationships, work-life, and future life plans—areas not covered by the EORTC QLQ-C30 which may indicate an underestimation of HRQoL (51).

Disutility for adverse events and infertility are informed by a TLR and included in the base case to reflect their specific health burdens (see Section 2), as EORTC-QLQ-C30 does not capture them directly, and their exclusion could risk underrepresenting their impact.

The age- and treatment-specific probabilities of infertility shown in Summary of Danish research on long-term consequences of HL treatment on Danish HL survivors. were informed by HD21 data. The underlying data sources are based on data on file, a manuscript has been submitted for publication and is currently under review, and assumptions were as follows: HD21 data; Ferdinandus (2023 abstract) (52) for year 1; Ferdinandus (2024 abstract) (53) for year 3; year 2 was calculated using linear interpolation; year 4 was taken from the Ferdinandus (2025) paper (8); and year 5 was assumed to be the same as year 4. Year 1 corresponds to age 34. From age 38 (year 4) onward, the probability of infertility is assumed to remain constant.



Table 51 Gonadal function recovery based on FSH level

	BrECADD		eBEACOPP	
	Male	Female	Male	Female
Year 1	████	████	████	████
Year 2	████	████	████	████
Year 3	████	████	████	████
Year 4	████	████	████	████
Year 5	████	████	████	████

████████████████████ Table 51 and the sex- and age dependent utility decrement for patients with age less than 45 years old from Krol et al. (38). Duration of adverse events is assumed to be 14 days/2 cycles.

10.2.3 HSUV results

Results from the mapping exercise are presented in Appendix I. Uncertainty was already captured in the EQ-5D-3L coefficient estimate for covariates, thus the 95% CI are not presented directly for the EQ-5D-5L utility score results. Overview of health state utility values and disutilities can be found in Table 53.

Table 52 Overview EQ-5D-3L health state utility values used in the base-case analysis.

	Results [95% CI]	Instrument Tariff (Value Set) Used	Comments
HSUV BrECADD Baseline	████████████████████	EQ-5D-3L DK	Mapped from EORTC-QLQ-C30
HSUV eBEACOPP Baseline	████████████████████	EQ-5D-3L DK	Mapped from EORTC-QLQ-C30
HSUV BrECADD Progression free (on treatment)	██	EQ-5D-3L DK	Mapped from EORTC-QLQ-C30



HSUV eBEACOPP Progression free (on treatment)		EQ-5D-3L DK	Mapped from EORTC- QLQ-C30
HSUV BrECADD Progression free (off treatment)		EQ-5D-3L DK	Mapped from EORTC- QLQ-C30
HSUV eBEACOPP Progression free (off treatment)		EQ-5D-3L DK	Mapped from EORTC- QLQ-C30
Progression free (off treatment)		EQ-5D-3L DK	Mapped from EORTC- QLQ-C30

Table 53 Overview of eQ-5D-5L and EORTC-QLQ-C30 health state utility values [and disutilities]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV BrECADD Baseline		EQ-5D-5L EQ-5D-3L	DK DK	Mapped from EQ- 5D-3L Mapped from EORTC- QLQ-C30
HSUV eBEACOPP Baseline		EQ-5D-5L EQ-5D-3L	DK DK	Mapped from EQ- 5D-3L Mapped from EORTC- QLQ-C30
HSUV BrECADD Progression free (on treatment)		EQ-5D-5L EQ-5D-3L	DK DK	Mapped from EQ- 5D-3L Mapped from EORTC- QLQ-C30



HSUV eBEACOPP	████	EQ-5D-5L	DK	Mapped from EQ-5D-3L
Progression free (on treatment)	████████	EQ-5D-3L	DK	Mapped from EORTC-QLQ-C30
HSUV BrECADD	████	EQ-5D-5L	DK	Mapped from EQ-5D-3L
Progression free (off treatment)	██████████	EQ-5D-3L	DK	Mapped from EORTC-QLQ-C30
HSUV BrECADD	████	EQ-5D-5L	DK	Mapped from EQ-5D-3L
Progression free (off treatment)	████████	EQ-5D-3L	DK	Mapped from EORTC-QLQ-C30
Disutilities				
Anemia	████	TTO	UK	N/A
Febrile neutropenia	████	TTO	UK, Australia, Taiwan, Thailand, South Korea, Brazil and Mexico	Vignette study
Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)	████	VAS and SG	UK	N/A
Infection	████	DCE	US	N/A
Leukopenia	████	SG	UK	N/A
Mucositis	████			
Neutropenia	████	TTO	UK, Australia, Taiwan, Thailand, South Korea, Brazil and Mexico	Vignette study
Thrombocytopenia	████	N/R	N/R	N/R
Infertility	████	VAS and TTO	Dutch	N/R

TTO; Time trade-off, VAS; visual analog scale, SG; standard gamble, Discrete choice evaluation



10.3 Health state utility values measured in other trials than the clinical trials forming the basis for relative efficacy

N/A

11. Resource use and associated costs

The model’s costs were estimated from a limited societal perspective, as recommended by DMC guidelines. This includes costs for acquisition, administration, concomitant medication, monitoring and follow-up care, adverse events, radiotherapy, subsequent treatments, and fertility-related expenses due to gonadal function loss which include patient costs. All costs are discounted annually at 3.5%, per Danish Ministry of Finance guidelines.

11.1 Medicines - intervention and comparator

Drug acquisition costs were sourced from Medicinpriser.dk and reported as pharmacy purchase prices, following DMC guidelines. Costs were calculated by combining dosing regimens, relative dose intensity adjustments and time-on-treatment with unit costs. Body weight and body surface area (BSA) were required to calculate drug doses and can be found in Section 3.4.2. Given all patients had discontinued treatment at the time of data cut-off, the acquisition cost was calculated based on the mean number of cycles administered which is based on the Danish RWE study described in Appendix K. Since vial sharing is used in the base-case, the model calculates the exact cost of the dose needed for the patients. All costs for medicine are included in the CEM and these are based on the approved treatment and supportive therapies and can be found in the “Medicine” tab. The CEM also includes all pack sizes and strengths that correspond to the route of administration. The lowest-cost supplier was selected, and all relevant pack-size combinations are included.

11.1.1 RDI

Drug acquisition costs were estimated by combining dosing regimens with adjustments for relative dose intensity (RDI) and time on treatment. Drug doses were calculated using body weight and body surface area (BSA). Mean body weight and BSA inputs were derived from HD21 for both treatment arms, and the resulting dose and cost estimates are presented in Table 61.

Table 54 Baseline characteristics

Parameter	All treatment arms	Source
Mean ITT Patient characteristics		
Body weight (kg)	76.15	



BSA (m ²)	1.91	HD-21 CSR Table 15.1.4.1 Data Cut: 31OCT2023
BSA (m ²)	1.90	

Abbreviations: BSA = body surface area; ITT = intention-to-treat

Relative dose adjustment (RDI) adjustment was included to reflect the ratio of actual to scheduled drug delivery; the actual dose delivered may differ from the planned dose per treatment cycle due to missing or delayed doses and toxicity-related dose reductions or interruptions.

Mean body weight and BSA were used to determine the number of vials required per patient given the per-kg/m² dose and the RDI. The base-case analysis assumed full wastage as patient numbers in each center would likely be too low to allow for any vial sharing. Given all patients had discontinued treatment at the time of data cut-off, the acquisition cost was calculated based on the mean number of cycles administered in HD21. The percent of patients de-escalating treatment were based on percent of patients with negative PET, sourced from HD21 for both PET-guided BrECADD and eBEACOPP. When switching On/Off for RDI in the cost-effectiveness model will not affect drug price calculations but it will trigger changes in cost calculations in the model.

Table 55 Medicines used in BrECADD regimen

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Brentuximab vedotin i.v.	1,8 mg/kg*	99%	Day 0	Yes
Etoposide i.v.	150 mg/m ²	99%	Day 1-3	Yes
Cyclophosphamide i.v.	1250 mg/m ²	99%	Day 1	Yes
Doxorubicin i.v.	40 mg/m ²	99%	Day 1	Yes
Dacarbazine i.v.	40 mg/m ²	99%	Day 2-3	Yes
Dexamethasone p.o.	40 mg/m ²	100%	Day 1-4	Yes

* maximum of 180 mg absolute dose

Table 56 Medicines used in eBEACOPP regimen

Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Doxorubicin i.v.	35 mg/m ²	99 %	Day 1	Yes
Etoposide i.v.	200 mg/m ²	99 %	Day 1-3	Yes
Cyclophosphamide i.v.	1250 mg/m ²	99 %	Day 1	Yes
Bleomycin i.v.	10 mg/m ²	92 %	Day 8	Yes
Vincristine i.v.	1,4 mg/m ²	93 %	Day 8	Yes



Medicine	Dose	Relative dose intensity	Frequency	Vial sharing
Procarbazine p.o.	100 mg/m ²	97 %	Day 1-7	Yes
Prednisone p.o.	40 mg/m ²	98 %	Day 1-14	Yes

11.2 Medicines - co-administration

Growth-factor support and blood transfusions from the HD21 trial were included as concomitant medications, reflecting their use in Danish clinical practice to prevent infections (supportive therapy). All concomitant medication costs for growth-factor support and blood transfusions were calculated per treatment cycle during frontline therapy.

Table 57 Concomitant medications

Resource category	Treatment	Dose (mg)	Admins per cycle	Proportion BrECADD	Proportion BEACOPP	Source
Growth-factor support	Filgrastim	0.4 mg	28	4.3%	5.5%	HD-21-study
	Pegfilgrastim	6 mg	1	76.2%	74.9%	HD-21-study
Blood transfusions	Platelets	N/A	N/A	16.7%	33.6%	HD-21-study
Blood transfusions	Red blood cells	N/A	N/A	24.0%	52.2%	HD-21-study

Table 58 Costs for concomitant medication

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Filgrastim	28 pr cycle	1.0127	N/A	Medicinpriser.dk
Pegfilgrastim	1 pr cycle	5.803	N/A	Medicinpriser.dk
Blood transfusion (platelets)	N/A	4.221	16PR02	DRG2025
Blood transfusion (red blood cells)	N/A	4.221	16PR02	DRG2025

11.3 Administration costs

Administration costs for hospital staff are modeled to account for resource and cost differences between BrECADD and eBEACOPP, as their cycle counts vary. For same-day infusions, one DRG rate is applied, while oral administration lacks a DRG tariff. For oral therapy, 10 minutes of nurse time is assumed, costing DKK 31, see Table 59 and Table 60 for details.

Table 59 Administration costs BrECADD

Administration type (eBEACOPP)	Frequency	Unit cost [DKK]	DRG code	Reference
--------------------------------	-----------	-----------------	----------	-----------



Bleomycin i.v.	Day 8	2136	17MA98	DRG 2025
Etoposide i.v.	Day 1-3	2136	17MA98	DRG 2025
Doxorubicin i.v.	Day 1	2136	17MA98	DRG 2025
Cyclophosphamide i.v.	Day 1	2136	17MA98	DRG 2025
Vincristine i.v.	Day 8	2136	17MA98	DRG 2025
Procarbazine p.o.	1-7	31	N/A	Catalogue for estimation of unit costs
Prednisone p.o.	1-14	31	N/A	Catalogue for estimation of unit costs

Table 60 Administration costs eBEACOPP

Administration type (BrECADD)	Frequency	Unit cost [DKK]	DRG code	Reference
Brentuximab vedotin i.v.	Day 0	2.136	17MA98	DRG 2025
Etoposide i.v.	Day 1-3	2.136	17MA98	DRG 2025
Doxorubicin i.v.	Day 2	2.136	17MA98	DRG 2025
Cyclophosphamide i.v.	Day 2	2.136	17MA98	DRG 2025
Dacarbazine i.v.	Day 3-4	2.136	17MA98	DRG 2025
Dexamethasone p.o.	Day 2-5	31	N/A	Medicine councils catalogue (unit costs)

11.4 Disease management costs

A small number of HD21 patients received concurrent frontline radiotherapy if absence of progression. The model includes these radiotherapy costs prior to progression, while post-progression radiotherapy costs are grouped under subsequent therapies. Radiotherapy proportions are 12.0% for BrECADD and 13.8% for eBEACOPP, with 21 treatment sessions on a megavoltage machine, as per Josting et al (54).

Table 61 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Radiotherapy	21 treatments	2.643	27MP04	DRG 2025



11.5 Costs associated with management of treatment emergent adverse events and adverse events

Costs for AEs and TEAEs (see Table 36 for number and proportion of safety events used in the model) Table 35. TEAEs of Any Grade Reported for at Least 10% of Patients by CTCAE Toxicity or PT (Safety Population). are accrued as a one-time cost at the beginning of the model. The DRG-tariffs for grade 3-4 AEs including TRMB are presented in Table 58 and Table 62. The cost per AE or TRAE was multiplied by the total incidence rate of each AE or TEAE and totaled for every treatment to calculate the total cost of managing AEs by treatment. The cost of managing AEs associated with subsequent treatments was not considered in this analysis. The model allows you to choose between including all adverse events (AEs) or only those related to treatment-related medical benefits (TEAE). In the base case, when all AEs are included, TRMB values are set to zero to prevent double counting. However, if you choose to include only TEAE-related AEs, TEAE will have its own values.

Table 62 Cost associated with management of adverse events 3+

	DRG code	Unit cost/DRG tariff
Anemia	17MA98	2.208
Thrombocytopenia	17MA98	2.208
Infection	17MA98	2.208
Cardiac disorders	17MA98	2.240
Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)	17MA98	552
Hepatobiliary disorders	17MA98	2.072
Nervous system disorders (sensory, motor, and other)	17MA98	2.012
Renal or urinary disorders	17MA98	2.136
Respiratory, thoracic or mediastinal disorders	17MA98	2.136

Table 63 Cost associated with management of TEAE

	DRG	Unit cost [DKK]
Anemia	17MA98	2.208
Thrombocytopenia	17MA98	2.208
Infection	17MA98	2.208
Cardiac disorders	17MA98	2.240
Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)	17MA98	552
Hepatobiliary disorders	17MA98	2.072
Nervous system disorders (sensory, motor, and other)	17MA98	2.212
Renal or urinary disorders	17MA98	2.136
Respiratory, thoracic or mediastinal disorders	17MA98	2.136

11.6 Subsequent treatment costs

The costs of subsequent therapies after disease progression were estimated by combining two factors: the proportion of patients receiving each therapy (calculated separately for BrECADD and eBEACOPP) and a fixed cost assigned to each therapy. These costs only cover drug acquisition or DRG tariffs, as the efficacy of subsequent therapies



was not explicitly modeled. The health economic models do not include AEs for subsequent treatment-related AEs, as they cannot be directly linked to the treatment choice. Consequently, the uncertainty in using this data could be considerable.

Table 64 Procedures for subsequent treatments for ITT

Treatment	BrECADD	eBEACOPP
Chemotherapy	147%	170%
ASCT	59%	75%
AlloSCT	10%	6%
Brentuximab	12%	27%
Radiation	16%	18%

In Danish clinical practice, the DHAP regimen (Dexamethasone, Cytarabine, and Cisplatin) is a chemotherapy treatment administered in 21-day cycles, based on the patient's response and tolerance. The model assumes two DHAP cycles. For brentuximab vedotin, a dose of 1.8 mg/kg is used, with 16 cycles specified according to the SmPC (55) and confirmed by expert opinion (PKA) .

Table 65 Subsequent treatments doses and frequencies

Treatment	Dose	Frequency	Vial sharing
DHAP			
Dexamethasone	40	Day 1 pr 21 days cycle	Yes
Cytarabine	4mg/m ²	Day 1 pr 21 days cycle	Yes
Cisplatin	100 mg/m ²	Day 2 pr 21 days cycle	Yes
Brentuximab vedotin	1,8mg/kg	Every third week	Yes
ASCT	N/A	N/A	N/A
AlloSCT	N/A	N/A	N/A
Radiation	N/A	N/A	N/A

Table 66 Cost for subsequent treatment

DHAB	Dose	AIP pr/mg	DKK	Source
Dexamethasone	40	0,5	39	Medicinpriser.dk
Cytarabine	4mg/m ²	0,03	29	Medicinpriser.dk
Cisplatin	100mg/m ²	494	1.886	Medicinpriser.dk
Total cost DHAP (2 cycles)			3028	
ASTC	N/A	N/A	103.174	DRG 26MP24
AlloSCT	N/A	N/A	51.697	DRG 17MA01
Brentuximab vedotin (16 cycles)	1,8mg/kg	N/A	796.490	Medicinpriser.dk
Radiation	N/A	N/A	2.643	DRG 27MP04



11.7 Patient costs

Patient costs are incorporated into the model as part of fertility treatment due to gonadal function loss. To estimate time and transport costs for female patients, male patients, and female partners of male HL patients, it was necessary to map the time spent and the number of visits (resources) at the fertility clinic, as this information is not available elsewhere. Mapping was conducted in collaboration with leading physician (MHT) at the Fertility Department at Odense University Hospital. This department was selected because it treats HL patients undergoing eBEACOPP therapy for fertility preservation. Detailed description of the resource use mapping can be found in Appendix L.2. All costs are estimated in accordance with the DMC's guidelines and the catalog of unit costs. Patient costs are categorized into pre- and post-oncology periods, as fertility treatment takes place during both.

Pre-oncologic period

In the pre-oncology period, the number of visits varies by gender. Female patients require [REDACTED] for ovarian cryopreservation, a more complex process, while male patients need only [REDACTED] for sperm freezing. Details are in Appendix L.2. Transportation and time spent costs are summarized in Table 67 Table 67 and Table 68 associated costs.

Post-oncologic period

In the post-oncology period, female patients have seven fertility options, with the choice depending on individual assessments. Each option varies in the number of visits and time required. Since data on the distribution of these options is unavailable, the average number of visits and time across all seven options was used to estimate costs (Total time in minutes for all treatment options ÷ number of fertility options = average time per option), which is then multiplied by the cost per minute from the DMC catalog of unit costs. Same approach is applied for female partners to male HL patients since they have two different fertility treatment options in the post-oncologic period. Further details can be found in Appendix L.2

The fertility specialist provided an estimate for the number of attempts typically required for each treatment in the post-oncologic period, as follows [REDACTED]

Table 67 Transport costs used in the model

Activity	Number of hospital visits	DKK
Pre-oncology fertility treatment		
Female HL patient	[REDACTED]	[REDACTED]
Male HL patient	[REDACTED]	[REDACTED]
Post-oncologic treatment		
Female HL patient	[REDACTED]	[REDACTED]



Activity	Number of hospital visits	DKK
Female partner to HL patient		

Table 68 Patient costs related to fertility treatment used in the model

Activity	Time spent [minutes]	DKK
Pre oncology fertility treatment		
Female HL patient		
Male HL patient		
Post-oncologic treatment		
Female HL patient		
Female partner to HL patient		

During the pre- and post-oncology periods, female and male patients as assumed to have an average of [REDACTED]. This is based on [REDACTED] (Table 67). Assuming that 70% (equal to the percentage of fertile population in the HD-21 study) of the 60 patients with Hodgkin lymphoma receiving eBEACOPP in Denmark undergo fertility treatment, this corresponds to [REDACTED]. This estimate is based on a conservative assumption of two treatment cycles per patient

11.8 Other costs (e.g. costs for home care nurses, out-patient rehabilitation and palliative care cost)

11.8.1 Costs related to fertility treatment

As mentioned, patient costs are divided into pre- and post-oncology periods since fertility treatment occurs in both. The costs are included in the model as a lump sum, with the four-year cost used in the base case. In the model, 70% of the DRG tariff is applied to the female population and 100% to the male population. This reflects the proportion of fertile patients observed in the HD21 study, which is comparable to the Danish Hodgkin lymphoma population. During the pre-oncology phase, the DRG tariff is applied for both female and male patients. In the post-oncology phase, it is based on the fertility treatment of female HL patients, and the partners of male HL patients.

Table 69 Fertility costs used in the model

Activity	DRG code	Unit cost/DRG tariff
Freezing of ovarian tissue	A (DC819)	52.716/
	B (BJXY51)	17MA01
Harvesting of sperm	A (DC819)	2.136/
	B (BJXY50)	17MA98
Female infertility after re-implantation of cryopreserved ovarian tissue	A (DN978B1)	48.340/
	B (DC819)	17MA01
Female infertility due to conditions in the male	A (DN974)	23.281/
	B (DC819)	13MA01



11.8.2 Cost for Monitoring and follow-up care

Monitoring and follow-up care costs were accrued for progression free- and post-progression health states. The model assumes that patients do not accrue monitoring costs after cure is achieved. Relevant components of follow-up care were consultations, CT-scan and PET-scan. Frequencies are based on Danish expert opinion, se appendix L, since the HD-21 study has a higher frequency compared with Danish settings. Reference values from the HD-21 study can be found in [REDACTED] 102.

