Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende polatuzumab vedotin til førstelinjebehandling af diffust storcellet B-cellelymfom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. polatuzumab vedotin
2. Forhandlingsnotat fra Amgros vedr. polatuzumab vedotin
3. Ansøgers endelige ansøgning vedr. polatuzumab vedotin

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Til Medicinrådet

Høringssvar fra Roche Pharmaceuticals vedrørende Medicinrådets udkast til vurdering af Polivy (polatuzumab vedotin) til behandling af førstelinje patienter med DLBCL

Roche Pharmaceuticals takker for det fremsendte udkast til vurderingsrapporten vedrørende Polivy (polatuzumab vedotin), som vi modtog d. 12. maj 2023. Vi har dog en række bemærkninger til vurderingsrapporten, som vi overordnet er skeptiske overfor og takker derfor for muligheden for at fremføre vores perspektiv på sagen.

Eventfri overlevelse (EFS24) og progressionsfri overlevelse (PFS24) efter 24 måneder som surrogatmål for overlevelse (OS)

EFS24 og PFS24 er validerede endepunkter indenfor diffust storcellet B-celle lymfom (DLBCL), som anvendes rutinemæssigt som milepæl til at afslutte opfølgning af patienter efter behandling i første linje - dvs. patienter herefter betragtes som helbredte. I den indsendte ansøgning præsenteres en række studier (både randomiserede, kontrollerede forsøg og observationelle studier), der illustrerer betydningen af EFS24 og PFS24 for OS. Alle studierne viser, at EFS og PFS er stærkt korreleret med OS og specifikt, at OS ved opnåelse af EFS24 og PFS24 for patienter med DLBCL er sammenlignelig med baggrundsbefolkningen. Studierne viser og konkluderer på den baggrund, at EFS24 og PFS24 kan anvendes som surrogatmål for OS i kliniske studier, hvilket er tilfældet i POLARIX-studiet. Den tilgængelige evidens tæller også et stort dansk studie med medlemmer af Medicinrådets fagudvalg vedrørende lymfekræft som forfattere [1]. Her konkluderes ligeledes, at OS for patienter med DLBCL efter opnåelse af EFS24 er sammenlignelig med baggrundsbefolkningen i Danmark.

I vurderingsrapporten vælger Medicinrådet at se bort fra den tilgængelige evidens for PFS24/EFS24 som surrogatmål for OS, og sætter i stedet OS for patienter i behandling med polatuzumab vedotin i kombination med rituximab, cyclophosphamid, doxorubicin og prednison (pola-R-CHP) lig med OS for patienter i behandling med rituximab, cyclophosphamid, doxorubicin, vincristin og prednison (R-CHOP) på trods af en 10,1%-points forskel [2,2; 17,9] i PFS efter 24 måneder for patienter i den ansøgte population (IPI-score 3-5). En effekt som kliniske eksperter i Danmark beskriver som synlig, væsentlig og signifikant. Dette underbygges endvidere af, at færre patienter fra POLARIX-studiet i behandling med pola-R-CHOP havde behov for yderligere behandlingslinjer end patienter i behandling med R-CHOP [2]. Baseret på POLARIX-studiet kan det således konkluderes, at pola-R-CHP reducerer andelen af patienter med relaps og antallet af systemiske behandlinger.

HTA-institutter andre steder i Europa (herunder NICE i England) har vurderet det danske studie vedrørende EFS24 som troværdig og valid evidens, og netop dette studie har været medvirkende til, at NICE modellerer og forventer en OS-gevinst ved pola-R-CHP. I hovedanalysen fra NICE regnes med en QALY-gevinst på **0,44 QALY** for patienter med IPI-score 2-5. Det er i stor kontrast til den hovedanalyse som Medicinrådet har foretaget, hvor der kun estimeres en QALY-gevinst på 0,02 på trods af, at ansøgningen er restrikteret til kun at indeholde patienter med IPI-score 3-5, som er den population som forventes at have størst gavn af pola-R-CHP.

Medicinrådets tilgang modsiger dermed den tilgængelige evidens vedrørende PFS24/EFS24 som surrogatmål for OS og underminerer samtidig evidens produceret af fagudvalgets medlemmer. Roche er

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af den årsag meget kritiske overfor den valgte tilgang og stiller spørgsmålstegn ved, hvorvidt Medicinrådet har forholdt sig til den tilgængelige evidens på området.
Roche opfordrer derfor Medicinrådet til at kigge nærmere på den tilgængelige evidens og genoverveje, hvorvidt den valgte tilgang er rimelig.

Kandidater til pola-R-CHP

Roche har ansøgt Medicinrådet om anbefaling af pola-R-CHP som standardbehandling til patienter med IPI-score 3-5, og har i den forbindelse naturligvis indsendt data for denne population. Medicinrådet fremhæver i vurderingen heraf, at alle patienter under 60-65 år med IPI-score 3-5 vil være kandidater til R-CHOEP, og at dette udgør en generel usikkerhed i analysen, da der i POLARIX-studiet sammenlignes med R-CHOP. Vi er enige i, at der kan være nogle af disse patienter, som potentielt vil modtage R-CHOEP, men det er ikke alle. Danske kliniske eksperter fremhæver, at aldersintervallet 60-65 er en gråzone, hvor nogle patienter ikke kan tåle etoposid f.eks. grundet komorbiditeter, men stadig vil være kandidater til behandling med pola-R-CHP. Vi mener derfor, at det er vigtigt, at Medicinrådet forholder sig til disse patienter frem for at anskue det som en generel usikkerhed. I sidste ende vil det alligevel være en lægefaglig vurdering, hvorvidt en patient skal behandles med R-CHOEP eller pola-R-CHP.

I Medicinrådets vurderingsrapport fremgår det, at kun et fåtal af patienter reelt vil blive behandlet med pola-R-CHP ved en anbefaling, men uden yderligere præcisering af hvilke patienter der anses som kandidater. Roche opfordrer til at præcisere den population, som Medicinrådet finder relevant. Roche er indstillet på at indgå i en dialog med Medicinrådet, såfremt Medicinrådet ønsker at begrænse populationen - og ligeledes levere data i det omfang det er tilgængeligt.

Andre økonomiske overvejelser

POLARIX-studiet er et stort randomiseret fase 3 studie, der som det første kliniske studie i over 20 år har dokumenteret en signifikant effekt hos DLBCL-patienter i førstelinjebehandling.
Som beskrevet får færre patienter i behandling med pola-R-CHP relaps sammenlignet med patienter i behandling med R-CHOP. Dette underbygges yderligere af, at færre patienter i behandling med pola-R-CHP kræver efterfølgende systemiske behandlinger.

Med flere komplekse og dyre lægemidler allerede under vurdering i Medicinrådet i efterfølgende linjer (CAR-T og bispecifikke antistoffer) er en reducering af andelen af patienter med relaps ikke kun ønskværdigt fra et klinisk og patient perspektiv, men også fra et økonomisk og ressourcemæssigt perspektiv. Et fravalg af pola-R-CHP i dag kan have store økonomiske konsekvenser i fremtiden, når dyre og ressourcekrævende lægemidler i senere linjer bliver introduceret - netop som det er set i andre nordiske lande, hvor CAR-T er taget i brug [3].

Mvh
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[1] Jakobsen, Lasse Hjort et al. “Minimal Loss of Lifetime for Patients With Diffuse Large B-Cell Lymphoma in Remission and Event Free 24 Months After Treatment: A Danish Population-Based Study.” Journal of clinical oncology : official journal of the American Society of Clinical Oncology vol. 35,7 (2017): 778-784. doi:10.1200/JCO.2016.70.0765

[2] Tilly, Hervé et al. “Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma.” The New England journal of medicine vol. 386,4 (2022): 351-363. doi:10.1056/NEJMoa2115304

[3] Koski, Lotta et al. “The Burden Of R/R DLBCL In Finland: PFS Of The First-Line Immunochemotherapy And HCRU Of The Patients Diagnosed In 2015–2017 In The Hospital District Of Southwest Finland” ISPOR Europe, Nov 6-9, 2022, Vienna, Austria. Abstract nr RWD109