Table 70 Frequency of monitoring of follow-up care

Resource	Frequency per year while assigned to the state			
	0-6 months post-diagnosis, pre-progression	6-48 months post-diagnosis, pre-progression	≥48 months post-diagnosis, pre-progression	Post-progression
Consultation	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
CT scan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
PET scan	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Table 71 Monitor and follow-up costs used in the model

Resource	Unit/DRG	DKK	Source
Consultation	Salary*	522	Catalogue for unit costs
CT scan	36PR02	8.492	DRG 2025
PET scan	36PR02	8.492	DRG 2025

* Overlæge, timeløn 1044 (Assumption: consultation and preparation time = 30 min)

12. Results

12.1 Base case overview

Table 72 Base case overview

Feature	Description
Comparator	eBEACOPP
Type of model	Partitioned survival model
Time horizon	70 years (life time)
Treatment line	1st line
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-3L (mapped)
Costs included	Acquisition Administration Concomitant medications Treatment emergent adverse events



Feature	Description
	Radiotherapy Subsequent therapies Patient costs Monitoring and follow-up care (other costs) Fertility treatment costs (other costs)
Dosage of medicine	Based on weight and BSA
Average time on treatment	
Parametric function for PFS	BrECADD: Gompertz eBEACOPP: Gompertz
Parametric function for OS	BrECADD: Weibull eBEACOPP: Weibull
Inclusion of waste	No
Average time in model health state (years)	
PFS	
OS	

12.1.1 Base case results

Table 73 Base case results, discounted estimates

	PET-guided BrECADD (DKK)	PET-guided eBEACOPP (DKK)	Incremental (DKK)
Drug acquisition costs			
Drug administration costs			
Concomittant therapy + Radiotherapy costs			
Adverse event costs			
Monitoring costs			
Loss of gonadal function			
Subsequent treatment			
Patient costs			
Total costs			
Total life years			
Total QALYs			
Incremental cost per life years gained			



12.2 Sensitivity analyses

The following sensitivity analyses will be presented for the base-case; deterministic one-way sensitivity analysis (OWSA), scenario analyses, and probabilistic sensitivity analysis (PSA).

12.2.1 Deterministic sensitivity analyses

OWSAs were conducted to explore the drivers of the CEM. Where available, CIs were used as high and low values of the parameters. For the cost inputs, SE was assumed to be 20% of the mean, 95% CIs were calculated based on the gamma distribution. In total 135 model inputs was included in the OWSA and the top 15 parameters ranked by order of the influence they have on the ICERs are illustrated in Figure 20 comprehensive list of tested variables is provided in Appendix G while **Error! Reference source not found.** outlines the variations applied to them.

Figure 20



Table 74

Parameter	Lower Bound	Upper Bound
Body weight (kg): ITT		
Monitoring and Follow-up Care Costs CT scan		
Monitoring and Follow-up Care Costs PET scan		
Subsequent Therapy - HD-21 PET-guided eBEACOPP: Brentuximab		
Subsequent Therapy Costs HD21: Brentuximab		
Discount Rate (Costs) - 0-39 years		
Administration Costs A6		
Administration Costs A1		
Administration Costs A5		

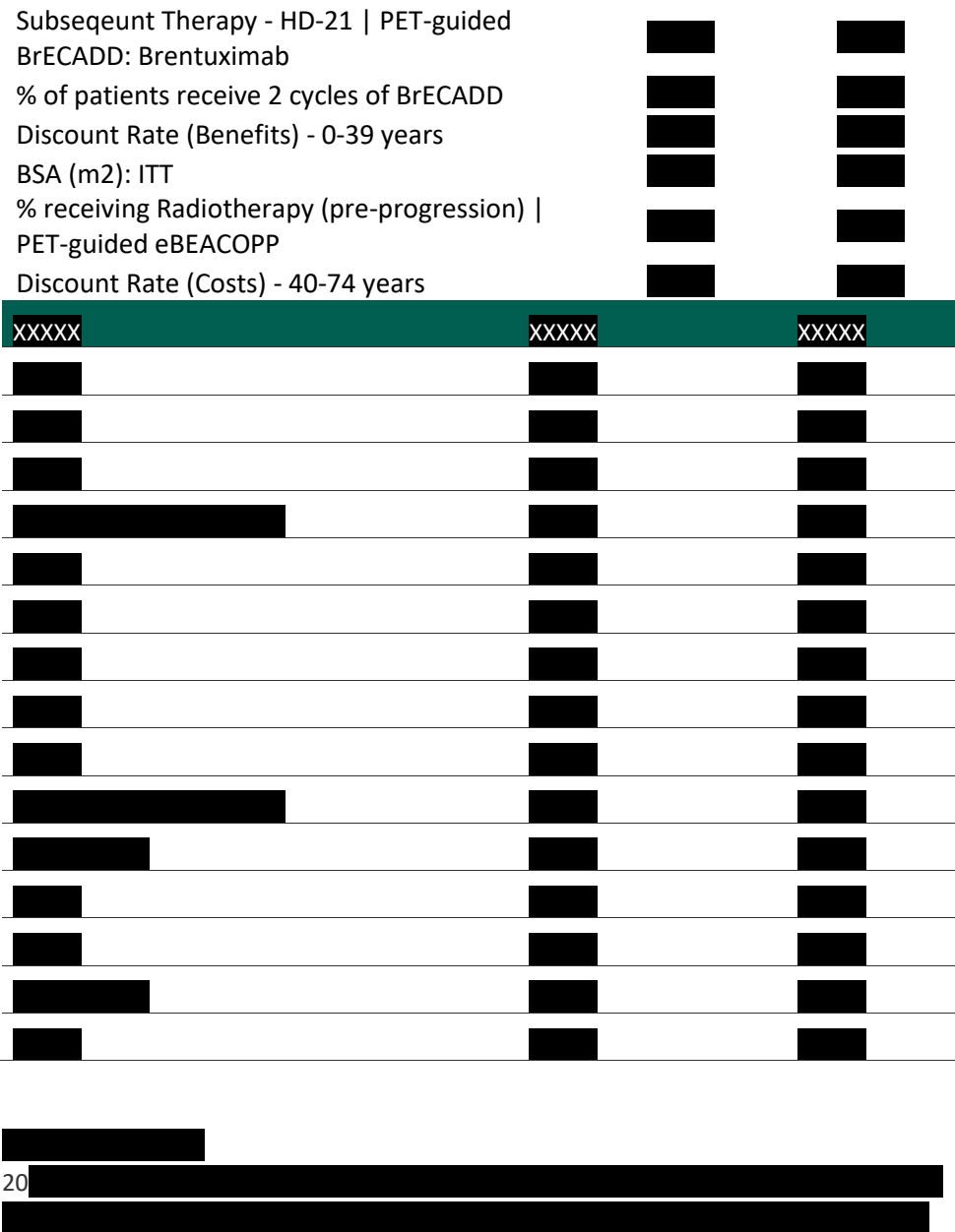


Figure 21

Table 75

Parameter	Base case	Scenario	ICER	Diff. From BSA
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Base case				
Cure timepoint (months)	60	73		
RDI	On	Off		
Vial wastage	On	Off		
PFS; extrapolation approach	Parametric Model (Gompertz)	KM		
PFS; extrapolation approach	Parametric Model (Gompertz)	Mixture cure model (Weibull)		
PFS; extrapolation approach	Parametric Model (Gompertz)	Mixture cure model (log-logistic)		
OS; extrapolation approach	Parametric Model (Weibull)	KM + Lifetables		
OS; extrapolation approach	Parametric Model (Weibull)	Mixture cure model (log-normal)		
OS; extrapolation approach	Parametric Model (Weibull)	Mixture cure model (exponential)		
Utility modelling approach	Repeated measures model	Observed data		

The scenario analyses suggest that the ICER is most sensitive to the overall survival (OS) extrapolation approach. , see Table 75 .

12.2.2 Probabilistic sensitivity analyses

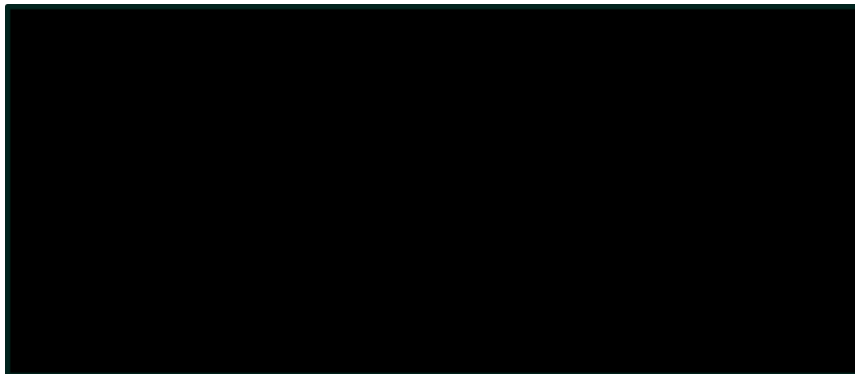
The PSA was conducted using 1,000 iterations, and results are presented as an incremental cost-effectiveness plane and a cost-effectiveness acceptability curve, see Figure 23 and Figure 24. The convergence plots of ICERs illustrate that the number of iterations conducted are sufficient in capturing the impact of parameter uncertainty see Figure 22). .



Figure 22 [REDACTED]

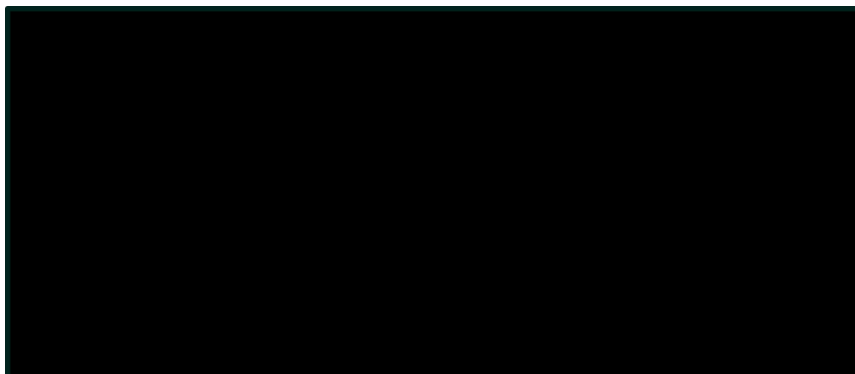


Figure 23 [REDACTED]



The incremental cost-effectiveness (ICE) scatterplot shows a relatively narrow scattering of simulated incremental cost and effect pairs, indicating limited overall uncertainty around the joint estimates.

Figure 24 [REDACTED]



13. Budget impact analysis

In Year 1-5, the eligible population is estimated at [REDACTED] patients (Section 3.2) and a 100% market share is assumed if the BrECADD regimen is recommended, see Table 76. Cost



inputs for the budget impact analysis are based on the cost analysis and are presented without discounting and excluding patient and results in Table 77.

Table 76 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
Recommendation					
BrECADD					
eBEACOPP					
BrECADD					
eBEACOPP					

13.1.1 Budget impact

Table 77 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5

Over the 5-year period, total costs are higher in the recommended scenario () than in the not recommended scenario X . The total budget impact (recommended minus not recommended) is predictable, stable, and decreases slightly over time, from Table 77.



14. List of experts

- Jacob Haaber Christensen, Senior Consultant, Odense University Hospital
- Martin Hutchings, Senior Consultant, Professor, Copenhagen University Hospital
- Peter Martin Hjørnet Kamper, Senior Consultant, Aarhus University Hospital
- Mette Honnens Tanvig, leading physician, Odense University Hospital

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Appendix A. Main characteristics of studies included

[Complete Table 78 for each study included. Comply with section 3 of the [methods guide](#).]

Table 78 Main characteristic of studies included

Trial name: 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. NCT number: NCT02661503	
Objective	To demonstrate reduced toxicity of the BrECADD treatment compared to the eBEACOPP treatment measured by treatment-related morbidity (TRMB) while maintaining efficacy.
Publications – title, author, journal, year	Assessing the efficacy and tolerability of PET-guided BrECADD versus eBEACOPP in advanced-stage, classical Hodgkin lymphoma (HD21): a randomised, multicentre, parallel, open-label, phase 3 trial.
Study type and design	International, open-label, prospective, phase 3, randomized main study with central stratified randomization between 2 parallel groups. No cross-over. All main analysis are final; long-term follow-up is ongoing.
Sample size (n)	Per Protocol: 1500 Intention To Treat: 1482
Main inclusion criteria	Each study participant was required to meet all of the following inclusion criteria to be randomized 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 randomization or study entry. 5. Written informed consent to participate in the study. 6. Agreement with the use of their personal data and tissue material being used for the study, with due regard for data protection. 7. Normal organ function (except for HL-related functional disorders). • Leukocyte count >3000/mm³ (3.0~10⁹/L) and thrombocyte count >100,000/mm³ (100x 10⁹/L) unless the patient had known marrow involvement of the disease (eg, bone marrow infiltration or splenomegaly). • Total bilirubin <1.5x the upper limit of the normal (ULN) unless the elevation was known to be due to Gilbert syndrome.



Trial name: 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. **NCT number:** NCT02661503

- Main exclusion criteria**
1. Incomplete diagnosis of the disease stage.
 2. Prior or concurrent disease that prevented treatment according to the protocol, in particular the following contraindications:
 - Chronic obstructive pulmonary disease with global respiratory insufficiency.
 - Status postmyocardial infarction, symptomatic coronary heart disease, permanent arrhythmias higher than Grade 2, status post-thromboembolic events (deep vein thrombosis, pulmonary embolism, symptomatic cerebrovascular event), left ventricular ejection fraction of <50% within the previous 6 months before start of study therapy.

Chronic stable atrial fibrillation under anticoagulation therapy was not an exclusion criterion.

 - Cardiac insufficiency New York Heart Association III or IV.
 - Corrected QT interval (QTc) interval >480 msec.
 - Serious arterial hypertension despite adequate medication.
 - Any active systemic viral, bacterial, or fungal infection requiring systemic antibiotics at time of first dose of study drug.
 - HIV (human immunodeficiency virus) infection.
 - Chronic active or persistent (polymerase chain reaction-positive) hepatitis B and/or hepatitis C.
 - Known cerebral or meningeal disease (HL or any other etiology), including signs or symptoms of PML (progressive multifocal leukoencephalopathy).
 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 (to exclude pregnancy it was obligatory to perform a β -hCG serum test at the time of study entry and before first dose of brentuximab vedotin in all female patients except for postmenopausal and surgically sterilized women); 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. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to the protocol. Patient's lack of accountability and inability to understand the nature, meaning, and consequences of the study and to formulate their own wishes correspondingly.
 11. Noncompliance: Refusal of blood products during treatment, epilepsy, drug dependency, change of residence to abroad, prior cerebral



Trial name: 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. **NCT number:** NCT02661503

injury or comparable circumstances that appeared to render protocol treatment and/or long-term follow-up impossible.

12. 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.

13. Unsafe contraception. Contraceptive methods were considered safe if they have a Pearl index of $\leq 1\%$, including according to Clinical Trial Facilitation and Coordination Group guidelines:

- Transdermal hormonal contraception,
- Contraceptive plaster,
- Injectable long-term contraceptives,
- Progesterone-releasing implant (Implanon),
- Progesterone intramuscular,
- Tubal ligation,
- Hormone-releasing intrauterine device, and
- Oral hormonal contraception, if combined (estrogen and progestogen containing).

Contraceptive methods that were considered unreliable included progestogen-only oral hormonal contraception, preservative plus spermicidal, single-barrier methods such as vaginal pessary, condom, female condom, rhythm methods, basal body temperature method, coitus interruptus, and double barrier method.

- Male patients were required to commit to effective contraception by means of barrier methods during the entire duration of the study until 6 months after receipt of study medication or to completely abstain from sexual intercourse.
- Female patients were required to commit to effective contraception by means of safe methods as previously described for the entire duration of the study until 6 months after receipt of study medication or to completely abstain from sexual intercourse.

14. Patients who had a relationship of dependence or employer-employee relationship to the sponsor (GHSG) or the investigator.

15. Commitment to an institution on judicial or official order.

16. Participation in another interventional trial that could interact with the HD21 study.

Intervention

N = 751, ITT = 742

BrECADD

Brentuximab vedotin: 1.8 mg/kg on day 1 of a 21 day cycle.
Cyclophosphamide: 1.250 mg/m² on day 2 of a 21 day cycle.
Doxorubicin: 40mg/m² on day 2 of a 21 day cycle.
Etoposide: 150 mg/m² on day 2-4 of a 21 day cycle.
Dacarbazine: 250 mg/m² on day 3-4 of a 21 day cycle.
Dexamethasone 40 mg on day 2-5 of 21 day cycle.



Trial name: 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.		NCT number: NCT02661503
	Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive. Additional: Peg. G-CSF, 6 mg on day 5 of a 21 day cycle. An antibiotic prophylaxis must be given 3 x/week during the whole duration of chemotherapy.s	
Comparator(s)	N = 749; ITT = 740 Escalated (e)BEACOPP Bleomycin 10 mg/m², day 8 Etoposide 200 mg/m², day 1-3 Doxorubicin 35 mg/m², day 1 Cyclophosphamide 1.250 mg/m², day 1 Vincristine 1.4 mg/m² (max 2 mg), day 8 Procarbazine 100 mg/m², day 1-7 Prednisone 40 mg/m², day 1-14 Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive. Additional: Peg. G-CSF, 6 mg on day 5 of a 21 day cycle. An antibiotic prophylaxis must be given 3 x/week during the whole duration of chemotherapy.	
Follow-up time	Median follow-up: 48 months	
Is the study used in the health economic model?	Yes	
Primary, secondary and exploratory endpoints	Endpoints included in this application: The co-primary endpoints for the study are included in this application. They are Treatment Related Morbidity and PFS (Lugano Criteria). Additionally, the secondary endpoints Gonadal Function Recovery, live births, Quality of Life, and Overall Survival are included in the application. Other endpoints: Other endpoints of the study not included in the application are: CR rates after completion of therapy Rate of second malignancies Number of serious adverse events within 30 days after end of treatment Therapy adherence	



Trial name: 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. **NCT number:** NCT02661503

Method of analysis

For non-inferiority trials, analysis in ITT analysis is not considered sufficiently conservative. Both co-primary endpoints were therefore analyzed both in the PP and ITT populations, with the PP population being supportive of the analysis in the ITT population. For the trial to be positive, the two analyses had to be concordant.

The rates of treatment-related morbidity were compared using the Cochran–Mantel–Haenszel test stratified by area of recruitment, International Prognostic Score, age, and sex with a two-sided significance level of $\alpha=0.05$.

Progression-free survival, as well as other time-to-event endpoints (Overall Survival, time to gonadal function recovery), were analysed by the Kaplan–Meier method, including HRs, corresponding CIs, and p values obtained from Cox regression models. The model for the primary test on superiority of progression-free survival was to be stratified by the area of recruitment, International Prognostic Score, age, and sex. The Schoenfeld residuals test was used to verify the proportional hazards assumption.

The final analysis of the primary efficacy endpoint included a test of superiority of BrECADD versus eBEACOPP, which was amended in the protocol after the successful interim analysis (10th protocol version, Dec 8, 2023). As both objectives were already met and the accumulation of 154 events was deemed unachievable within the trial duration, the final analysis was set at 48 months follow-up within this amendment. Determined by alpha spent in the interim analysis and an actual information rate of 71%, a two-sided significance level of 0.0392 remained for the final analysis.

Quality of Life

PRO assessments utilized the EORTC QLQ-C30, EORTC QLQ-FA12, and EORTC QLQ-CIPN20. The results were analyzed by treatment group in the ITT population for patients with PRO measurements at baseline and at least 1 postbaseline measurement.

Subscale scores were calculated from the EORTC QLQ-C30. The summary score was calculated from the mean of QLQ-C30 scales excluding the Global Health Status/QOL scale and the Financial Difficulties scale.

Subscale scores were calculated for the following EORTC QLQ-FA12 items: physical fatigue, emotional fatigue, and cognitive fatigue and the summary score calculated from the mean of the EORTC QLQ-FA12 subscales. Subscale scores were also calculated for sensory, motor, and autonomic symptoms based on EORTC QLQ-CIPN20 questionnaire, and the summary score was calculated over time from the mean of the subscale scores. Individual EORTC QLQ-CIPN20 item scores were also calculated over time.

The descriptive statistics of actual values and changes from baseline for the summary scores, subscale scores and/or



Trial name: 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. **NCT number:** NCT02661503

individual items for the EORTC QLQ-C30, EORTC QLQ-FA12, and EORTC QLQ-CIPN20 were summarized over time.

Analyses were also performed using repeated-measures linear mixed models. The change from baseline score was used as the dependent variable, and the independent variables included treatment groups, visit, the interaction between treatment groups and visit, baseline score, the interaction term between baseline score and visit and stratification covariates.

The estimated mean change from baseline score with 95% CI was calculated at each time point for each subscale score and/or individual items by treatment group. In addition, the estimated mean differences of the change from baseline scores between treatment groups along with

95% CIs and p-values were presented for EORTC QLQ-C30, EORTC QLQ-FA12, and EORTC QLQ-CIPN20 at each time point. Published manuals for EORTC QLQ-C30 were used to describe scoring, handling, and imputation of missing data.