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21.06.2023
CAF/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.06.2023
Leverandør	Roche
Lægemiddel	Polivy (polatuzumab vedotin)
Ansøgt indikation	Polatuzumab vedotin i kombination med rituximab, cyklofosfamid, doxorubicin og prednison (R-CHP) er indiceret til behandling af voksne patienter med tidligere ubehandlet diffust storcellet B-cellelymfom (DLBCL).
Nyt lægemiddel/indikationsudvidelse	Indikationsudvidelse

Prisinformation

Amgros har forhandlet følgende pris på Polivy (polatuzumab vedotin):

Tabel 2: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Polivy	140 mg	1 stk.	69.133,18	[redacted]	[redacted]
Polivy	30 mg	1 stk.	14.814,26	[redacted]	[redacted]

[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler inkluderet i Medicinrådets vurderingsrapport.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift, 6 cykler (SAIP, DKK)
Polivy	140 mg	1 stk.	1,8 mg/kg IV* 6 gange i 21 dages cykler	[redacted]	[redacted]
Rituximab	500 mg	1 stk.	375 mg/m^2** IV 6 gange i 21 dages cykler	[redacted]	[redacted]
Cyclophosphamid	1 g	1 stk.	750 mg/m^2**IV 6 gange i 21 dages cykler	[redacted]	[redacted]
Doxorubicin	2 mg/ml	100 ml	50 mg/m^2** IV 6 gange i 21 dages cykler	[redacted]	[redacted]
Vincristin	1 mg/ml	2 ml	1,4 mg/m^2** IV 6 gange i 21 dages cykler	[redacted]	[redacted]
Prednison	25 mg	100 stk.	100 mg PO på dag 1-5 i hver 21 dages cyklus	[redacted]	[redacted]

*Gennemsnitsvægt 70 kg
**Overfladeareal 1,9 m^2

Tabel 3 viser lægemiddeludgifterne for behandlingsregimerne Polivy i kombination med rituximab, cyklofosfamid, doxorubicin og prednison (pola-R-CHP) og kombinationen rituximab, cyklofosfamid, doxorubicin, vincristin og prednison (R-CHOP).

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Behandlingsregime	Lægemiddeludgifter for 6 cykler (SAIP, DKK)
Pola-R-CHP	[redacted]
R-CHOP	[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Under vurdering		Link til status
Sverige	Under vurdering		Link til status
England	Anbefalet	Anbefalet til patienter med en IPI-score på 2-5	Link til anbefaling

Konklusion

[redacted].

Application for the assessment of polatuzumab vedotin (Polivy) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for first-line treatment of diffuse large B-cell lymphoma

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1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Polivy
Generic name	Polatuzumab vedotin

Overview of the pharmaceutical	
Marketing authorization holder in Denmark	Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen, Tyskland
ATC code	L01FX14
Pharmacotherapeutic group	Antineoplastic agents; other antineoplastic agents; monoclonal antibodies
Active substance	Polatuzumab vedotin
Pharmaceutical form	Powder for concentrate for solution for infusion
Mechanism of action	Polatuzumab vedotin is a CD79b- targeted antibody-drug conjugate that preferentially delivers a potent anti-mitotic agent (monomethyl auristatin E, or MMAE) to B- cells, which results in the killing of malignant B-cells. The polatuzumab vedotin molecule consists of MMAE covalently attached to a humanised immunoglobulin G1 monoclonal antibody via a cleavable linker. The monoclonal antibody binds with high affinity and selectivity to CD79b, a cell surface component of the B-cell receptor. CD79b expression is restricted to normal cells within the B- cell lineage (with the exception of plasma cells) and malignant B-cells; it is expressed in >95% of diffuse large B- cell lymphoma. Upon binding CD79b, polatuzumab vedotin is rapidly internalised and the linker is cleaved by lysosomal proteases to enable intracellular delivery of MMAE. MMAE binds to microtubules and kills dividing cells by inhibiting cell division and inducing apoptosis.
Dosage regimen	The recommended dose of Polivy is 1.8 mg/kg, given as an intravenous infusion every 21 days in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for 6 cycles.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Polivy in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL).
Other approved therapeutic indications	Polivy in combination with bendamustine and rituximab is indicated for the treatment of adult patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) who are not candidates for haematopoietic stem cell transplant.
Will dispensing be restricted to hospitals?	Yes.
Combination therapy and/or co-medication	Combination therapy with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP).

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	**Polivy 30 mg powder for concentrate for solution for infusion** Each vial of powder for concentrate for solution for infusion contains 30 mg of polatuzumab vedotin. After reconstitution, each mL contains 20 mg of polatuzumab vedotin. **Polivy 140 mg powder for concentrate for solution for infusion** Each vial of powder for concentrate for solution for infusion contains 140 mg of polatuzumab vedotin. After reconstitution, each mL contains 20 mg of polatuzumab vedotin.
Orphan drug designation	Yes

2. Abbreviations

Abbreviation	
1L	First line
2L	Second line
acMMAE	Antibody-Conjugated Mono-Methyl Auristatin E
ADA	Anti-Drug Antibody
AE	Adverse event
AIC	Akaike Information Criterion
ALK	Anaplastic lymphoma kinase
ASCT	Autologous Stem Cell Transplantation
BCL2	B-cell lymphoma 2
BCL6	B-cell lymphoma 6
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
CD20	Cluster of differentiation 20
CEAC	Cost-effectiveness acceptability curve
CNS	Central nervous system
CR	Complete response
CTC	Common Terminology Criteria
DFS	Disease-Free Survival
DLBCL	Diffuse large B-cell lymphoma

DLG	Danish Lymphoma Group
DMC	Danish Medicines Council
DMCG	Danish Multidisciplinary cancer group
DRG	Diagnosed related groups
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS_{all}	Event-Free Survival-All Causes
EFS_{eff}	Event-Free Survival-Efficacy
EMA	European Medicine Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life-Core 30 Questionnaire
EPAR	European public assessment report
ETTV	Early treatment termination visit
FACT/GOG-NTX	Functional Assessment of Cancer Treatment/Gynecologic Oncology Group-Neurotoxicity
FACT-Lym LymS	Functional Assessment of Cancer Therapy-Lymphoma Lymphoma Subscale
FDG-PET	Fluorodeoxyglucose Positron Emission Tomography
HHV8	Human herpesvirus-8
HIV	Human immunodeficiency virus
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health-related quality of life
HSUV	Health-state utility value
HTLV-1	Human T-lymphotrophic 1 virus
IF-RT	Involved-field radiation therapy
iPET	Positron Emission Tomography
IPI	Inventory Performance Index
IV	Intravenously
LVEF	Left ventricular ejection fraction
KM	Kaplan Meier
MMAE	Monomethyl auristatin E
MUGA	Multiple-gated acquisition
NA	Not applicable
NALT	New anti-lymphoma therapy
NHL	Non-Hodgkin lymphoma

NOS	Not otherwise specified
NR	Not reached
OS	Overall survival
PD	Progression of disease
PET-CT	Positron Emissions Tomography – Computerized Tomography
PFS	Progression-free survival
PH	Proportional hazard
PO	Per Oral
Pola+BR	Polatuzumab + bendamustine and rituximab
Pola+R-ICE	Polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide
Pola+R-CHP	Polatuzumab-rituximab-cyclophosphamide, doxorubicin, and prednisone
PPS	Post-progression survival
RCT	Randomized clinical trial
R/R	Relapse or refractory
R-Benda	Rituximab + Bendamustine
R-CHOP	Rituximab-Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone
R-CHOEP	Rituximab-Cyclophosphamide, Doxorubicin, Vincristine etoposide, and Prednisone
R-CHP	Rituximab, cyclophosphamide, doxorubicin, and prednisone
R-DHAP	Rituximab + Dexamethasone, Cytarabine, and Cisplatin
R-GDP	Rituximab + Gemcitabine, Cisplatin, and Dexamethasone
R-GemOx	Rituximab + Gemcitabine and Oxaliplatin
R-ICE	Rituximab + Ifosfamide, Carboplatin, and Etoposide
RKKP	Regions' Clinical Quality Development Programme
SC	Subcutaneously
TCV	Treatment completion visit
TTOT	Time to off treatment
WHO	World Health Organization

3. Tables and Figures

[redacted]

[redacted]