Two analyses were performed for missing data. First, missing subscale scores were imputed using last observation carried forward and death was imputed as the worst score, and then linear mixed models based on the imputed data were performed. Second, 2 pattern groups were defined based on whether patients completed primary BrECADD or eBEACOPP therapy, and then pattern mixture models were performed.

Subgroup analyses

All subgroup analyses for efficacy and safety were pre-specified.

No subgroups had statistical power.

Analyses methods:

Time-to-event endpoints (Overall Survival, time to gonadal function recovery, Progression-Free-Survival etc), were analysed by the Kaplan–Meier method, including HRs, corresponding CIs, and p values obtained from Cox regression models.

RR for the compound safety endpoint TRMB was calculated using stratified Cochran-Mantel-Haenszel test.

Subgroups analyzed for efficacy and safety by GHSG:

Age: 18-39, 40-49, and 50-60.

Gender: male and female.

IPS: 0-1, 2-3, 4-7.

Stage: II, III, IV.

Numbers of cycles of chemotherapy: 4 & 6.

Subgroups analyzed for efficacy and safety by Takeda:

Age: 18-44, 45-60.



Trial name: 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.	NCT number: NCT02661503
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Gender: male & female.
 Enrolment Region: Europe & non-Europe.
 IPS: 0-2 & 3-7.
 Baseline Ann Arbor disease stage: II, III, IV.
 B-symptoms present at baseline: present & not present.
 Baseline ECOG PS: 0, 1, and 2.

Subgroups analyzed for fertility by GHSG and Takeda:
 Males and females.

Other relevant information	The study was planned, sponsored, conducted, and reported by the German Hodgkin Study Group independently of Takeda. Following positive read-out Takeda purchased the data and have submitted an EMA application as MAH of brentuximab vedotin based on these data.
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Trial name: Danish Real-World Study of BrECADD efficacy	NCT number: not applicable
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Objective	To determine Failure-Free-Survival and PET-2 response in a single Danish center routinely using BrECADD for contemporary advanced stage HL patients
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Publications – title, author, journal, year	Not applicable. Data is currently unpublished.
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Study type and design	Single centre, single arm, retrospective, real-world study.
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Sample size (n)	██████
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Main inclusion criteria	Advanced stage HL Aged 18-60.
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Main exclusion criteria	Unfit to receive chemotherapy.
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Intervention	BrECADD Brentuximab vedotin: 1.8 mg/kg on day 1 of a 21 day cycle. Cyclophosphamide: 1.250 mg/m2 on day 2 of a 21 day cycle. Doxorubicin: 40mg/m2 on day 2 of a 21 day cycle. Etoposide: 150 mg/m2 on day 2-4 of a 21 day cycle. Dacarbazine: 250 mg/m2 on day 3-4 of a 21 day cycle. Dexamethasone 40 mg on day 2-5 of 21 day cycle.
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Trial name: Danish Real-World Study of BrECADD efficacy NCT number: not applicable	
	Four cycles if interim PET2 is negative. Six cycles if interim PET2 is positive. Additional: Peg. G-CSF, 6 mg on day 5 of a 21 day cycle. An antibiotic prophylaxis must be given 3 x/week during the whole duration of chemotherapy.
Comparator(s)	Not Applicable
Follow-up time	Median follow-up was 11 months, Max follow-up was 1.9 years and min follow up was 0.13 years
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Not applicable
Method of analysis	Time to event analysis (Failure Free Survival) was conducted using Kaplan-Meier method
Subgroup analyses	Not Applicable
Other relevant information	The study was sponsored and conducted by Dr. Jacob Haaber-Christensen at Odense University Hospital. Takeda Denmark supported the study financially and have received data for use in this application.



Appendix B. Efficacy results per study

Table 79 Results of 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. (NCT02661503) as analyzed by the GHSG

Results of 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 (NCT02661503)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	References
Treatment Related Morbidity 30 days post treatment	BrECADD	738	42% (312/738)							RR calculated using stratified Cochran-Mantel-Haenszel test (2)
	eBEACOPP	732	59% (430/732)	17%	NR	NR	RR: 0.72	0.66–0.80	< 0.0001	
4-yr PFS rate	BrECADD	742	94.3% (92.6 - 96.1)							Progression-free survival, as well as other time-to-event endpoints, were analysed by the Kaplan–Meier method, including HRs, corresponding CIs, and p values obtained from Cox regression models. The model for the primary test on superiority of progression-free survival was to be stratified by the area of recruitment,
	eBEACOPP	740	90.9% (88.7 - 93.1)	3.4%	NR	NR	HR: 0.66	0.45 - 0.97	0.035	



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Gonadal function recovery, females	BrECADD	176	95.3 (92.0% – 98.8%)	19.8%	NR	NR	HR: 1.69	1.34 – 2.14	NR	International Prognostic Score, age, and sex. The Schoenfeld residuals test was used to verify the proportional hazards assumption	(32)
	eBEACOPP	171	72.5% (66.1% – 79.5%);								
Gonadal function recovery, males	BrECADD	201	86.0% (81.1% – 91.1%)	46.1%	NR	NR	HR: 3.31	2.53-4.31	NR	The cumulative incidence of recovery of FSH was analysed per treatment group according to Kaplan-Meier including hazard ratios and corresponding 95% confidence intervals (CI).	
	eBEACOPP	219	39.2% (33.2% - 46.4%).								
Live Births, females	BrECADD	248	14	2.0 %	NR	NR	HR: NR	NR	0.531	The cumulative incidence of first parenthood after therapy was analysed per treatment group	(32)
	eBEACOPP	241	12								



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Live Births, males	BrECADD	347	7	4.0 %	NR	NR	HR: NR	NR	0.014	according to Kaplan-Meier and compared by using Gray's test.	
	eBEACOPP	355	3								
Successful reproduction among participants with stated desire to have children	BrECADD	246	16%	7.0 %	NR	NR	HR: NR	NR	NR	The cumulative incidence of first parenthood after therapy was analysed per treatment group according to Kaplan-Meier and compared by using Gray's test.	(32)
	eBEACOPP	355	9%								
4-yr OS rate	BrECADD	742	98.6% (97.7 - 99.5)	0.4%	NR	NR	NR	NR	NR	OS was analysed by the Kaplan-Meier method, including HRs, corresponding CIs, and p values obtained from Cox regression models.	(2)
	eBEACOPP	355									



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		

BEACOPP
98.2
(92.2 – 99.3)



Table 80 Results of 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. (NCT02661503) as analyzed by Takeda

Results of 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 (NCT02661503)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	
Treatment Related Morbidity 30 days post treatment	BrECADD	747	42.2% (315/747)							RR calculated using stratified Cochran-Mantel-Haenszel test
	eBEACOPP	741	58.7% (435/741)	-16.5%	-21.6; -11.4	< 0.0001	RR: 0.715	0.645–0.792	< 0.0001	
4-yr PFS rate	BrECADD	751	94.8% [events: 39/751] (92.6 - 96.1)							Hazard ratio of PFS was calculated by unstratified Cox proportional hazards modeling
	eBEACOPP	749	91.7% [events: 62/749] (88.7 - 93.1)	3.1%	NR	NR	HR: 0.619	0.415 - 0.925	0.018	
Infertility one year post treatment,	BrECADD	337	40.7% (137/337)							For the primary analysis for infertility, the infertility rate was defined as the proportion of patients with FSH values above the upper limit of normal (ULN)
	eBEACOPP	341	63.6% (217/341)	-22.9	NR	NR	NR	NR	NR	



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Safety population										among the patients for whom FSH values were available at 1-year Post Treatment Follow-Up (PTFU).	
Infertility one year post treatment, Safety population, females	BrECADD	162	26.5% (43/162)	19.6%	NR	NR	NR	NR	NR	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.	
	eBEACOPP	175	46.1% (94/175)								
Infertility one year post treatment, Safety population, males	BrECADD	167	53.7% (77/167)	26.8	NR	NR	NR	NR	NR	The population was the safety population; the analyses did not take natural age associated increase of FSH levels into account.	
	eBEACOPP	174	80.5% (140/174)								
Infertility one year post treatment among	BrECADD	145	36.6% (53/145)	27.0	NR	NR	NR	NR	NR	For the supportive analysis for infertility, the infertility rate was defined as the proportion of patients with FSH values above the upper limit of normal (ULN)	
	eBEACOPP	140	63.6%								



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
patients who were fertile at baseline			(89/140)							among the patients for whom FSH values were available at 1-year Post Treatment Follow-Up (PTFU).	
Infertility one year post treatment, females fertile at baseline	BrECADD	51	11.8% (6/51)	23.6	NR	NR	NR	NR	NR	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.	
	eBEACOPP	87	35.4% (17/87)								
Infertility one year post treatment, males fertile at baseline	BrECADD	94	50% (47/94)	23.6	NR	NR	NR	NR	NR	The population was the safety population for whom FSH levels indicated fertility at baseline; the analyses did not take natural age associated increase of FSH levels into account.	
	eBEACOPP	92	78.3% (72/92)								
Live Births, females	BrECADD	330	9.7% (32/330)	1.4 %	NR	NR	1.17 fold	NR	NR	Numbers of live births were collected in the safety	(25)



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
Live Births, partners to male participants	eBEACOPP	325	8.3 (27/325)							population, regardless of age of participants.	
	BrECADD	417	5.0% (21/417)							Data was from the primary data-cut following the prespecified post-treatment follow-up of 3 years.	
				2.6 %	NR	NR	2.1 fold	NR	NR		
	eBEACOPP	416	2.4 (10/416)								
Pregnancies females	BrECADD	330	11.8% (39/330)							Numbers of pregnancies were collected in the safety population regardless of age of the participants.	(25)
				0.7 %	NR	NR	1.06 fold	NR	NR		
	eBEACOPP	325	11.1% (36/325)							Data was from the primary data-cut following the prespecified post-treatment follow-up of 3 years.	
	BrECADD	417	6.0% (25/417)	3.6%	NR	NR	2.50 fold	NR	NR		



Results of 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 (NCT02661503)

				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study Arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value		
male participants	eBEACOPP	416	2.4% (10/416)								
	BrECADD	751	98.7% (97.5 - 99.3)							OS was estimated by the Kaplan–Meier method, including HRs, corresponding CIs, and p values obtained from unstratified Cox regression models.	
	BEACOPP	749	98.1 (96.6 – 99.0)	0.6%	NR	NR	HR: 0.914	0.403 – 2.072	0.830		



Table 81 Result of Danish Real World study on BrECADD efficacy at a single Danish center; as of May 2026 patient number is increased to [REDACTED].

Results of Danish Real-World Study of Efficacy of BrECADD (NCT number: Not Applicable)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation
Outcome	Study arm	N	Result (CI)	Difference	95% CI	P value	Difference	95% CI	P value	
Event Free Survival rate	BrECADD									Failure Free Survival was defined as time from treatment to the first occurrence of either disease progression, relapse, treatment stop, or death from any cause. Median follow-up was 11 months.
	NA	NA	NA	NA	NA	NA	NA	NA	NA	
PET2-negativity	BrECADD									PET2-negativity was defined as Deauville score 1-3.
	NA	NA	NA	NA	NA	NA	NA	NA	NA	



Appendix C. Comparative analysis of efficacy

[For meta-analyses, the table below can be used. For any type of comparative analysis (i.e. paired indirect comparison, network meta-analysis or MAIC analysis), describe the methodology and the results here in an appropriate format (text, tables and/or figures).]

Table 82 Comparative analysis of studies comparing [intervention] to [comparator] for patients with [indication]

Outcome	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
Example: median overall survival		NA	NA	NA	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). Yes/No
Example: 1-year survival		10.7	2.39–19.01	0.01	HR: 0.70	0.55–0.90	0.005	The HRs for the studies included were synthesized using random effects meta-analysis (DerSimonian–Laird). The absolute difference was estimated by applying the resulting HR to an assumed 1-year survival rate of 64.33% in the comparator group.
Example: HRQoL		–4.5	–8.97 to –0.03	0.04	NA	NA	NA	HRQoL results for the studies included were synthesized using the standardized mean difference (SMD). The estimated



Outcome	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
	Studies included in the analysis	Difference	CI	P value	Difference	CI	P value	
							meta-analytical SMD of –0.3 (95% CI –2.99 to –0.01) was transformed to the scale of ZZZ* assuming a population standard deviation of 15 on the ZZZ* scale. *Fill in the name of an appropriate measure of HRQoL.	
Insert outcome 4								



Appendix D. Extrapolation

Extrapolation models for the intervention and comparator are fitted in a joint model using; Weibull was selected for OS, and Gompertz is selected for PFS

Figure 25 KM plot for OS for BrECADD and eBEACOPP

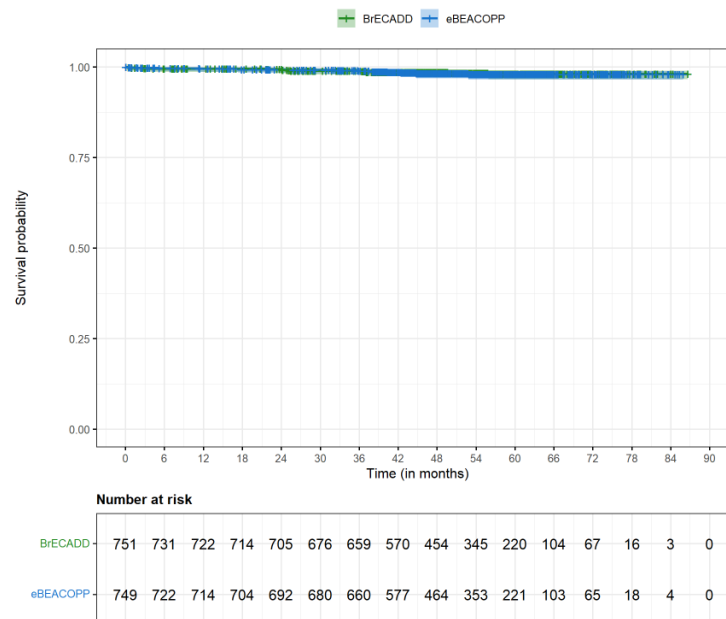
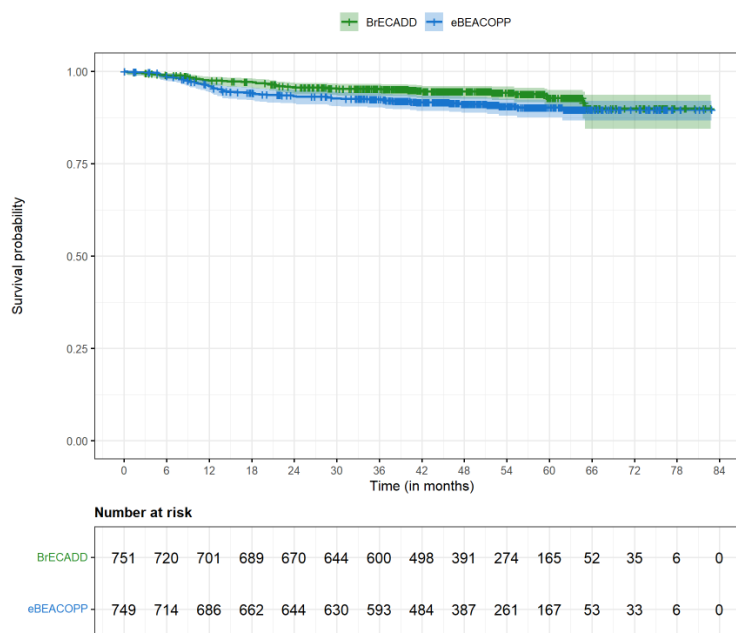


Figure 26 KM Plot PFS for BrECADD and eBEACOPP





D.1 Extrapolation of OS

D.1.1 Data input

Analyses were based on patient-level data from the HD21 trial for patients aged 18-60 years at diagnosis (data cutoff: October 31, 2023)

D.1.2 Model

Standard parametric model (joint)

D.1.3 Proportional hazards

Diagnostic plots assessing whether the PH and AFT assumptions hold between the two treatment arms are presented in

, and **Error! Reference source not found.** The two curves appear to overlap
. The Schoenfeld individual test **Error! Reference source not found.** which evaluates whether the residuals depend on time, was non-significant ($P=0.5871$), suggesting the PH assumption may still hold when evaluated over the full trial duration. Therefore, joint (i.e., including treatment as a predictor) models were considered to leverage more power from higher number of events. The Q-Q plot
appears linear, however, there are very limited data points. Caution must be taken to draw any conclusion on the AFT assumption based on the Q-Q plot, because of the immature OS data.

Figure 27 Log-cumulative Hazards

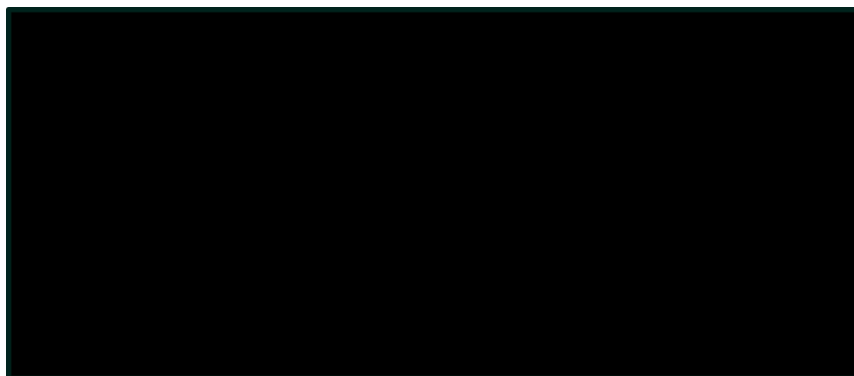




Figure 28 Schoenfeld Residuals OS



Figure 29 AFT Q-Q plot OS



D.1.4 Evaluation of statistical fit (AIC and BIC)

The best statistical fit was explored and is presented in Table 83 AIC and BIC for , resulting in the use of Weibull (lowest value).

Table 83 AIC and BIC for OS

Distribution	AIC	BIC
Exponential	455.1	465.7
Weibull	453.7	469.6
Gompertz	456.4	472.4
Log-logistic	453.7	469.6
Log-normal	454.6	470.5
Gamma	453.7	469.6

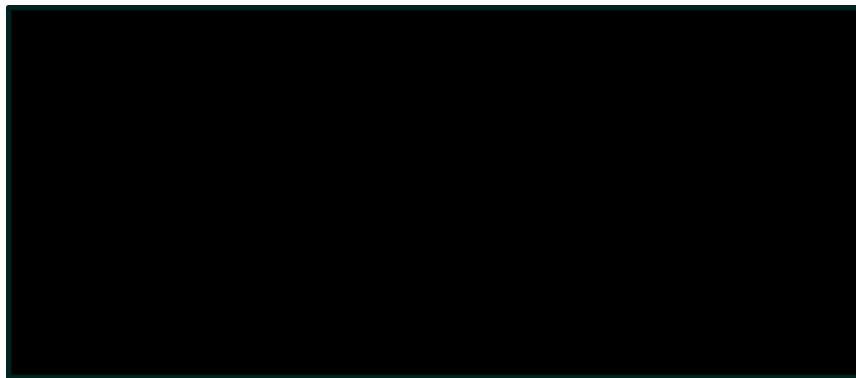


D.1.5 Evaluation of visual fit

Weibull was the best fitting distribution based on visual fit. Due to the immaturity of the data, all distributions provided a similar fit to the observed data. For all the fitted distributions, the long-term projected survival rates were high suggesting that long-term OS based on all distributions needs to be capped by general mortality in the CEM. Weibull, log-logistics, Gamma had the lowest and similar fit statistics and similar long-term projections. Therefore, Weibull (joint fit) was selected as base-case. Clinical opinion suggested to select the top two highest distributions. Therefore, Gompertz can also be considered for an even longer projected overall survival, however the difference between Weibull and Gompertz is expected to be small in terms of long-term projections. Long-term projections for OS should be interpreted with caution.

D.1.6 Evaluation of hazard functions

Figure 30 



D.1.7 Validation and discussion of extrapolated curves

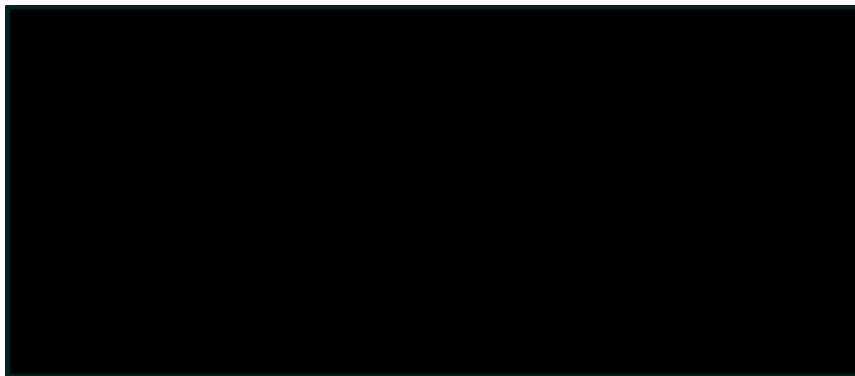
Due to the immaturity of the data, all distributions provided a similar fit to the observed data **Error! Reference source not found.** For all the fitted distributions, the long-term projected survival rates were high **Error! Reference source not found.** suggesting that long-term OS based on all distributions needs to be capped by general mortality in the CEM. Weibull, log-logistics, Gamma had the lowest and similar fit statistics and similar long-term projections. Therefore, Weibull (joint fit) was selected as base-case. Clinical opinion suggested to select the top two highest distributions. Therefore, Gompertz can also be considered for an even longer projected overall survival, however the difference between Weibull and Gompertz is expected to be small in terms of long-term projections. Long-term projections for OS should be interpreted with caution.



Figure 31 Short term predictions OS



Figure 32 Long term prediction OS



D.1.8 Adjustment of background mortality

Adjustments are done in accordance with the DMC guidelines to the health economic model.

D.1.9 Adjustment for treatment switching/cross-over

N/A

D.1.10 Waning effect

N/A

D.1.11 Cure-point

Studies of HL suggest that patients can be considered “cured” by their frontline chemotherapy. This is especially evident in patients with HL who survive relapse-free (have not entered progression) beyond five years following diagnosis. This occurrence is expected for patients within HD-21 with longer follow-up a long, flat plateau of the KM curves for PFS and OS should be evident, suggesting that a proportion of patients may achieve long-term remission.



In the base case, a standardized mortality ratio of 2.0 (95% CI, 1.4-2.9) was applied to the life-table-based probabilities as a relative risk meaning if a patient has the chance for cure, then the SMR no longer applies to them upon cure because the disease was beaten, but the SMR still does apply to those patients who were not cured. The model SMR is applied independent as a concept, but the way it is applied to the population is adjusted when you also apply a cure fraction; if you do not apply the cure, the SMR exists, but once you do apply the cure, then the SMR adjusts. This ratio was sourced from a large UK cohort study with a long follow-up [REDACTED] (57), as recommended in Vries et al and Favier et al. (12, 58) [REDACTED]. The ratio was chosen as it reflects the most recent patients in the study. The study provided evidence that cured HL patients may have higher mortality risk due to increased risk of myocardial infarction from treatment with chemotherapy [REDACTED]. Assuming a standard mortality rate (SMR) of 2.0 is likely conservative in terms of overall cost-effectiveness results.

D.2 Extrapolation of PFS

D.2.1 Data input

Analyses were based on patient-level data from the HD21 trial for patients aged 18-60 years at diagnosis (data cutoff: October 31, 2023)

D.2.2 Model

Standard parametric model (joint)

D.2.3 Proportional hazards

Diagnostic plots assessing whether the PH and AFT assumptions hold between the two treatment arms are presented in Figure 40 appear to cross very early on (at around six months and do not seem parallel thereafter, suggesting that the PH assumption could be violated. The Schoenfeld individual test Figure 41 which evaluates whether the residuals depend on time, was non-significant ($P=0.308$), however the solid line is not straight around zero, but rather parabolic in shape, which suggests a violation. The Q-Q plot Figure 42 shows a potentially non-linear pattern, suggesting that the AFT assumption could be violated and that AFT models such as log-normal and log-logistic may not be appropriate.



Figure 33 Log Cumulative Hazard PFS

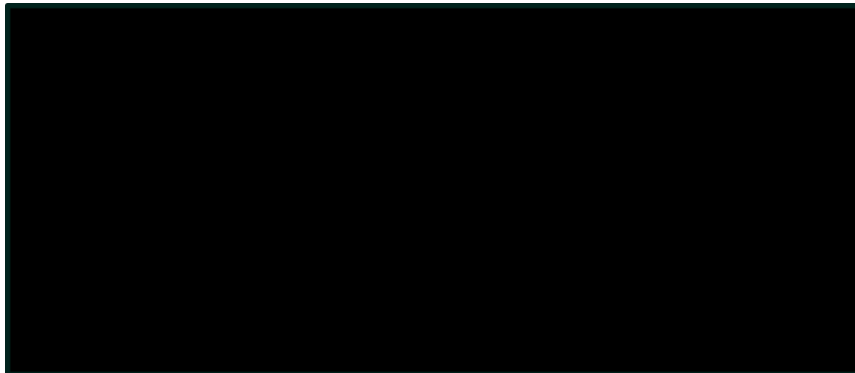




Figure 34 Schoenfeld Residuals PFS



Figure 35 AFT Q-Q Plot PFS



D.2.4 Evaluation of statistical fit (AIC and BIC)

The best statistical fit was explored and is presented in Table 84 AIC and BIC for PFS resulting in the use of Gompertz.

Table 84 AIC and BIC for PFS

Model- Joint Fit	Distribution	AIC	BIC
	Exponential	1625.0	1635.6
	Weibull	1618.8	1634.7

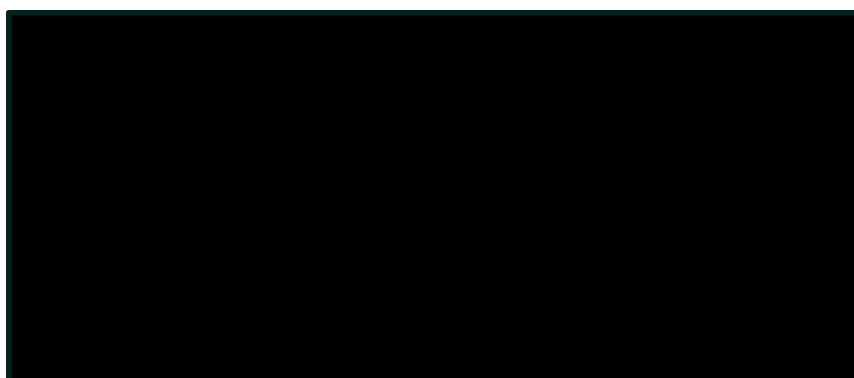


Gompertz	<u>1609.9</u>	<u>1625.9</u>
Log-logistic	1617.8	1633.8
Log-normal	1611.9	1627.8
Gamma	1619.3	1635.2
Generalized Gamma	1611.5	1632.8

D.2.5 Evaluation of visual fit

Gompertz was the best fitting distribution based on visual fit. Evaluation of hazard functions.

Figure 36 Smoothed Hazard PFS



D.2.6 Validation and discussion of extrapolated curves

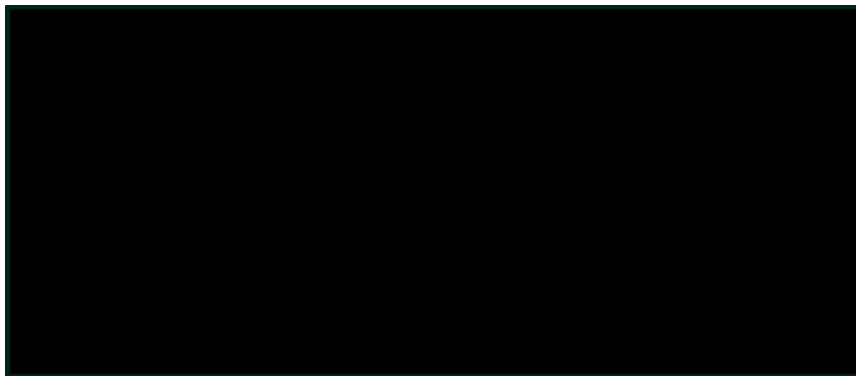
Gompertz was the best fitting distribution based on visual fit. Gompertz was also the only distribution that plateaued early enough and captured the tail end of the observed PFS curves. The second best-fitting distribution was Generalized Gamma. These selections were supported by clinical opinion, which suggested to use the highest projecting distributions. When choosing between independent fits and joint fits, joint fits maybe more appropriate because independent fits may lack clinical validity as they suggest higher projected survival for eBEACOPP than BrECADD. Joint fits leverage more power from higher number of events and the drop at [REDACTED] in the BrECADD arm (outlier) would be less influential.



Figure 37 Short term prediction PFS



Figure 38 Long term prediction PFS



D.2.7 Adjustment of background mortality

Adjustments are done in accordance with the DMC guideline to the health economic model.

D.2.8 Adjustment for treatment switching/cross-over

N/A

D.2.9 Waning effect

N/A

D.2.10 Cure-point

Studies of HL suggest that patients can be considered “cured” by their frontline chemotherapy. This is especially evident in patients with HL who survive relapse-free (have not entered progression) beyond five years following diagnosis. This occurrence is



expected for patients within HD-21 with longer follow-up a long, flat plateau of the KM curves for PFS and OS should be evident, suggesting that a proportion of patients may achieve long-term remission.

Appendix E. Serious adverse events

All treatment emergent SAEs observed in the HD21 study are summarized on the following pages of appendix E.

Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

[illegible]

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

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The diagram illustrates the relationship between a single character and a word. On the left, the character '木' (tree) is shown with its four strokes. On the right, the word '樹' (tree) is shown with its twelve strokes, including the '木' radical and the '頁' (page) radical.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Grade 3 or higher febrile neutropenia adverse events are counted. MedDRA Version 25.1 was applied.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Grade 3 or higher febrile neutropenia adverse events are counted. MedDRA

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

[illegible]

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Patient incidence: a patient counts once for each preferred term, high level term, and system organ class.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Neuropsychiatric disorders	100 (13.38)	100 (13.50)	200 (13.42)
Respiratory disorders	100 (13.38)	100 (13.50)	200 (13.42)
Cardiovascular disorders	100 (13.38)	100 (13.50)	200 (13.42)
Gastrointestinal disorders	100 (13.38)	100 (13.50)	200 (13.42)
Genitourinary disorders	100 (13.38)	100 (13.50)	200 (13.42)
Musculoskeletal disorders	100 (13.38)	100 (13.50)	200 (13.42)
Endocrine disorders	100 (13.38)	100 (13.50)	200 (13.42)
Immune system disorders	100 (13.38)	100 (13.50)	200 (13.42)
Other	100 (13.38)	100 (13.50)	200 (13.42)

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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

A series of black bars of varying lengths and positions, creating a rhythmic pattern. The bars are arranged in a way that suggests a sequence or a progression, with some bars being longer than others and some appearing in pairs.

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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Neuropsychiatric disorders	100 (13.38)	100 (13.50)	200 (13.42)
Respiratory disorders	100 (13.38)	100 (13.50)	200 (13.42)
Cardiovascular disorders	100 (13.38)	100 (13.50)	200 (13.42)
Endocrine disorders	100 (13.38)	100 (13.50)	200 (13.42)
Immune system disorders	100 (13.38)	100 (13.50)	200 (13.42)
Reproductive system disorders	100 (13.38)	100 (13.50)	200 (13.42)
Skin disorders	100 (13.38)	100 (13.50)	200 (13.42)
Other	100 (13.38)	100 (13.50)	200 (13.42)

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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.43)
Neoplasms benign and unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of unspecified site	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasms malignant	90 (12.04)	90 (12.15)	180 (12.09)
Neoplasm of unspecified site	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of breast	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of colon	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of stomach	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of lung	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of prostate	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pancreas	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of kidney	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of liver	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of spleen	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of skin	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of thyroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of parathyroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of adrenal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pituitary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of hypothalamus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pineal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of choroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of retina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of optic nerve	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ear	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of nose	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of mouth	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pharynx	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of esophagus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of stomach	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of duodenum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of jejunum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ileum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cecum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of sigmoid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of rectum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of anus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of epididymis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vas deferens	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of prostate	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of kidney	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of adrenal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pituitary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of hypothalamus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pineal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of choroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of retina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of optic nerve	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ear	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of nose	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of mouth	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pharynx	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of esophagus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of stomach	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of duodenum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of jejunum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ileum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cecum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of sigmoid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of rectum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of anus	10 (1.34)	10 (1.35)	20 (1.34)

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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.

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Version 25.1 was applied.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

[illegible]

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03AUG2024 18:33

Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

Safety Population		Safety Population		Safety Population		Safety Population	
Primary System Organ Class	High Level Term	Preferred Term	Number of Patients	Percentage of Patients	Number of Patients	Percentage of Patients	Number of Patients
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Neoplasms benign and unspecified	40 (5.35)	40 (5.40)	80 (5.37)
Neoplasm of unspecified site	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of skin	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of breast	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of colon	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasms malignant	60 (8.03)	60 (8.15)	120 (8.06)
Neoplasm of unspecified site	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of skin	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of breast	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of colon	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of prostate	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of stomach	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pancreas	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of lung	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of esophagus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of rectum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of thyroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of parathyroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of adrenal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pituitary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of hypothalamus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pineal	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of choroid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of retina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of optic nerve	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ear	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of nose	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of mouth	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pharynx	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of larynx	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of trachea	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bronchus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pleura	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of peritoneum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pericardium	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of heart	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of aorta	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of artery	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vein	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of lymph node	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of spleen	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of liver	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of gallbladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of biliary tract	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pancreas	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of duodenum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of jejunum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ileum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cecum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of sigmoid	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of rectum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of anus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vulva	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of epididymis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vas deferens	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of scrotum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of prostate	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ureter	10 (1.34)	10 (1.35)	20 (1.34)

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Neuropsychiatric disorders	100 (13.38)	100 (13.50)	200 (13.42)
Respiratory disorders	100 (13.38)	100 (13.50)	200 (13.42)
Cardiovascular disorders	100 (13.38)	100 (13.50)	200 (13.42)
Gastrointestinal disorders	100 (13.38)	100 (13.50)	200 (13.42)
Musculoskeletal disorders	100 (13.38)	100 (13.50)	200 (13.42)
Endocrine disorders	100 (13.38)	100 (13.50)	200 (13.42)
Immune system disorders	100 (13.38)	100 (13.50)	200 (13.42)
Genitourinary disorders	100 (13.38)	100 (13.50)	200 (13.42)
Skin disorders	100 (13.38)	100 (13.50)	200 (13.42)
Eye disorders	100 (13.38)	100 (13.50)	200 (13.42)
Ear, nose and throat disorders	100 (13.38)	100 (13.50)	200 (13.42)
Psychiatric disorders	100 (13.38)	100 (13.50)	200 (13.42)
Conjunctival disorders	100 (13.38)	100 (13.50)	200 (13.42)
Ear disorders	100 (13.38)	100 (13.50)	200 (13.42)
Nose disorders	100 (13.38)	100 (13.50)	200 (13.42)
Throat disorders	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the eye	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear, nose and throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the conjunctiva	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nose	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the skin	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the endocrine system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the immune system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the genitourinary system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the respiratory system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the cardiovascular system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the musculoskeletal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the gastrointestinal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nervous system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the conjunctiva	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear, nose and throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the eye	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nose	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the skin	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the endocrine system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the immune system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the genitourinary system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the respiratory system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the cardiovascular system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the musculoskeletal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the gastrointestinal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nervous system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the conjunctiva	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear, nose and throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the eye	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nose	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the skin	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the endocrine system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the immune system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the genitourinary system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the respiratory system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the cardiovascular system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the musculoskeletal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the gastrointestinal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nervous system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the conjunctiva	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear, nose and throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the eye	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nose	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the skin	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the endocrine system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the immune system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the genitourinary system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the respiratory system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the cardiovascular system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the musculoskeletal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the gastrointestinal system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nervous system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the infectious and parasitic diseases	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the neoplasms	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the conjunctiva	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear, nose and throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the eye	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the ear	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the nose	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the throat	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the skin	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the endocrine system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the immune system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the genitourinary system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the respiratory system	100 (13.38)	100 (13.50)	200 (13.42)
Disorders of the cardiovascular system	100 (13.38)	100 (13.50)	200 (13.42)
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Grade 3 or higher febrile neutropenia adverse events are counted. MedDRA

Version 25.1 was applied.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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A series of black bars of varying lengths and thicknesses, arranged in a pattern that suggests a stylized letter 'E' or a comb. The bars are positioned horizontally, with some being longer and thicker than others, creating a sense of depth and movement.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

[illegible]

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

A series of black and white photographs showing the construction of a wooden structure, likely a fence or wall. The images are arranged in a grid-like fashion, showing different stages and components of the build. On the left, there are vertical posts and horizontal rails. In the center, there are more vertical posts, some with horizontal rails attached. On the right, there are more vertical posts, some with horizontal rails attached. The images are arranged in a way that shows the progression of the construction from left to right.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

The image is a 3x4 grid of 12 black and white photographs documenting a person's recovery from a stroke. The photos are arranged in three rows and four columns, showing the progression of motor function and coordination. The first row shows the person's face and head, with the first photo showing a neutral expression and the subsequent photos showing a smile. The second row shows the person's hands, with the first photo showing a clenched fist and the subsequent photos showing the hand opening and the fingers moving. The third row shows the person's feet, with the first photo showing a foot that is not moving and the subsequent photos showing the foot moving and the person standing. The photos are arranged in a grid, showing the progression of motor function and coordination.

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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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

Category	Sub-category	Value	Unit	Percentage	Percentage of Total
Agriculture	Cereals	120	kg	12%	12%
	Vegetables	80	kg	8%	8%
	Fruits	60	kg	6%	6%
	Flowers	40	kg	4%	4%
	Other	20	kg	2%	2%
Livestock	Cattle	150	kg	15%	15%
	Poultry	100	kg	10%	10%
	Pigs	80	kg	8%	8%
	Other	20	kg	2%	2%
Aquaculture	Fish	90	kg	9%	9%
	Shellfish	60	kg	6%	6%
	Other	30	kg	3%	3%
Forestry	Timber	70	kg	7%	7%
	Other	30	kg	3%	3%
Other	Wildlife	50	kg	5%	5%
	Other	20	kg	2%	2%

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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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Version 25.1 was applied.

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Program: x:\takhd21\#biostat\csr-new\prod\tables\t-teae-sae-sochpt.sas
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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neutropenia	100 (13.38)	100 (13.50)	200 (13.44)
Febrile neutropenia	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils decreased	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count decreased	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils low	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count low	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils decreased, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count decreased, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils low, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count low, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils decreased, grade 3 or higher	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count decreased, grade 3 or higher	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils low, grade 3 or higher	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count low, grade 3 or higher	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils decreased, grade 3 or higher, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count decreased, grade 3 or higher, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophils low, grade 3 or higher, febrile	100 (13.38)	100 (13.50)	200 (13.44)
Neutrophil count low, grade 3 or higher, febrile	100 (13.38)	100 (13.50)	200 (13.44)

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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neoplasms	100 (13.38)	100 (13.50)	200 (13.43)
Neoplasms benign and unspecified	30 (4.02)	30 (4.05)	60 (4.04)
Neoplasm of unspecified site	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of skin	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of breast	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasms malignant	70 (9.34)	70 (9.45)	140 (9.34)
Neoplasm of unspecified site	20 (2.68)	20 (2.70)	40 (2.68)
Neoplasm of skin	20 (2.68)	20 (2.70)	40 (2.68)
Neoplasm of breast	20 (2.68)	20 (2.70)	40 (2.68)
Neoplasm of prostate	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of colon	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of rectum	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of stomach	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of pancreas	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of lung	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of bladder	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
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Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of uterus, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of ovary, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of testis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of penis, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of vagina, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of cervix, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of endometrium, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of fallopian tube, unspecified	10 (1.34)	10 (1.35)	20 (1.34)
Neoplasm of			

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.