4. Summary

4.1 Introduction

On May 25, 2022, the European Commission (EC) approved polatuzumab vedotin (Polivy) in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (R-CHP) for the treatment of adult patients with previously untreated diffuse large B-cell lymphoma (DLBCL). The approval is based on results from POLARIX, a multicentre, randomised, double-blind, placebo-controlled phase 3 study designed to investigate the efficacy, safety, pharmacokinetics and patient-reported outcomes of polatuzumab vedotin (Pola) in combination with rituximab plus cyclophosphamide, doxorubicin and prednisone (R-CHP) compared to rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) in patients with previously untreated DLBCL. This application, submitted to the Danish Medicines Council (DMC) on October 14, 2022, provides the basis for the assessment of polatuzumab vedotin in comparison with Danish standard of care.

For the majority of Danish patients in the first-line setting, R-CHOP is the standard of care. Since the introduction of R-CHOP 20 years ago, no new treatment options for previously untreated DLBCL patients have been introduced. Initial treatment with R-CHOP cures about 60-70% of patients, however about 30-40% relapse or are refractory to treatment. For patients who are not cured with first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) offers a second chance for cure. However, this is only available for younger, fit patients who demonstrate chemosensitive disease. Thus, optimising the initial treatment options in the first-line setting with curative intent would have a substantial impact on the disease burden.

According to Danish clinical experts there is especially a need for better treatment options for patients with poor prognosis, in particular older patients with aaIPI score 2-3 (corresponding to IPI score 3-5) who are currently being treated with R-CHOP and who cannot receive an intensified treatment with the addition of etoposide. These patients are therefore considered to be the main candidates for polatuzumab vedotin in combination with R-CHP in the first-line setting and will be the scope of this application.

4.2 Clinical assessment

METHODS: The assessment is based on one clinical question defined by PICO, addressing the efficacy and safety of pola+R-CHP compared to R-CHOP in adult patients with previously untreated DLBCL and baseline aaIPI score 2-3, corresponding to IPI score 3-5. In POLARIX, 62% of patients had IPI score 3-5. The distinction between IPI score 2 vs 3-5 was one of the main stratification factors in the study. As POLARIX directly compares Pola+R-CHP with the comparator relevant in Danish clinical practice, and provides sufficient documentation for efficacy and safety in the relevant patient population, a literature search for additional evidence has not been performed.

Efficacy results, including progression-free survival (PFS), event-free survival (EFS), and complete response (CR) from the primary (and final) PFS analysis of POLARIX (June 28, 2021) and overall survival (OS) from the interim OS analysis (June 28, 2021) and the final OS analysis (June 15, 2022), are reported for the ITT population with IPI score 2-5 and the subpopulation with IPI score 3-5. Health-related quality of life as assessed by EORTC QLQ-C30 and FACT-Lym LymS is reported for the ITT population. Safety outcomes, including adverse events (AEs) by severity, serious AEs (SAEs) and discontinuation due to AEs, are reported for the safety-evaluable populations with IPI score 2-5 and IPI score 3-5. In addition, a qualitative description of the safety profiles are included.

RESULTS: POLARIX met its primary endpoint at the PFS protocol-specified primary analysis, showing a statistically significant improvement in PFS for pola+R-CHP vs. R-CHOP in patients with DLBCL and baseline IPI score 2-5 (aaIPI score 1-3). The greatest magnitude of PFS benefit was seen in the IPI score 3-5 subgroup (stratified hazard ratio (HR) was 0.65 (95% CI, 0.47 to 0.88; p=0.0053). Median PFS was not reached. Similar to the IPI score 2-5 population, a higher proportion of patients were alive and progression free at the 1- and 2-year milestones in the pola+R-CHP arm compared with R-CHOP arm in the IPI score 3-5 population (81.5% vs. 76.2% at 1 year and 75.2% vs. 65.1% at 2 years). At the time of the final OS analysis with an additional 12 months of follow-up, only few additional PFS events had occurred, which supports that the majority of disease relapse or progression occurs within 24 months of initiation of therapy. Results for EFS in both the IPI score 2-5 and the IPI score 3-5 population were highly consistent with the results of PFS and supportive of the clinical benefit for pola+R-CHP compared with R-CHOP. Results from the final OS analysis were consistent with results from interim analysis at the first CCOD. Results remained immature with a low event-to-patient ratio. The stratified HR was 0.90 (95%, 0.61 to 1.34; p=0.61) in the IPI 3-5 subgroup. Similar to the IPI score 2-5 population, the proportion of patients alive at the 1- and 2-year milestones in the IPI score 3-5 population did not differ between the Pola+R-CHP and R-CHOP arms (90.4% vs. 93.6% at 1 year and 86.7% vs. 85.5% at 2 years). However, these results are to be expected due to the advent of new, effective treatment for relapsed or refractory DLBCL in recent years. Importantly, evidence derived from randomised controlled trials (RCTs) has shown PFS and EFS to be valid surrogates for OS. Patients who remain progression-free 24 months post initiation of first-line treatment have a survival that is comparable to the general population.