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

MedDRA Primary System Organ Class	BrECADD	eBEACOPP	Total
High Level Term	N=747	N=741	N=1488
Preferred Term	n (%)	n (%)	n (%)
Neutropenia	100 (13.4)	100 (13.5)	200 (13.4)
Febrile neutropenia	100 (13.4)	100 (13.5)	200 (13.4)
Leukopenia	100 (13.4)	100 (13.5)	200 (13.4)
Thrombocytopenia	100 (13.4)	100 (13.5)	200 (13.4)
Platelet count decreased	100 (13.4)	100 (13.5)	200 (13.4)
Neutrophil count decreased	100 (13.4)	100 (13.5)	200 (13.4)
White blood cell count decreased	100 (13.4)	100 (13.5)	200 (13.4)
Granulocyte count decreased	100 (13.4)	100 (13.5)	200 (13.4)
Platelet count low	100 (13.4)	100 (13.5)	200 (13.4)
Neutrophil count low	100 (13.4)	100 (13.5)	200 (13.4)
White blood cell count low	100 (13.4)	100 (13.5)	200 (13.4)
Granulocyte count low	100 (13.4)	100 (13.5)	200 (13.4)
Platelet count very low	100 (13.4)	100 (13.5)	200 (13.4)
Neutrophil count very low	100 (13.4)	100 (13.5)	200 (13.4)
White blood cell count very low	100 (13.4)	100 (13.5)	200 (13.4)
Granulocyte count very low	100 (13.4)	100 (13.5)	200 (13.4)

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Grade 3 or higher febrile neutropenia adverse events are counted. MedDRA

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Treatment-Emergent Serious Adverse Events by MedDRA Primary System Organ Class, High Level Term and Preferred Term Safety Population

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Preferred Term	n (%)	n (%)	n (%)

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Appendix F. Health-related quality of life

N/A

Appendix G. Probabilistic sensitivity analyses

OWSA

Table 85 List of tested parameters in the OWSA

Discount Rate (Costs) - 0-39 years
Discount Rate (Benefits) - 0-39 years
Discount Rate (Costs) - 40-74 years
Discount Rate (Benefits) - 40-74 years
Discount Rate (Costs) - >74 years
Discount Rate (Benefits) - >74 years
HRQoL ITT Progression Free On Treatment: PET-guided BrECADD
HRQoL ITT Progression Free On Treatment: PET-guided eBEACOPP
HRQoL ITT Progression Free Off Treatment: PET-guided BrECADD
HRQoL ITT Progression Free Off Treatment: PET-guided eBEACOPP
HRQoL ITT Progressed Disease
Body weight (kg): ITT
BSA (m2): ITT
Dose Intensity: ITT PET-guided BrECADD: Brentuximab
Dose Intensity: ITT PET-guided BrECADD: Etoposide
Dose Intensity: ITT PET-guided BrECADD: Doxorubicin
Dose Intensity: ITT PET-guided BrECADD: Cyclophosphamide
Dose Intensity: ITT PET-guided BrECADD: Dacarbazine

Dose Intensity: ITT | PET-guided BrECADD: Dexamathasone

Dose Intensity: ITT | PET-guided eBEACOPP: Bleomycin

Dose Intensity: ITT | PET-guided eBEACOPP: Etoposide

Dose Intensity: ITT | PET-guided eBEACOPP: Doxorubicin

Dose Intensity: ITT | PET-guided eBEACOPP: Cyclophosphamide

Dose Intensity: ITT | PET-guided eBEACOPP: Vincristine

Dose Intensity: ITT | PET-guided eBEACOPP: Procarbazine

Dose Intensity: ITT | PET-guided eBEACOPP: Prednisone

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Brentuximab

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Etoposide

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Doxorubicin

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Cyclophosphamide

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Dacarbazine

Time on Treatment: ITT | PET-guided BrECADD (6 cycles): Dexamathasone

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Brentuximab

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Etoposide

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Doxorubicin

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Cyclophosphamide

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Dacarbazine

Time on Treatment: ITT | PET-guided BrECADD (4 cycles): Dexamathasone

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Bleomycin

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Etoposide

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Doxorubicin

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Cyclophosphamide

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Vincristine

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Procarbazine

Time on Treatment: ITT | PET-guided eBEACOPP (6 cycles): Prednisone

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Bleomycin

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Etoposide

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Doxorubicin

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Cyclophosphamide

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Vincristine

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Procarbazine

Time on Treatment: ITT | PET-guided eBEACOPP (4 cycles): Prednisone

% of patients receive 2 cycles of BrECADD

% of patients receive 2 cycles of eBEACOPP

% receiving Concomitant medications | PET-guided BrECADD: Filgrastim

% receiving Concomitant medications | PET-guided BrECADD: Pegfilgrastim

% receiving Concomitant medications | PET-guided BrECADD: Blood transfusion - platelet

% receiving Concomitant medications | PET-guided BrECADD: Blood transfusion - RBC

% receiving Concomitant medications | PET-guided eBEACOPP: Filgrastim

% receiving Concomitant medications | PET-guided eBEACOPP: Pegfilgrastim

% receiving Concomitant medications | PET-guided eBEACOPP: Blood transfusion - platelet

% receiving Concomitant medications | PET-guided eBEACOPP: Blood transfusion - RBC

% receiving Monitoring Resource (0-0.5 year) | Consultation

% receiving Monitoring Resource (0-0.5 year) | CT scan

% receiving Monitoring Resource (0-0.5 year) | PET scan

% receiving Monitoring Resource (0.5-4 years) | Consultation

% receiving Monitoring Resource (0.5-4 years) | CT scan

% receiving Monitoring Resource (>4 years) | Consultation

% receiving Monitoring Resource (>4 years) | CT scan

% receiving Monitoring Resource (post-progression) | Consultation

% receiving Monitoring Resource (post-progression) | CT scan

% receiving Monitoring Resource (post-progression) | PET scan

Frequency per Cycle (0-0.5 year) | Consultation

Frequency per Cycle (0-0.5 year) | CT scan

Frequency per Cycle (0-0.5 year) | PET scan

Frequency per Cycle (0.5-4 years) | Consultation

Frequency per Cycle (0.5-4 years) | CT scan

Frequency per Cycle (>4 years) | Consultation

Frequency per Cycle (>4 years) | CT scan

Frequency per Cycle (post-progression) | Consultation

Frequency per Cycle (post-progression) | CT scan

Frequency per Cycle (post-progression) | PET scan

% receiving Radiotherapy (pre-progression) | PET-guided BrECADD

% receiving Radiotherapy (pre-progression) | PET-guided eBEACOPP

Subsequent Therapy - HD-21 | PET-guided BrECADD: Chemotherapy

Subsequent Therapy - HD-21 | PET-guided BrECADD: ASCT

Subsequent Therapy - HD-21 | PET-guided BrECADD: AlloSCT

Subsequent Therapy - HD-21 | PET-guided BrECADD: Nivolumab

Subsequent Therapy - HD-21 | PET-guided BrECADD: Pembrolizumab

Subsequent Therapy - HD-21 | PET-guided BrECADD: Brentuximab

Subsequent Therapy - HD-21 | PET-guided BrECADD: Bendamustine

Subsequent Therapy - HD-21 | PET-guided BrECADD: Radiation

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Chemotherapy

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: ASCT

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: AlloSCT

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Nivolumab

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Pembrolizumab

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Brentuximab

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Bendamustine

Subsequent Therapy - HD-21 | PET-guided eBEACOPP: Radiation

Administration Costs | A1

Administration Costs | A2

Administration Costs | A3

Administration Costs | A4

Administration Costs | A5

Administration Costs | A6

Monitoring and Follow-up Care Costs | Consultation

Monitoring and Follow-up Care Costs | CT scan

Monitoring and Follow-up Care Costs | PET scan

Adverse Events Management Costs | Grade 3: Anemia

Adverse Events Management Costs | Grade 3: Febrile neutropenia

Adverse Events Management Costs | Grade 3: Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)

Adverse Events Management Costs | Grade 3: Infection

Adverse Events Management Costs | Grade 3: Leukopenia

Adverse Events Management Costs | Grade 3: Mucositis

Adverse Events Management Costs | Grade 3: Neutropenia

Adverse Events Management Costs | Grade 3: Thrombocytopenia

Adverse Events Management Costs | TRMB: Anemia

Adverse Events Management Costs | TRMB: Thrombocytopenia

Adverse Events Management Costs | TRMB: Infection

Adverse Events Management Costs | TRMB: Cardiac disorders

Adverse Events Management Costs | TRMB: Gastrointestinal disorder (excl. Nausea, vomiting, and mucositis)

Adverse Events Management Costs | TRMB: Hepatobiliary disorders

Adverse Events Management Costs | TRMB: Nervous system disorders (sensory, motor, and other)

Adverse Events Management Costs | TRMB: Renal or urinary disorders

Adverse Events Management Costs | TRMB: Respiratory, thoracic or mediastinal disorders

Radiotherapy Costs | Deliver a fraction of treatment on a megavoltage machine

Subsequent Therapy Costs | HD21: Chemotherapy

Subsequent Therapy Costs | HD21: ASCT

Subsequent Therapy Costs | HD21: AlloSCT

Subsequent Therapy Costs | HD21: Nivolumab

Subsequent Therapy Costs | HD21: Pembrolizumab

Subsequent Therapy Costs | HD21: Brentuximab

Subsequent Therapy Costs | HD21: Bendamustine

Subsequent Therapy Costs | HD21: Radiation

Table 86 List of variations in the OWSA

Parameter	Base-case value	Low value	High value	Source of variation
Annual discount rate of health outcomes	3.5 %	2.8%	4.2%	Assumption
Annual discount rate of costs	3.5 %	2.8%	4.2%	Assumption
Utility values: PF on treatment: PET-guided BrECADD		0.44	0.66	SE was assumed to be 10% of the mean, 95% CIs were calculated based on beta distribution
Utility values: PF on treatment: PET-guided eBEACOPP		0.44	0.65	
Utility values: PF off treatment: PET-guided BrECADD		0.59	0.88	
Utility values: PF off treatment: PET-guided eBEACOPP		0.57	0.85	
Utility value: Progressed disease		0.49	0.73	
BSA (m ²)	1.91	1.53	2.28	SE was assumed to be 10% of the mean, 95% CIs were calculated based on normal distribution
Body weight (kg)	76.15	61.23	91.08	
Dose intensity PET-guided BrECADD: Brentuximab (IV)	99.1%	98.8%	99.4%	SE was derived from IPD, 95% CIs were calculated based on beta distribution
Dose intensity PET-guided BrECADD: Etoposide (IV)	99.2%	98.7%	99.5%	
Dose intensity PET-guided BrECADD: Doxorubicin (IV)	99.1%	98.8%	99.3%	
Dose intensity PET-guided BrECADD: Cyclophosphamide (IV)	99.3%	99.1%	99.5%	
Dose intensity PET-guided BrECADD: Dacarbazine (IV)	99.0%	98.8%	99.3%	

Dose intensity PET-guided BrECADD: Dexamathasone (PO)	10 0.0 %	100.0%	100.0%	
Dose intensity PET-guided eBEACOPP: Bleomycin (IV)	92. 2%	90.8%	93.4%	
Dose intensity PET-guided eBEACOPP: Etoposide (IV)	99. 1%	98.7%	99.4%	
Dose intensity PET-guided eBEACOPP: Doxorubicin (IV)	99. 1%	98.7%	99.4%	
Dose intensity PET-guided eBEACOPP: Cyclophosphamide (IV)	99. 3%	99.0%	99.6%	
Dose intensity PET-guided eBEACOPP: Vincristine (IV)	93. 0%	91.9%	94.1%	
Dose intensity PET-guided eBEACOPP: Procarbazine (PO)	97. 2%	96.6%	97.8%	
Dose intensity PET-guided eBEACOPP: Prednisone (PO)	98. 4%	97.9%	98.9%	
% Receiving radiotherapy: PET-guided BrECADD	12. 0%	9.8%	14.4%	95% CIs were calculated based on beta distribution
% Receiving radiotherapy: PET-guided eBEACOPP	13. 8%	11.4%	16.3%	
Subsequent therapy PET-guided BrECADD: Chemotherapy	14 7.1 %	147.1%	147.1%	95% CIs were calculated based on beta distribution
Subsequent therapy PET-guided BrECADD: ASCT	58. 8%	45.2%	71.8%	
Subsequent therapy PET-guided BrECADD: AlloSCT	9.8 %	3.3%	19.2%	
Subsequent therapy PET-guided BrECADD: SCT (undefined)	0.0 %	0.0%	0.0%	
Subsequent therapy PET-guided BrECADD: Other transplant	0.0 %	0.0%	0.0%	
Subsequent therapy PET-guided BrECADD: Nivolumab	13. 7%	5.8%	24.3%	
Subsequent therapy PET-guided BrECADD: Pembrolizumab	9.8 %	3.3%	19.2%	
Subsequent therapy PET-guided BrECADD: Brentuximab	11. 8%	4.5%	21.8%	
Subsequent therapy PET-guided BrECADD: Bendamustine	2.0 %	0.1%	7.1%	
Subsequent therapy PET-guided BrECADD: radiation	15. 7%	7.2%	26.7%	
Subsequent therapy PET-guided eBEACOPP: Chemotherapy	17 0.1 %	170.1%	170.1%	

Subsequent therapy PET-guided eBEACOPP: ASCT	74.6%	63.6%	84.2%
Subsequent therapy PET-guided eBEACOPP: AlloSCT	6.0%	1.7%	12.7%
Subsequent therapy PET-guided eBEACOPP: SCT (undefined)	0.0%	0.0%	0.0%
Subsequent therapy PET-guided eBEACOPP: Other transplant	0.0%	0.0%	0.0%
Subsequent therapy PET-guided eBEACOPP: Nivolumab	3.0%	0.4%	8.2%
Subsequent therapy PET-guided eBEACOPP: Pembrolizumab	7.5%	2.5%	14.8%
Subsequent therapy PET-guided eBEACOPP: Brentuximab	26.9%	17.0%	38.0%
Subsequent therapy PET-guided eBEACOPP: Bendamustine	1.5%	0.0%	5.4%
Subsequent therapy PET-guided eBEACOPP: Radiation	17.9%	9.8%	27.9%

Scenario analysis

Table 87 List of parameters varied in the scenario analyses

Scenario analysis	Base-case value	Analysis value	Rationale of change
Cure timepoint (months)	60	73	When extrapolations were based on the KM curves, a later cure time point increased the incremental QALYs and LYs since the biggest separation of the curves was observed at the tails.
RDI	On	Off	The impact of RDI was minor due to the comparable input values.
Vial wastage	On	Off	Drug costs were reduced for PET-guided BrECADD.
Modeling approach	Partitioned Survival Model	State Transition Model	Total LYs decreased for PET-guided BrECADD and PET-guided eBEACOPP due to the shortened LYs in PPS health state. The incremental LYs and QALYs increased due to the lower increased LYs and QALYs for PET-guided eBEACOPP. The decreased LYs in PPS health states also led to lower costs in the subsequent treatments and PPS follow-up and monitoring costs, resulting in less cost savings for PET-guided BrECADD. Overall, the decreased ICER was driven by the increased incremental QALYs.

Time-to-progression model	KM curves	Mixture cure model (Weibull)	The impact of using MCMs was significant compared to the base case result of state transition model due to the sensitive incremental outcomes driven by the immature data.
Time-to-progression model	KM curves	Mixture cure model (Log-normal)	
PPS modeling approach	Transition probabilities with exponential parametric model	Fixed pay-off with Gompertz fitting model	The impact of using fixed pay-off approach was significant compared to the base case result of state transition model due to the sensitive incremental outcomes driven by the immature data.
PPS modeling approach	Transition probabilities with exponential parametric model	Fixed pay-off with Log-normal fitting model	
PPS modeling approach	Transition probabilities with treatment effect	Transition probabilities without treatment effect	Incremental LYs increased due to the lower PPS of PET-guided BrECADD compared to PET-guided eBEACOPP.

Appendix H. Literature searches for the clinical assessment

H.1 Efficacy and safety of the intervention and comparator(s)

N/A

Table 88 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
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N/A

Abbreviations:

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
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N/A

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
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N/A

H.1.1 Search strategies

N/A

Table 91 of search strategy table for [name of database]

No.	Query	Results
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N/A

H.1.2 Systematic selection of studies

N/A

Table 92 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
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N/A

Table 93 Overview of study design for studies included in the analyses

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
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N/A

H.1.3 Excluded fulltext references

N/A

H.1.4 Quality assessment

N/A

H.1.5 Unpublished data

N/A

Appendix I. Literature searches for health-related quality of life

I.1 Health-related quality-of-life search

I.1.1 Targeted literature search for mapping algorithm

A TLR was performed to identify the most relevant published direct and indirect algorithm(s) mapping the EORTC QLQ-C30 to EQ-5D health utility values, with priority placed on studies of adult patients with Hodgkin’s lymphoma or other blood cancers. A direct mapping approach links responses for the HRQoL instrument to utility values directly, thereby fixing the value set to the one used in the mapping approach. In contrast, indirect mapping links HRQoL instrument responses to EQ-5D questionnaire responses. The latter provides more flexibility, because any valid country value set can be applied to generate utility values. The TLR broadly followed the standards set out in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).

I.1.2 Search strategies

Table 94 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid	8. December 2023	25.01.2024
Medline	Ovid		25.01.2024
The Oxford Health Economic Research Centre	N/R		25.01.2024

Table 95 PICOS criteria for study selection

PICOS	Inclusion Criteria	Exclusion criteria
Population	Adult patients with Hodgkin’s lymphoma Adult patients with other blood cancers	Pediatric patients Patients with other cancers or different diseases
Intervention/Comparators	N/A	N/A
Outcomes	Mapping of EORTC QLQ-C30 to EQ-5D (3L or 5L) Direct or indirect mapping of interest**	Any other mapping, from any patient-reported outcome other than QLQ-C30 or to any utility elicitation method other than EQ-5D

Study design	Any study design that may report a mapping algorithm, including:	Reviews
	• Randomized controlled trials • Cohort studies • Cross-sectional studies • Health economic analyses	
Additional limits	English language only No date or country restriction†	N/A

Table 96 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Ovid	8. Dec 2023 until 25. Jan 2024	25.01.2024
Medline	Ovid	8. Dec 2023 until 25. Jan 2024	25.01.2024
HERC	Manually search	8. Dec 2023 until 25. Jan 2024	25.01.2024

Abbreviations: The Oxford Health Economic Research Centre

Table 97 Medline search strategy

Search Number	Search Terms	Results
1	(eq-5d or eq5d or "eq 5 d" or "european quality of life 5" or "european quality of life five" or "euroqol 5" or "euroqol five" or "EuroQoL 5 D").mp.	15,488
2	(qlq-c30 or qlqc30 or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30").mp.	5,872
3	(mapping or mapped or crosswalk*).mp.	494,349
4	1 and 2 and 3	52

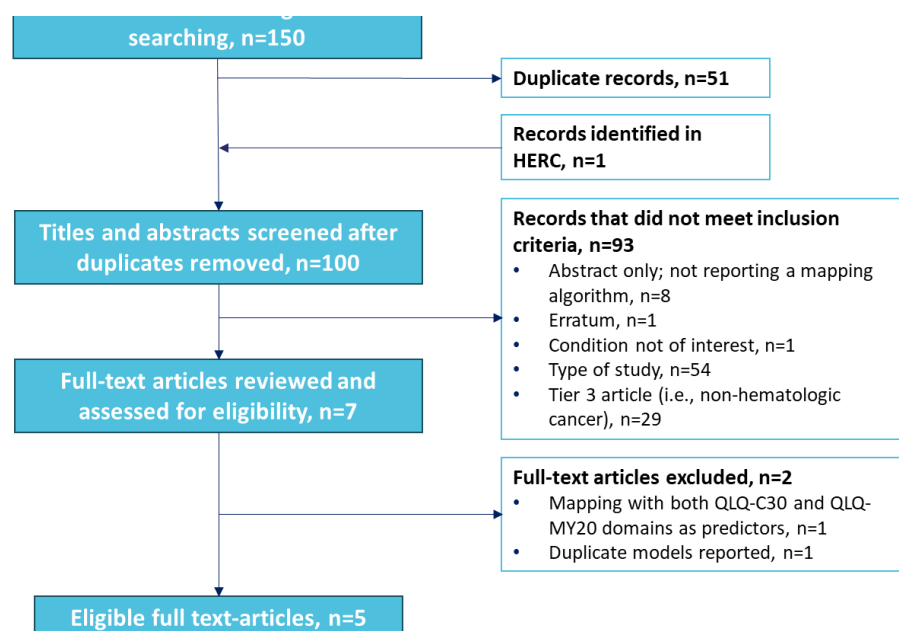
Table 98 Embase search strategy

Search Number	Search Terms	Results
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1	exp "European Quality of Life 5 Dimensions questionnaire"/	16,283
2	(eq-5d or eq5d or "eq 5 d" or "european quality of life 5" or "european quality of life five" or "euroqol 5" or "euroqol five" or "EuroQoL 5 D").mp.	33,137
3	1 or 2	33,137
4	exp "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30"/	5,562
5	(qlq-c30 or qlqc30 or "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30").mp.	13,820
6	4 or 5	13,820
7	(mapping or mapped or crosswalk*).mp.	428,969
8	3 and 6 and 7	98

After the search strategy was completed and duplicate records were removed, 100 articles were identified for screening. Of these, 93 (93%) did not meet the inclusion criteria during title and abstract screening. At the abstract level, 54/100 (54%) articles were excluded for clearly not being a mapping study, 29/100 (29%) for reporting a mapping algorithm for non-hematologic cancers, 8/100 (8%) for being abstract-only and not reporting a mapping algorithm, 1/100 (1.0%) for reporting a condition not of interest (i.e., not cancer), and 1/100 (1%) for being an erratum. The remaining seven of the 100 (7%) full-text articles were retrieved and screened. Of these, 2/7 (29%) were excluded (one due to mapping with both EORTC QLQ-C30 and EORTC Quality of Life Questionnaire – Myeloma 20 (QLQ-MY20) domains as predictors, and one because it was a duplicate report of models reported in another included publication). Five articles were included for the final extraction. A summary of the included articles is provided in the next section.

Table 99 Flow diagram for included and excluded studies



All studies employed commonly used statistical methods and used either internal or external validation to demonstrate the accuracy of their predictions. Generally, models performed better at predictions in the utility range above 0.5.

All but one of the studies (Young 2015) used direct mapping approaches, which produce health state utility values using a fixed value set. Direct mapping approaches have the advantage of potentially using simpler approaches such as OLS regressions but are mappings between scores from the HRQoL instrument (i.e., the QLQ-C30 in this case) and health state utility values calculated using a specific value set. Because this value set cannot be modified in a direct approach, this may be problematic for use in an economic model if the value set does not match the population of interest. In contrast, Young 2015 used an indirect approach (also known as response mapping) to map to the EQ-5D-3L, which produces probabilities for responses to each of the EQ-5D-3L questions, which can then be applied to a chosen value set to derive health state utility values. Although indirect approaches require the use of slightly more sophisticated statistical techniques, such as multinomial logistic regression, they allow for the choice of a value set permitting the resulting health state utility values to reflect any population of interest for which there exists a value set. Of the five studies identified, the Proskorovsky 2014 and Young 2015 mappings are the most widely used and applicable for use in a UK cost-effectiveness model. The Versteegh 2012 study could also be used; however, only if the Dutch value set were of interest, since the study used a direct mapping, excluding the possibility of using a different value set. The Versteegh 2010 study could also be applicable (using the UK value set) but only about 12% of observations in the HD21 dataset fall into the poor health group, thus limiting the applicability of this mapping. Although the population was closest to the HD21 population, the Xu 2020 study should be avoided due to quality concerns (it was unclear whether the authors re-ran the

mapping model with only the significant coefficients or just excluded the non-significant ones in reporting and the provided utility calculator supplement), and the use of direct mapping with the EQ-5D-5L and Chinese value set.

To retain flexibility to apply a value set from a different country for the cost-effectiveness model, the indirect mapping published by Young 2015 was selected for use in the present study over the direct mapping to UK utilities by Proskorovsky 2014.

I.1.3 Quality assessment and generalizability of estimates

N/A

I.1.4 Unpublished data

The RWE data is described in Appendix K.

Appendix J. Literature searches for input to the health economic model

J.1 External literature for input to the health economic model

J.1.1 Targeted literature search for disutilities

The search engine for disutiites for infertility used was PubMed, refreshed for search on March 3rd, 2025 and identified 644 studies/reports for review with no initial duplicates identified and previewed those within the last 10 years and 2 months. The search string was as follows: (infertility OR infertile) AND (assisted reproductive technology OR ART OR in vitro fertilization OR IVF) AND (disutility OR quality of life OR QoL) AND ("2015/01/01": "2025/03/01"[PDAT]).

Table 51 Sources included in the search

Database	Platform/source	Relevant period for the search	Date of search completion
PubMed	OVID	within the last 10 years and 2 months	03 March 2025

Table 100 PICOS criteria for study selection

PICOS	Inclusion Criteria	Exclusion criteria
Population	Newly diagnosed patients with advanced HL (defined as stage IIb, III, and IV) and no restriction on age†	Patients without HL Animal or in vitro studies
Intervention/Comparators	N/A	N/A
Outcomes	Utilities/Disutilities*	Outcomes not of interest
Study design	RCTs Non-randomized clinical trials Single-arm trials Observational studies to include, but not limited to: Cohort studies Database studies Registries Naturalistic studies At the citation screening stage: Both prospective and retrospective studies will be	Animal, in-vitro, ex-vivo or pharmacokinetic studies Editorials, erratum, trial protocol, guideline, etc Letters Case studies Case reports Narrative reviews SLRs/NMAs will be used for reference chasing only

included
No restriction on the number of enrolled patients, although single-patient case studies were excluded.
Studies to be deemed eligible:
Studies assessing the validity, reliability and responsiveness of **generic and disease-specific** HRQoL questionnaires were considered for inclusion
Studies reporting predictors of HRQoL
Studies reporting disease-specific or generic HRQoL outcomes for patients with HL

Additional limits	For the 2023 and 2025 update: English Language	For the 2023 and 2025 update: Articles not published in English

A PRISMA diagram was not provided, as the TLR was conducted alongside additional literature searches for other model inputs. Therefore, the resulting diagram does not accurately reflect the disutility search.

Appendix K. Protocol for Danish real-world study of usage of BrECADD.

Protocol for a Real-World Study of BrECADD in Denmark

Odense University Hospital, Denmark

Baggrund:

Intensiv systemisk kemoterapi som behandlingsprincip ved avanceret klassisk Hodgkins lymfom (aHL) er forbundet med en stor chance for helbredelse. Men denne behandling er forbundet med betydelig risiko for alvorlige og potentielt livslange, vedvarende senfølger. I HD21 studiet blev en ny behandlingskombination af brentuximab vedotin, etoposid, cyclophosphamid, doxorubicin, dacarbazin og dexamethason (BrECADD), afprøvet i fase 3 studie (Lancet, juli, 24), hvor der skete en sammenligning med aktuelle standard behandling, BEACOPPesc. Formålet med studiet, var at dokumentere, at BrECADD regimet havde en sammenlignelig behandlings effektivitet som BEACOPPesc, men at toksiciteten var mindre. Antallet af behandlinger var styret af interim PET-CT scanning efter to behandlingscyklusser; Patienter som havde opnåede komplet metabolisk response (i HD21 studiet defineret som Deauville score 1-3) blev behandlet med 2 yderligere behandlingsserier, ved partiel response (i HD21 studiet defineret som Deauville score >3) blev behandlet med yderligere 4 behandlingsserier.

HD21 studiet er et randomiseret, multicenter, fase 3-undersøgelse, blev gennemført på 233 centre i 9 lande. Patienter var voksne (≤ 60 år) med ny-diagnoseret aHL. Patienterne blev ligeligt randomiseret (1:1) til enten 4 eller 6 serier (med 21-dages intervaller) af etoposid (200 mg/m² intravenøst på dag 1-3), doxorubicin (35 mg/m² intravenøst på dag 1) og cyclophosphamid (1250 mg/m² intravenøst på dag 1), samt standarddoser af bleomycin (10 mg/m² intravenøst på dag 8), vincristin (1,4 mg/m² intravenøst på dag 8), procarbazin (100 mg/m² oralt på dag 1-7) og prednison (40 mg/m² oralt på dag 1-14; BEACOPPesc eller BrECADD.

Samlet blev 1500 patienter inkluderet, hvoraf 749 blev randomiseret til BrECADD og 751 til BEACOPPesc. I alt 1482 patienter blev inkluderet i intention-to-treat-analysen. Den mediane alder var 31 år. 838 (56%) af de 1482 patienter var mænd, og 644 (44%) var kvinder.

Behandlingsrelateret morbiditet var signifikant lavere ved BrECADD (312 [42%] af 738 patienter) end ved BEACOPPesc. (430 [59%] af 732 patienter; relativ risiko 0,72 [95% CI

0,65-0,80]; $p < 0,0001$). Ved en median opfølgning på 48 måneder forbedrede BrECADD den progressionsfri overlevelse med en hazard ratio på 0,66 (0,45-0,97; $p = 0,035$); den estimerede 4-årige progressionsfri overlevelse var 94,3% (95% CI 92,6-96,1) for BrECADD og 90,9% (88,7-93,1) for BEACOPPesc.

Således demonstrerede HD21 studiet, at BrECADD regimet, er bedre tolereret og mere effektiv end BEACOPPesc som førstelinjebehandling for voksne patienter med aHL.

Forskningsplan:

I Danmark sker anvendelsen af BrECADD regimet i varierende hyppighed i de 5 sygehusregioner, da anvendelsen af regimet kræver tilladelse fra de regionale lægemiddel komiteer, hvor tilladelse ikke gives ensartet: I Region Syddanmark, har det været muligt at anvende BrECADD regimet siden data fra HD21 studiet første gang blev offentliggjort, således er 16 patienter behandlet uden for protokol. Et mindre antal patienter er blevet behandlet i de andre 4 sygehus regioner. Vi ønsker at lave en real world evidens opgørelse af danske patienter behandlet med BrECADD og BEACOPPesc de sidste 5 år i Danmark med opgørelse af følgende:

1. Der er bred international enighed og evidens for, at response kriterierne for metaboliske komplet remission er Deauville score 1-3, hvilket er det der er anvendt uden for protokol.
Vi ønsker at opgøre hvor mange patienter der blev behandlet med hhv. 4 og 6 serier BrECADD.
2. Patient karakteristika.
3. Failure Free Survival

Data kilder og metoder:

Data vil blive samlet vha gennemgang af journaler fra behandlende afdeling ved OUH og LYFO registeret.

Studiet vil først blive påbegyndt efter indhentning af nødvendige tilladelser.

Data analyser:

Alle data vil blive deskriptivt analyseret.

Appendix L. Cost estimation

For the pre- and post-oncological phase, there are many possible fertility treatments. It is not possible to categorize patients based on the treatment they receive, as each case is assessed individually and no data is available. Therefore, an average time calculation for fertility treatment for all options has been used to account for the fact that some treatments are very time-consuming, while others require less time. For patient time the rate of 188 DKK is used to calculate the total patient and partner costs associated with the treatment. For all visits it is assumed that the partner attends and joint transport is used, and the transport rate is 140 DKK pr visit.

L.1 Monitor and follow-up care

Table 101

[illegible]

Table 102 [REDACTED]

[REDACTED]					

L.2 Mapping of resource use and associated costs for fertility treatment

Table 103

Category	Value	Value
Category 1	10	10
Category 2	20	20
Category 3	30	30
Category 4	40	40
Category 5	50	50
Category 6	60	60
Category 7	70	70
Category 8	80	80
Category 9	90	90
Category 10	100	100
Category 11	110	110
Category 12	120	120
Category 13	130	130
Category 14	140	140
Category 15	150	150
Category 16	160	160
Category 17	170	170
Category 18	180	180
Category 19	190	190
Category 20	200	200
Category 21	210	210
Category 22	220	220
Category 23	230	230
Category 24	240	240
Category 25	250	250
Category 26	260	260
Category 27	270	270
Category 28	280	280
Category 29	290	290
Category 30	300	300
Category 31	310	310
Category 32	320	320
Category 33	330	330
Category 34	340	340
Category 35	350	350
Category 36	360	360
Category 37	370	370
Category 38	380	380
Category 39	390	390
Category 40	400	400
Category 41	410	410
Category 42	420	420
Category 43	430	430
Category 44	440	440
Category 45	450	450
Category 46	460	460
Category 47	470	470
Category 48	480	480
Category 49	490	490
Category 50	500	500
Category 51	510	510
Category 52	520	520
Category 53	530	530
Category 54	540	540
Category 55	550	550
Category 56	560	560
Category 57	570	570
Category 58	580	580
Category 59	590	590
Category 60	600	600
Category 61	610	610
Category 62	620	620
Category 63	630	630
Category 64	640	640
Category 65	650	650
Category 66	660	660
Category 67	670	670
Category 68	680	680
Category 69	690	690
Category 70	700	700
Category 71	710	710
Category 72	720	720
Category 73	730	730
Category 74	740	740
Category 75	750	750
Category 76	760	760
Category 77	770	770
Category 78	780	780
Category 79	790	790
Category 80	800	800
Category 81	810	810
Category 82	820	820
Category 83	830	830
Category 84	840	840
Category 85	850	850
Category 86	860	860
Category 87	870	870
Category 88	880	880
Category 89	890	890
Category 90	900	900
Category 91	910	910
Category 92	920	920
Category 93	930	930
Category 94	940	940
Category 95	950	950
Category 96	960	960
Category 97	970	970
Category 98	980	980
Category 99	990	990
Category 100	1000	1000

Table 104 [REDACTED]

[REDACTED]	
[REDACTED]	
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

Table 105 [REDACTED]

[REDACTED]		
	[REDACTED]	[REDACTED]
	[REDACTED]	[REDACTED]
[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		
[REDACTED]		
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]		[REDACTED]
[REDACTED]		[REDACTED]
[REDACTED]		
[REDACTED]		

Category	Value
Category 1	10
Category 2	10
Category 3	10
Category 4	10
Category 5	30
Category 6	10
Category 7	10
Category 8	10
Category 9	10
Category 10	10
Category 11	10
Category 12	10
Category 13	10
Category 14	10
Category 15	10
Category 16	10
Category 17	10
Category 18	10
Category 19	10
Category 20	10

Table 106

[illegible]

Appendix M. Supportive analyses; efficacy, safety, and comparative efficacy/safety

M.1 Treatment Related Morbidity

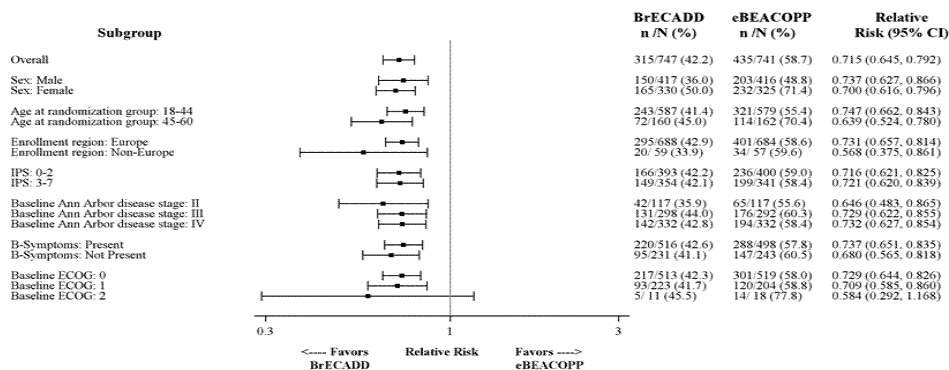
The primary endpoint of the study, Treatment Related Morbidity (TRMB), was analyzed in the ITT population at time of the primary data cut-off date. TRMB was found to be statistically and clinically significantly diminished in the BrECADD arm as compared to the BEACOPP arm, Table 107 (25).

Table 107: Rate of treatment related morbidity.

	Occurrence of at least one TRMB n/N	Occurrence of at least one TRMB %	Unstratified Relative Risk, 95% CI P-value	Absolute Difference, % 95% CI
BrECADD	315/747	42.7	0.72 0.65 – 0.80 < 0.0001	-16.5 -21.6 – -11.4
BEACOPP	435/741	58.7		

Similarly, RRs of all predefined subgroups favored BrECADD over BEACOPP, Figure 39 (25).

Figure 39: Forrest plot of RR for TRMB across predefined subgroups.



Rate of components of TRMB

Treatment related morbidity was a composite endpoint composed of grade 4 anemia, grade 4 thrombocytopenia, or grade 4 infection, as well as grade 3-4 organ toxicity. Table 108 reports the incidences of the various components of TRMB.

In accordance with the aim of the study, the largest impact on individual components of TRMB is observed in the rate of life-threatening acute grade 4 thrombocytopenia.

Table 108. Rate of the components of TRMB.

	BrECADD	eBEACOPP
No of patients (%)	N=747	N=741
Number of patients with TRMB	315 (42.2)	435 (58.7)
Acute Hematologic Toxicity Grade 4	233 (31.2)	386 (52.1)
Anemia	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	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	< 0.0001	
RR (Unstratified BrECADD/eBEACOPP) ^b	0.718	
95% CI	(0.648, 0.797)	
RR (Stratified BrECADD/eBEACOPP) ^c	0.715	
95% CI	(0.645, 0.792)	
% Difference (BrECADD-eBEACOPP)	-16.5	
Exact 95% CI	(-21.6, -11.4)	

CMH: Cochran-Mantel-Haenszel; GI: gastrointestinal. Percentages are calculated using the safety population as denominator. a: 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 using unstratified CMH test. c: RR calculated using stratified CMH test.

M.2 Progression Free Survival

The co-primary endpoint centrally confirmed PFS regardless of missed visits and regardless of initialization of new anti-cancer therapy met non-inferiority with a statistically significant reduction in risk in the BrECADD treatment arm compared with eBEACOPP at the primary data cut-off date (31st December 2022) (25). The final analysis of PFS was done at the October 31st 2023 data set in the ITT population as a supportive analysis because the PFS IA achieved statistically significant noninferiority.

Table 109 and Table 110 Table 109, Table 109, and Table 111summarizes the primary and supportive PFS analyses, respectively (25).

Table 109 PFS at primary data cut-off date, 40 months median follow-up

	PFS-rate %	Hazard Ratio, 98.87% CI P-value	Hazard Ratio, 95% CI P-value
BrECADD	94.8	0.62 0.37 – 1.04	0.62 0.42 – 0.93
BEACOPP	91.7	0.018	0.018

Table 110 PFS at final data cut-off date, 48 months median follow-up

	PFS-rate %	Hazard Ratio, 95% CI P-value
BrECADD	94.1	0.66 0.45 – 0.97
BEACOPP	91.3	0.035

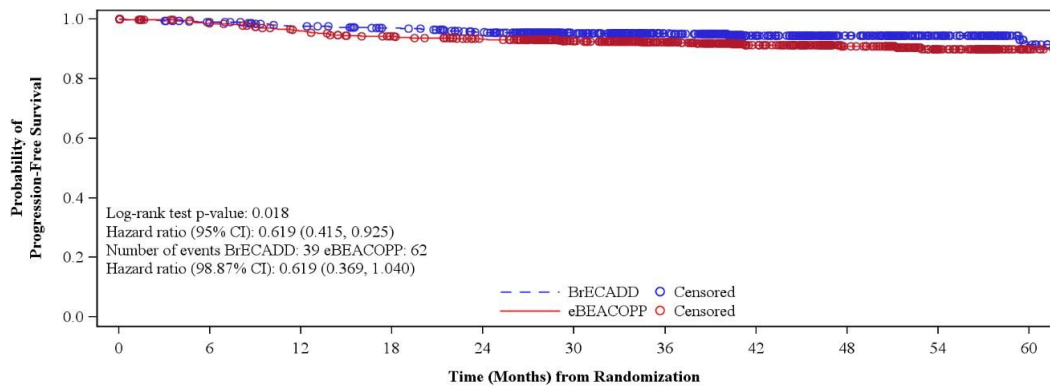
Table 111 PFS and OS events at final cut-off (31 October 2023) and estimated 3- and 5-year PFS and OS rates (55)

Intention to treat (ITT) population	
BrECADD n = 751	eBEACOPP n = 749

Number of PFS events (%)	44 (5.9)	65 (8.7)
PFS Hazard Ratio (95% CI)	0.664 (0.453, 0.973)	
Estimated PFS (95% CI)		
At 3 years	95.2 (93.4, 96.6)	92.4 (90.2, 94.1)
At 5 years	92.8 (90.0, 94.9)	90.2 (87.5, 92.3)
Overall Survival Number or Deaths (%)	12 (1.6)	13 (1.7)
OS Hazard Ratio (95% CI)	0.919 (0.419, 2.015)	
Estimated OS Rate (95% CI)		
At 3 years	98.9 (97.8, 99.4)	98.9 (97.8, 99.4)
At 5 years	98.1 (97.8, 99.4)	97.9 (96.4, 98.8)

Figure 40 show the KM curve of PFS at the primary analysis (25).

Figure 40 KM curves of PFS

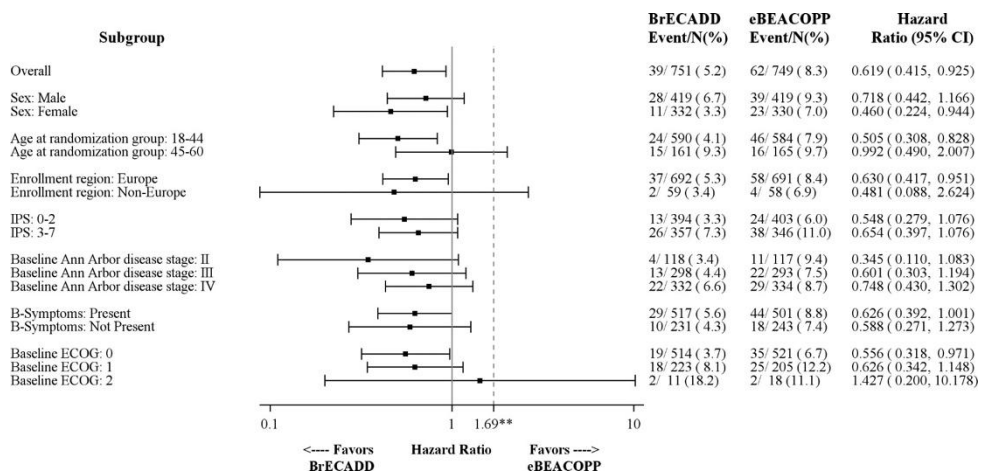


Number of Patients-at-Risk

BrECADD	751	720	701	687	659	556	441	332	232	140	58
eBEACOPP	749	714	686	662	638	542	447	314	225	142	65

Similarly, a HR favoring BrECADD was observed across most prespecified subgroups, Figure 41 (25).

Figure 41 Forrest Plot of PFS at primary data cut



M.3 Infertility and live births

For the primary analysis for infertility, the infertility rate was defined as the proportion of patients with FSH values above the upper limit of normal (ULN) among the patients for whom FSH values were available at 1-year Post Treatment Follow-Up (PTFU). 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. The population was the safety population and did not take natural age associated increase of FSH levels into account.

The outcome was rate of infertility at one year post treatment among patients for whom FSH values were available (25). No testing for differences were performed.

Data presented are for the full safety population, females and males, **Table 112**.

Table 112 Infertility rates at one year post treatment follow-up in the safety population for whom FSH levels were available

	All genders n/N %	Females n/N %	Males n/N %
BrECADD	137/337 40.7	43/162 26.5	77/167 53.7
BEACOPP	217/341 63.6	94/175 46.1	140/174 80.5
Numeric Difference, %	22.9	19.6	26.8

A supportive analysis was performed among patients in the safety population for whom FSH levels at baseline indicated fertility at baseline, Table 113.

Table 113 Infertility rates at one year post treatment follow-up in the safety population for whom FSH levels were available and for whom FSH levels at baseline indicated fertility, Takeda.

	Full Safety Population, n/N %	Females n/N %	Males n/N %
BrECADD	53/145 36.6	6/51 11.8	47/94 50.0
BEACOPP	89/140 63.6	17/87 35.4	72/92 78.3
Numeric Difference, %	27.0	23.6	28.3

No pregnancies were reported during the treatment period of the randomized main study. Pregnancies were registered during post treatment follow-up (median follow-up, 40 months, data cut-off 31st December 2022) in the safety population. Data is summarized by gender in Table 114 and Table 115.

Table 114 Rates of pregnancies and live births, females, Takeda.

	Pregnant Individuals n/N %	Live Births n/N %
Females		

BrECADD	39/330 11.8	32/330 9.7
BEACOPP	36/325 11.1	27/325 8.3
Difference		
Numeric	0.7	1.4
Relative (Int/Com), %	106	117

Table 115 Rates of partner pregnancies and live births, males, Takeda.

Partners of male participants	Pregnant Individuals	Live Births
	n/N %	n/N %
BrECADD	25/417 6.0	21/417 5.0
BEACOPP	10/416 2.4	10/416 2.4
Difference		
Numeric	3.6	2.6
Relative (Int/Con), %	250	208

M.4 Overall Survival

The HD21 randomized cohort is composed of patients aged ≤ 60 years whose lymphoma is treated with curative intent. For such a patient population, survival times are anticipated to be several decades. Results of OS analyses in HD21 are thus expected to be immature at all planned analyses for the HD21 study.

OS is therefore an endpoint assessed to ensure no detriment. Results of the OS analysis are descriptive, with no formal statistical testing applied.

OS was defined as the time from the date of randomization to the date of death due to any cause. OS observations were censored for patients without documented death on the date that the patient was last known to be alive.

At a median OS follow-up of 44.3 months, less than 2% of the patient population had died. Table 116 summarize KM-estimated 4-yr OS rates and descriptive hazard ratio (unstratified Cox proportional hazard model) and descriptive Log-Rank P-value. Table 111 additionally summarises OS events and estimated OS rates at 3 and 5 years.

Table 116 KM-estimated 4-yr overall survival, Takeda

	4-yr OS %	95% CI %	Hazard Ratio, 95% CI P-value
BrECADD	98.7	97.5 – 99.3	0.914 0.403 – 2.072
BEACOPP	98.1	96.6 – 99.0	0.830

M.5 Results from the comparative analysis

The below data is from the Clinical Study Report (25).

Table 117 Outcomes of comparative analyses

Outcome measure	BrECADD	eBEACOPP	Result
Progression Free Survival, 4-yr	94.1	91.3	HR: 0.66 95% CI: 0.45 – 0.97 P = 0.035
Treatment Related Morbidity, TRMB, 4-yr n/N %	315/747 42.2%	435/741 58.7%	Unstratified RR: 0.718 95% CI: 0.65 – 0.80 P < 0.0001 Stratified RR: 0.715 95% CI: 0.65 – 0.79 P < 0.0001 Difference: -16.5% 95% CI: -21.6 – -11.4)
Infertility, 1-yr all gender, n/N %	137/337 40.7	217/341 63.6	Numeric Difference: 22.9%
Infertility, 1-yr Women, n/N %	43/162 26.5	94/175 46.1	Numeric Difference: 19.6%
Infertility, 1-yr Men, n/N %	77/167 53.7	140/174 80.5	Numeric Difference: 26.8%

Outcome measure	BrECADD	eBEACOPP	Result
Infertility among fertile participants at baseline, 1-yr all gender, n/N %	53/145 36.6	89/140 63.6	Numeric Difference: 27.0%
Infertility among fertile women at baseline, 1-yr, n/N %	6/51 11.8	17/48 35.4	Numeric Difference: 23.6%
Infertility among fertile men at baseline, 1-yr, n/N %	47/94 50.0	72/92 78.3	Numeric Difference: 28.3%
Pregnancies among Female participants n/N %	39/330 11.8	36/325 11.1	<u>Difference</u> Numeric: 0.7% Relative (Int/Con): 106%
Pregnancies among partners of male participants n/N %	25/417 6.0	10/416 2.4	<u>Difference</u> Numeric: 3.6% Relative (Int/Con): 250%
Live Births, % Female participants n/N %	32/330 9.7	27/325 8.3	<u>Difference</u> Numeric: 1.4% Relative (Int/Con): 117%
Live Births, % Partners of male participants n/N %	21/417 5.0	10/416 2.4	<u>Difference</u> Numeric: 2.6% Relative (Int/Con): 208%
Overall Survival, 4-yr, %	98.7 95% CI: 97.5 – 99.3	98.1 95% CI: 96.6 – 99.0	HR: 0.914 95% CI: 0.403 – 2.072 P = 0.830

Appendix N. Rationale for events included in TRMB

The events compounded in the outcome Treatment Related Morbidity (TRMB) are based on the following reasoning (from the HD21 study protocol (13)):

“Acute non-hematological organ toxicity

Organ related toxicities of CTCA grade 3 or 4 affect around 15% of patients treated with six courses of escalated BEACOPP based on experience from the HD15 and HD18 trials. By definition, grade 3 or 4 toxicities are associated with severe and/or irreversible symptoms indicating medical intervention up to life threatening consequences/situations. In addition, they can result in treatment postponement and/or dose reduction and might have impact on health related quality of life. Based on experience from previous studies, the following SOC (System Organ Class) categories were classified as clinically relevant:

Cardiac disorders,

Gastrointestinal disorders (excluding vomiting, nausea and mucositis),

Hepatobiliary disorders,

Nervous system disorders,

Renal and urinary disorders, and

Respiratory, thoracic and mediastinal disorders.

Inflammations of the mucous membranes, alopecia, nausea and vomiting, and drug-induced fever are not considered within the scope of this primary endpoint since they are reversible and can be managed without difficulties.

Acute hematological toxicity

Essentially all patients experience grade 3/4 hematological toxicities after treatment with escalated BEACOPP. Hematological toxicities grade 1-3 are usually easily manageable by haemato-oncologist. We thus do not consider grade 1-3 hematological toxicity being relevant for the co-primary endpoint TRMB. In contrast, grade 4 anemia and thrombocytopenia represent potentially life-threatening events requiring urgent medical intervention and are included into this endpoint. Grade 4 neutropenia is observed in nearly all patients despite obligatory growth factor support. Accordingly, neutropenia is not suited as co-primary endpoint. However, severe neutropenia might result in severe and life-threatening infections. With regard to the obvious clinical relevance of grade 4 infections, we included this event into the definition of TRMB.”

Appendix O. Overview of the individual components of the comparator, eBEACOPP

Overview of comparator	
Generic name	Bleomycin
ATC code	L01DC01
Mechanism of action	Induces DNA strand breaks via free radicals
Method of administration	IV
Dosing	10 mg/m ² , day 8
Dosing in the health economic model (including relative dose intensity)	10 mg/m ² IRD: 92 %
Should the medicine be administered with other medicines?	Yes Etoposide 200 mg/m ² , day 1-3 Doxorubicin 35 mg/m ² , day 1 Cyclophosphamide 1.250 mg/m ² , day 1 Vincristine 1.4 mg/m ² (max 2 mg), day 8 Procarbazine 100 mg/m ² , day 1-7 Prednisone 40 mg/m ² , day 1-14
Treatment duration/ criteria for end of treatment	4 or 6 cycles dependent on response to treatment after 2 cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	15.000IE, 10 stk. pul.t.inj.+inf.,opl.

Overview of comparator	
Generic name	Etoposide
ATC code	L01CB01

Overview of comparator

Mechanism of action	Inhibits topoisomerase II, causing DNA strand breaks
Method of administration	IV, oral tablets
Dosing	200 mg/m ² , day 1-3
Dosing in the health economic model (including relative dose intensity)	200 mg/m ² , RDI:99 %
Should the medicine be administered with other medicines?	Yes Bleomycin 10 mg/m ² , day 8 Doxorubicin 35 mg/m ² , day 1 Cyclophosphamide 1.250 mg/m ² , day 1 Vincristine 1.4 mg/m ² (max 2 mg), day 8 Procarbazine 100 mg/m ² , day 1-7 Prednisone 40 mg/m ² , day 1-14
Treatment duration/ criteria for end of treatment	4 or 6 cycles dependent on response to treatment after 2 cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	IV strength 20 mg/ml; 5ml konc.t.inf. diluted liquid and 20 ml konc.t.inf. diluted liquid

Overview of comparator

Generic name	Doxorubicin
ATC code	L01DB01
Mechanism of action	Intercalates into DNA and inhibits topoisomerase II
Method of administration	IV
Dosing	35 mg/m ² , day 1
Dosing in the health economic model (including relative dose intensity)	35 mg/m ² , RDI:99 %

Overview of comparator

Should the medicine be administered with other medicines?

Yes

Bleomycin 10 mg/m², day 8
Etoposide 200 mg/m², day 1-3
Cyclophosphamide 1.250 mg/m², day 1
Vincristine 1.4 mg/m² (max 2 mg), day 8
Procarbazine 100 mg/m², day 1-7
Prednisone 40 mg/m², day 1-14

Treatment duration/ criteria for end of treatment

4 or 6 cycles dependent on response to treatment after 2 cycles.

Need for diagnostics or other tests (i.e. companion diagnostics)

No

Package size(s)

2mg/ml, 100 ml konc.t.inf.væsk.opl.

Overview of comparator

Generic name

Cyclophosphamide

ATC code

L01AA01

Mechanism of action

Alkylating agent causing DNA cross-linking

Method of administration

IV, oral tablets

Dosing

1.250 mg/m², day 1

Dosing in the health economic model (including relative dose intensity)

1.250 mg/m², RDI: 99 %

Should the medicine be administered with other medicines?

Yes

Bleomycin 10 mg/m², day 8
Etoposide 200 mg/m², day 1-3
Doxorubicin 35 mg/m², day 1
Vincristine 1.4 mg/m² (max 2 mg), day 8
Procarbazine 100 mg/m², day 1-7
Prednisone 40 mg/m², day 1-14

Treatment duration/ criteria for end of treatment

4 or 6 cycles dependent on response to treatment after 2 cycles.

Need for diagnostics or other tests (i.e. companion diagnostics)

No

Overview of comparator

Package size(s)	1 htg. a 500 mg pulv.t.inj.fluid, solution
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Overview of comparator

Generic name	Vincristine
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ATC code	L01CA02
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Mechanism of action	Inhibits microtubule formation, preventing mitosis
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Method of administration	IV
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Dosing	1.4 mg/m ² (max 2 mg), day 8
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Dosing in the health economic model (including relative dose intensity)	1.4 mg/m ² , RDI: 93 %
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Should the medicine be administered with other medicines?	Yes Bleomycin 10 mg/m ² , day 8 Etoposide 200 mg/m ² , day 1-3 Doxorubicin 35 mg/m ² , day 1 Cyclophosphamide 1.250 mg/m ² , day 1 Procarbazine 100 mg/m ² , day 1-7 Prednisone 40 mg/m ² , day 1-14
---	---

Treatment duration/ criteria for end of treatment	4 or 6 cycles dependent on response to treatment after 2 cycles.
---	--

Need for diagnostics or other tests (i.e. companion diagnostics)	No
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Package size(s)	1mg/ml, 1 ml injection fluid solution
-----------------	---------------------------------------

Overview of comparator

Generic name	Procarbazine
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ATC code	L01XB01
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Mechanism of action	Alkylating agent interfering with DNA replication
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Method of administration	Oral capsules
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Dosing	100 mg/m ² , day 1-7
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Overview of comparator

Dosing in the health economic model (including relative dose intensity) 100 mg/m², RDI:97 %

Should the medicine be administered with other medicines? **Yes**
Bleomycin 10 mg/m², day 8
Etoposide 200 mg/m², day 1-3
Doxorubicin 35 mg/m², day 1
Cyclophosphamide 1.250 mg/m², day 1
Vincristine 1.4 mg/m² (max 2 mg), day 8
Prednisone 40 mg/m², day 1-14

Treatment duration/ criteria for end of treatment 4 or 6 cycles dependent on response to treatment after 2 cycles.

Need for diagnostics or other tests (i.e. companion diagnostics) No

Package size(s) 50mg, 50 tablets

Overview of comparator

Generic name Prednisone

ATC code H02AB07

Mechanism of action Anti-inflammatory and immunosuppressant; binds to glucocorticoid receptors

Method of administration Oral tablets

Dosing 40 mg/m², day 1-14

Dosing in the health economic model (including relative dose intensity) 40 mg/m², RDI: 98 %

Should the medicine be administered with other medicines? **Yes**
Bleomycin 10 mg/m², day 8
Etoposide 200 mg/m², day 1-3
Doxorubicin 35 mg/m², day 1
Cyclophosphamide 1.250 mg/m², day 1
Vincristine 1.4 mg/m² (max 2 mg), day 8
Procarbazine 100 mg/m², day 1-7

Treatment duration/ criteria for end of treatment 4 or 6 cycles dependent on response to treatment after 2 cycles.

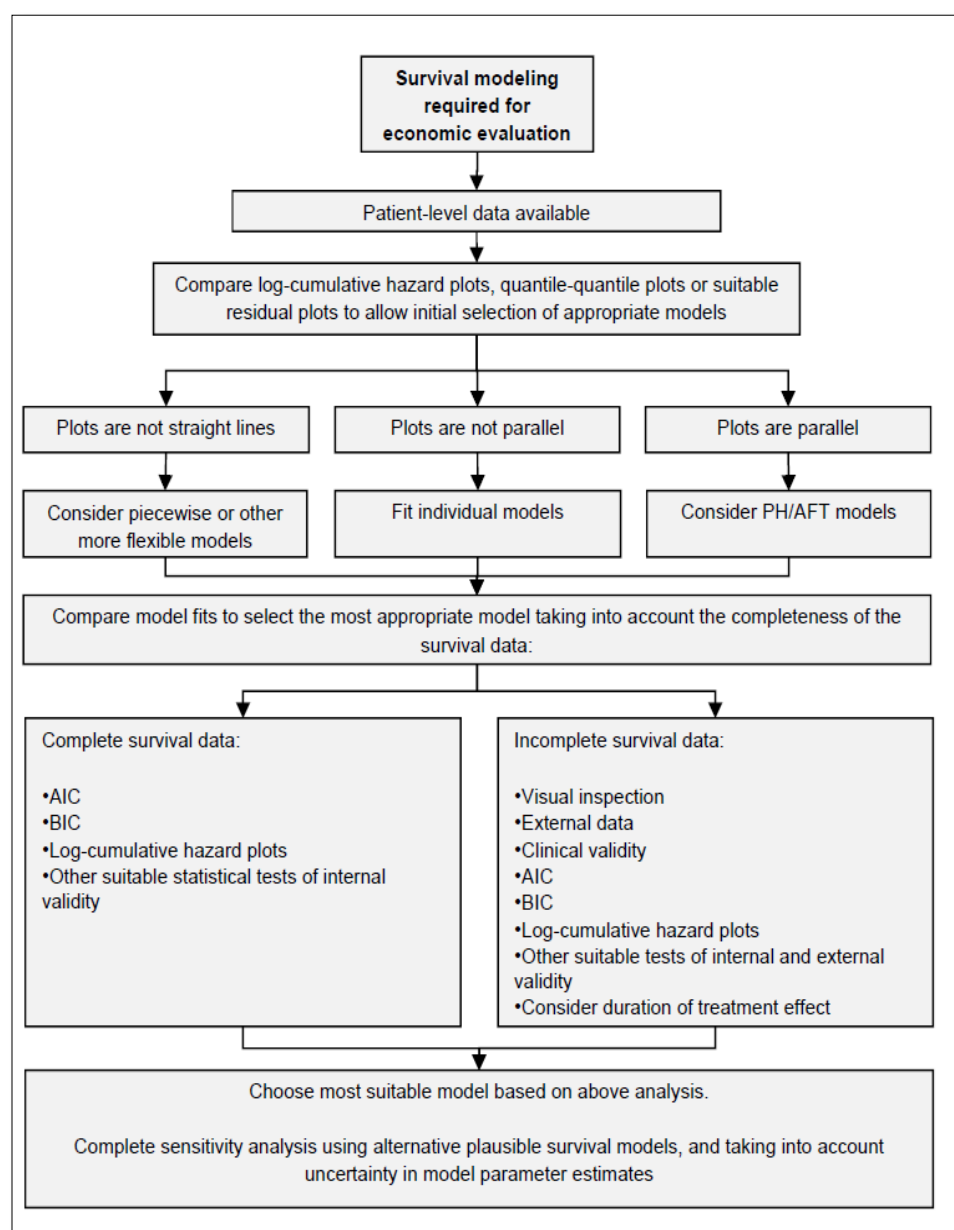
Overview of comparator

Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	5mg, 100 stk. Tablets

Appendix P. Tables and figures related to the health economic analysis

P.1 Section 8.1

Figure 42 Survival model selection process algorithm by the NICE Decision Support Unit Technical Services Document 14



P.2 Section 8.1.1.1

Figure 43 KM plot for OS

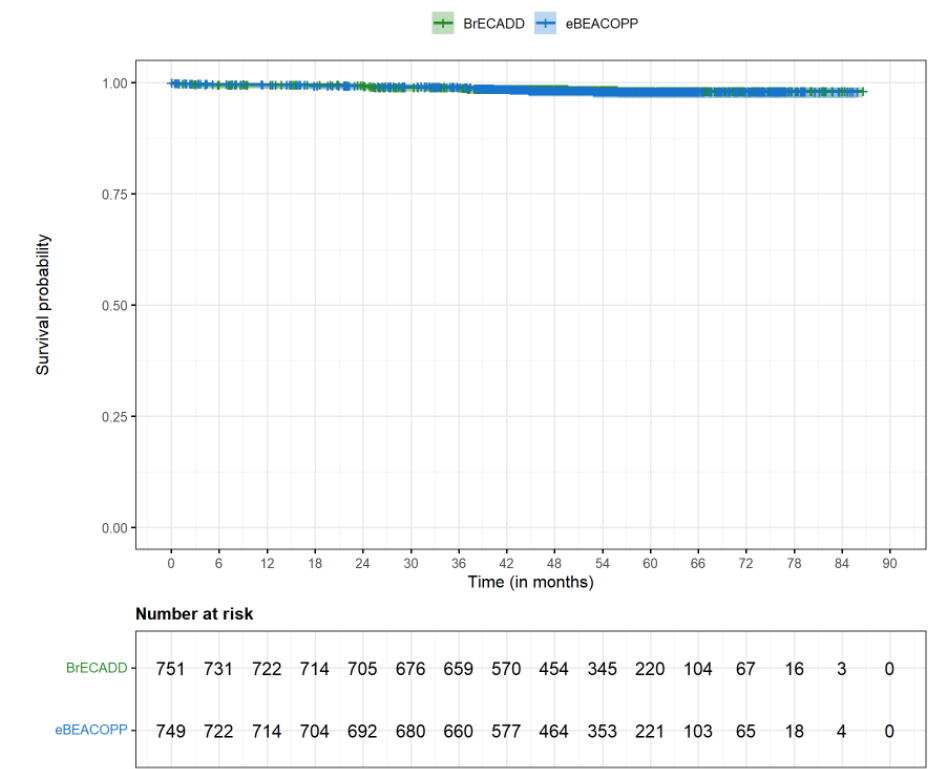


Figure 44



Figure 45 KM plot for PFS

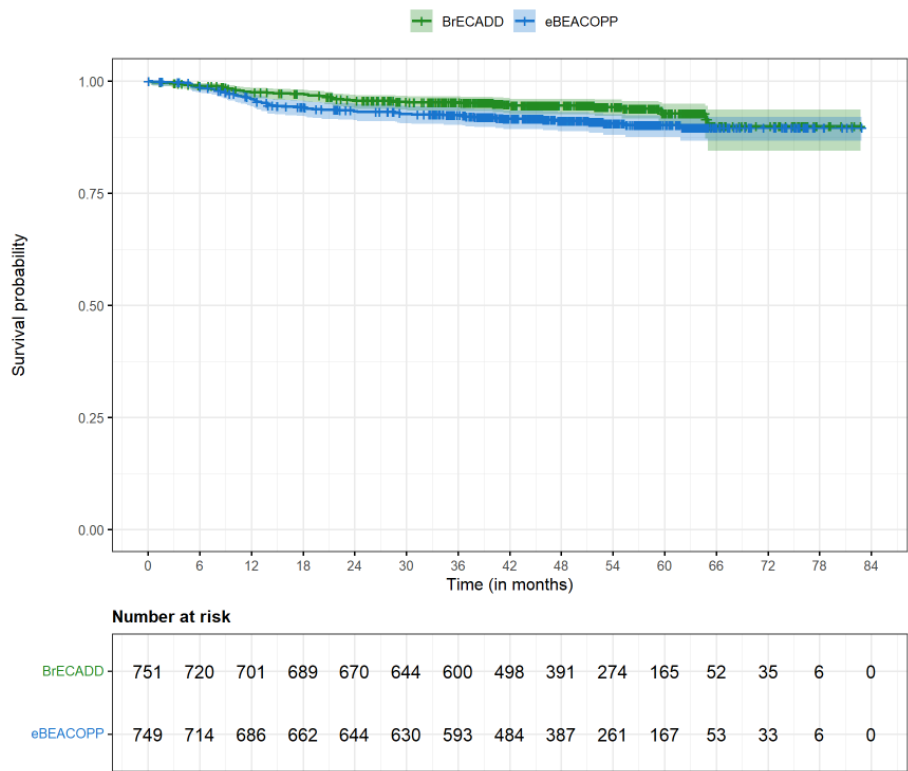
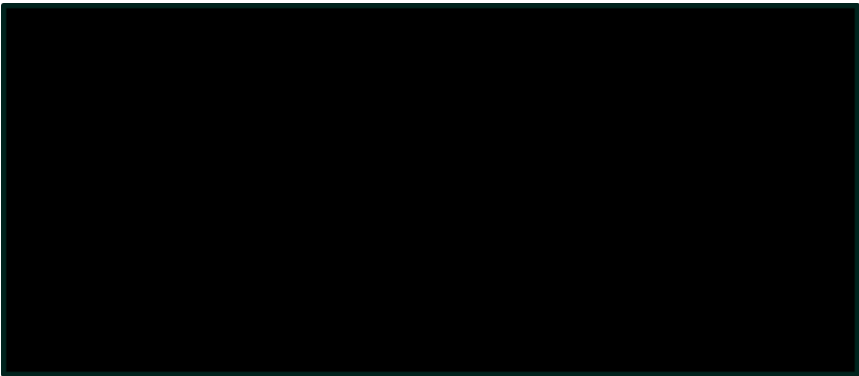


Figure 46



Appendix Q. Age dependent incidence and survival of HL in Denmark (2019-2023)

Figure 47 Age dependent incidence of HL in Denmark (2019-2023) (26).

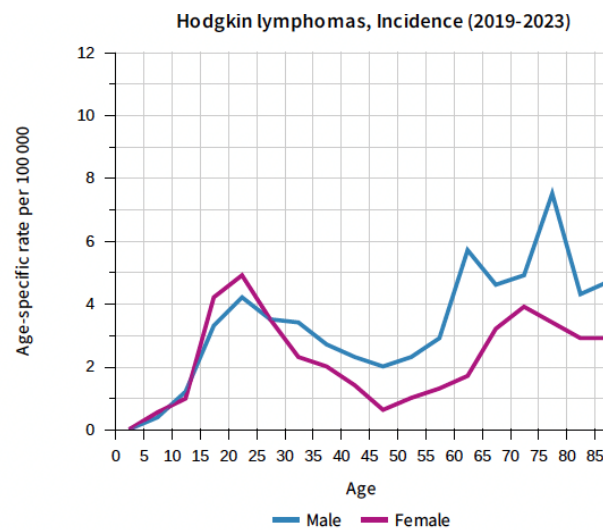
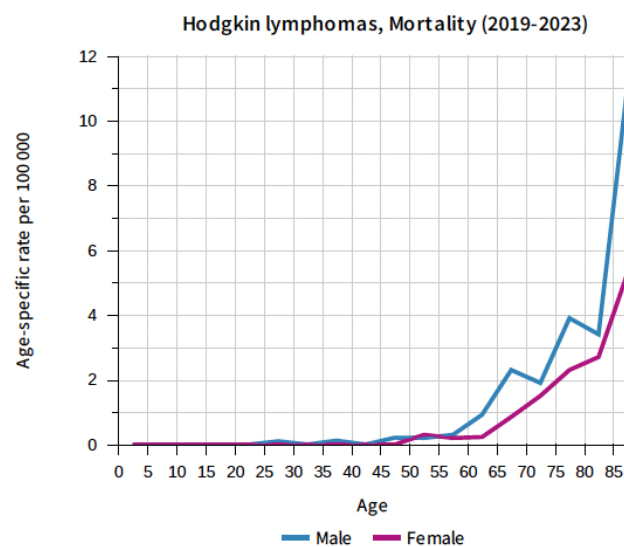


Figure 48 Age dependent mortality of HL in Denmark (2019-2023) (26).



Appendix R. Study design and CONSORT diagram for the HD21 study.

Figure 49 Study overview of HD21

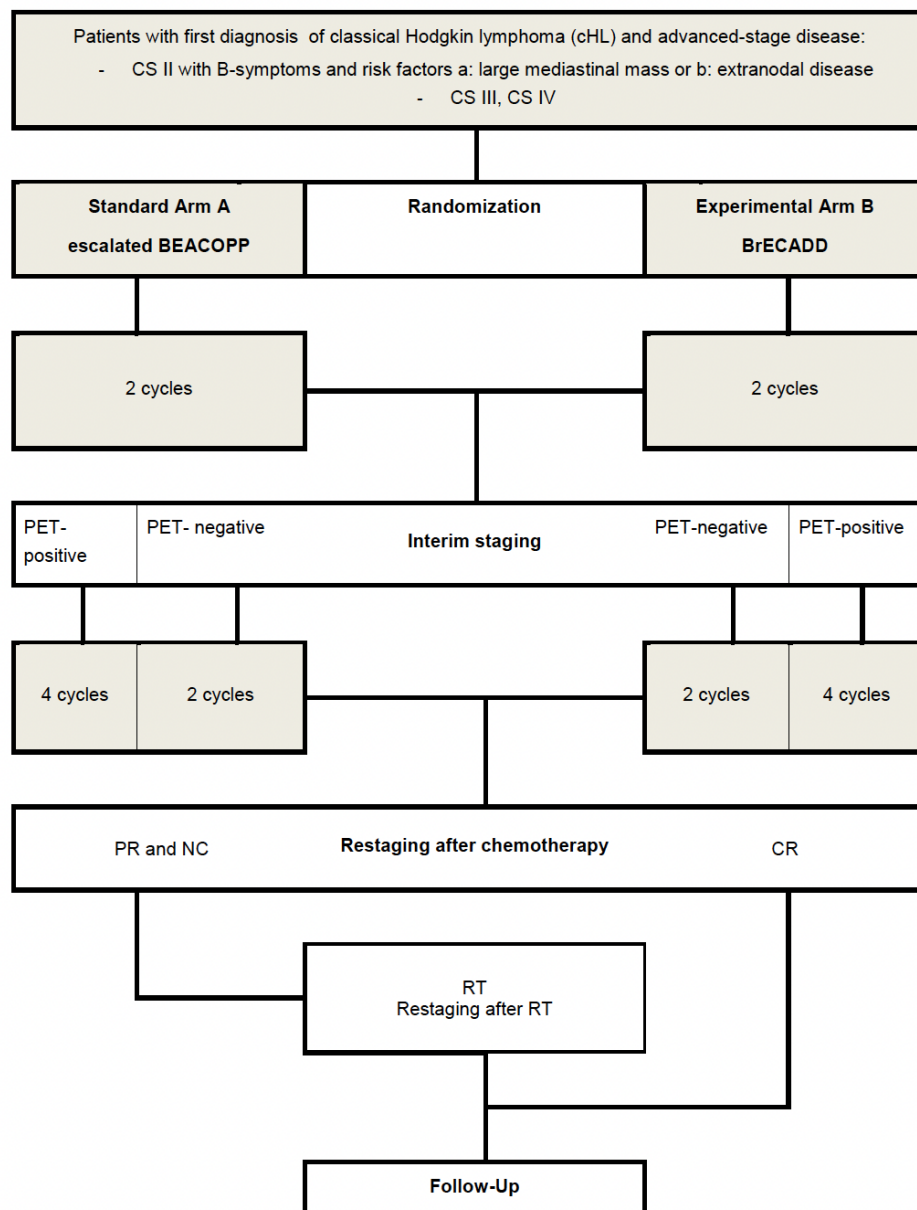
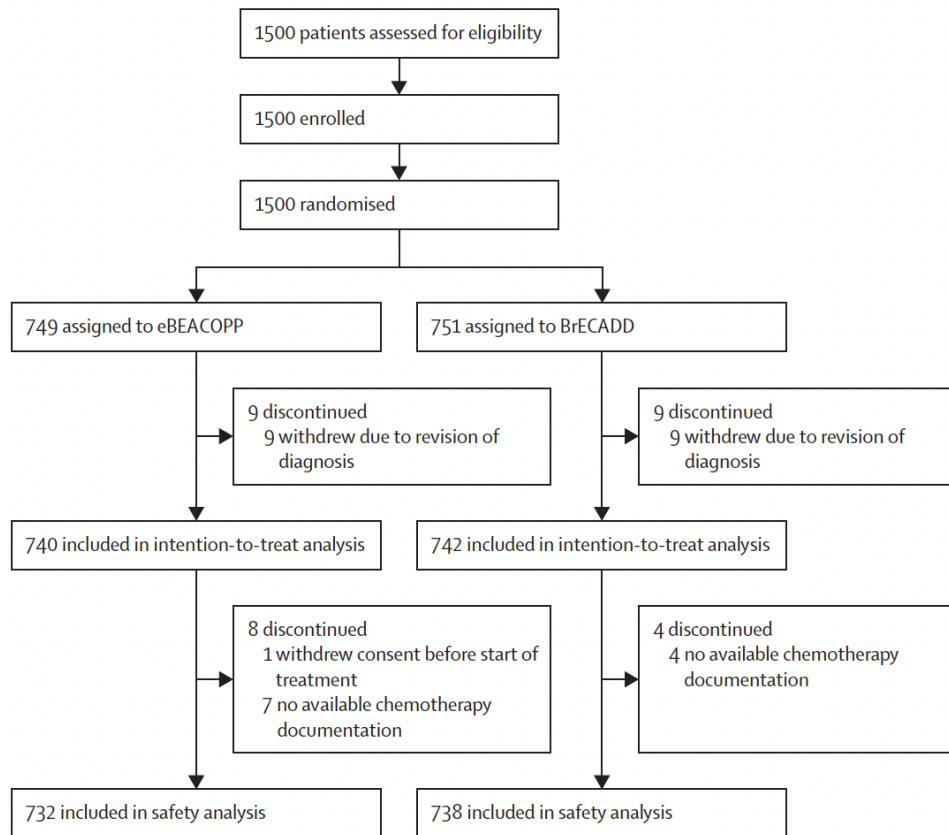


Figure 50 CONSORT diagram for HD21 study



Appendix S. Enlarged figures

The below figures are enlarged versions of figure 7A-B and 8A-B, as denoted respectively.

Figure 7A: Time to recovery of gonadal functions, females.

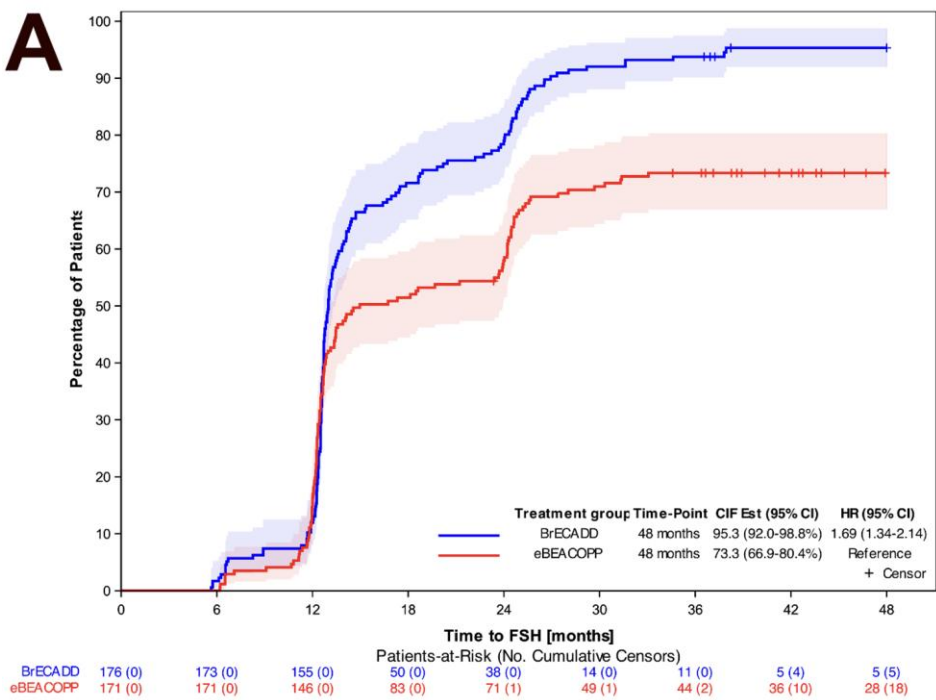


Figure 7B: Time to recovery of gonadal function, males.

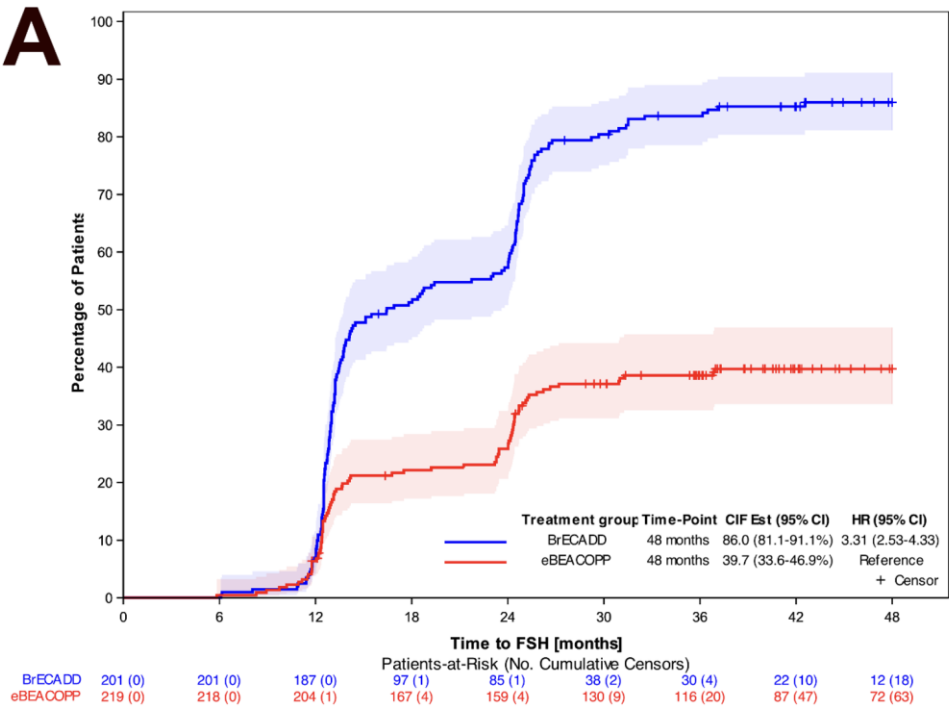


Figure 8A: Time to first parenthood, females.

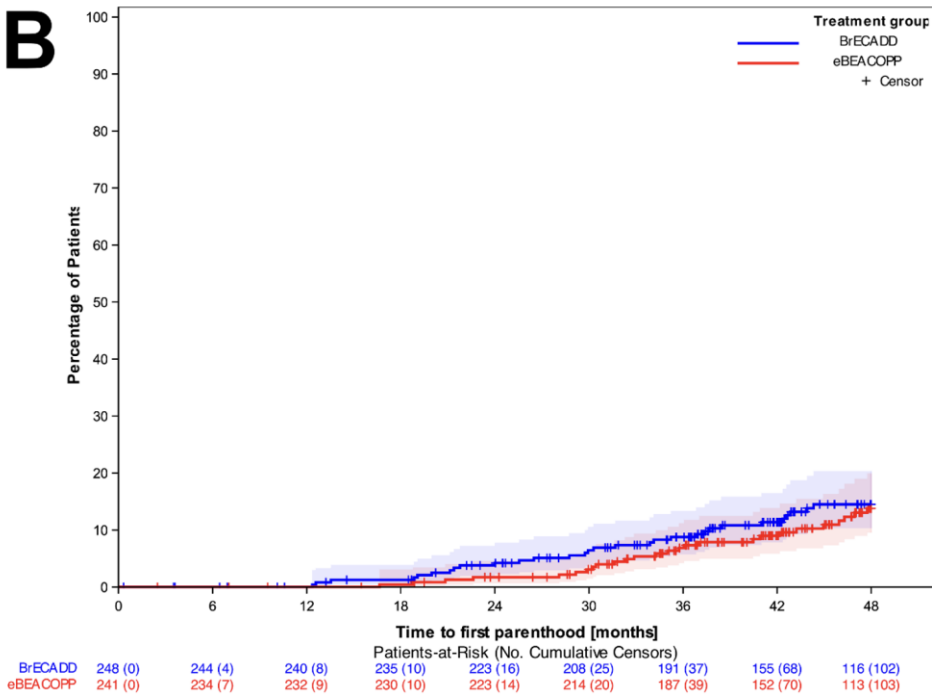
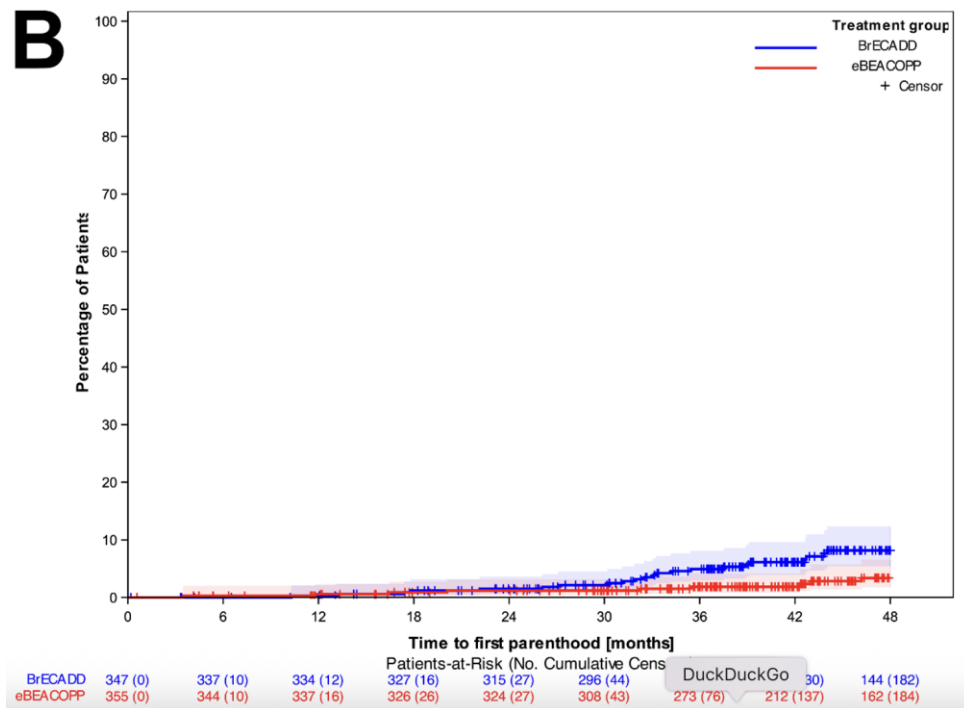
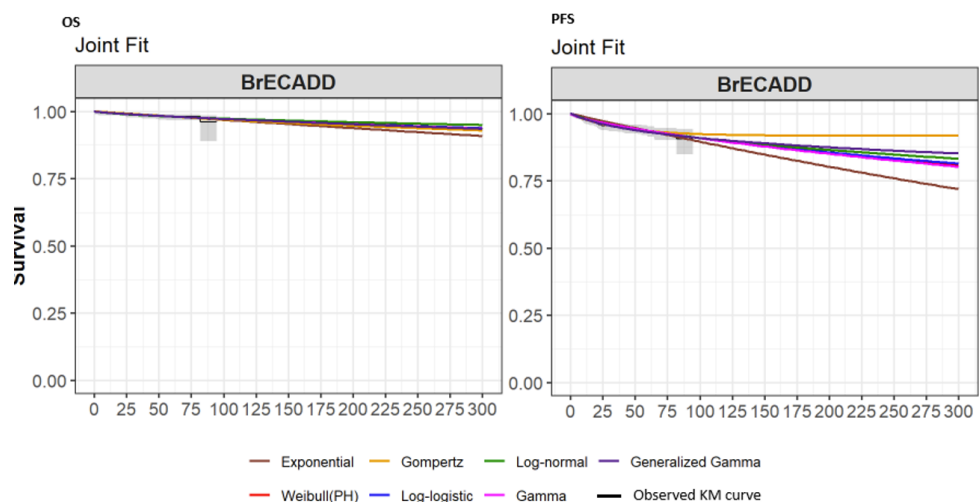


Figure 8B: Time to first parenthood, males.



S.1 Appendix: Figures showing the different extrapolations and Kaplan–Meier curves for OS and PFS



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