Treatment with pola+R-CHP resulted in a delay in deterioration of patient-reported physical functioning and fatigue compared with R-CHOP. Overall, patients on Pola+R-CHP were able to maintain aspects of their baseline health-related quality of life (HRQoL) and experienced an improvement in disease-related symptoms after starting treatment.

The pola+R-CHP regimen was generally well tolerated and toxicities were manageable. The safety profile of Pola+R-CHP was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease. No new safety signals were identified.

CONCLUSION: Pola+R-CHP is the first approved treatment in first-line DLBCL to demonstrate a significant and clinically meaningful benefit over the standard of care, R-CHOP, since its introduction. The greatest magnitude of PFS benefit was observed in the IPI score 3-5 subgroup. Importantly, the Pola+R-CHP regimen was generally well tolerated and toxicities were manageable, and aspects of HRQoL was maintained.

4.3 Health economic assessment

A cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of Polatuzumab + Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola+R-CHP) vs. Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) for patients with diffuse large B-cell lymphoma (DLBCL) with the Inventory Performance Index of 3-5. A partitioned survival model approach was used and informed by data from the most recent data-cut from June 2022 of the POLARIX trial [1,2]. Model outcomes include life years (LYs), quality-adjusted life years (QALYs), costs of drug acquisition, administration, supportive care costs, AE management cost, patient- and transportation cost, cost per LY gained and cost per QALY gained. Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were used to investigate the uncertainty of the model parameters.

As per the Danish Medicines Council (DMC) guidance, the cost-effectiveness analysis applied a restricted Danish societal perspective, using the best available clinical and economic evidence. Local Danish data inputs were used wherever available. The current model was based on results from the POLARIX trial.

In the base case analysis, Pola+R-CHP resulted in QALYs gained in comparison to R-CHOP. Costs associated with Pola+R-CHP were higher compared to R-CHOP for the health state PFS, however lower for Pola+R-CHP compared to R-CHOP in the PD health state. This was explained by the higher proportion of patients remaining in the PFS health state in the Pola+R-CHP arm versus the R-CHOP arm, underlining the new intervention's effectiveness compared to current standard treatment in Denmark. The base-case ICER resulted in [redacted] per QALY at AIP level.

[redacted]

5. The patient population, the intervention and choice of comparator

5.1 The medical condition and patient population

5.1.1 Disease condition

Non-Hodgkin's lymphoma (NHL) is the most common haematological malignancy worldwide, accounting for nearly 3% of cancer diagnoses and deaths. Diffuse large B-cell lymphoma (DLBCL), a subtype of NHL, accounts for approximately 40% of NHL cases [3]. The incidence of DLBCL in Denmark is 8/100.000 per year [4]. The incidence increases with age; median age at diagnosis is 67 years [4].

Primary disease symptoms include enlarged lymph nodes, night sweats, unusual weight loss, loss of appetite, extreme tiredness or fatigue, fever and extreme itchiness [4,5], which can often lead to impairment in aspects of health-related quality of life, including physical functioning and fatigue [6]. DLBCL tends to be a fast-growing (aggressive) lymphoma, but it often responds well to treatment. Initial treatment aims to be curative; however, about 4 out of 10 patients relapse or are refractory to first-line standard of care, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) [7,8]. This remains a major cause of morbidity and mortality for DLBCL, and thus there is a need for new and improved treatment options. Without treatment, DLBCL patients have an estimated life expectancy of less than one year [5].

5.1.2 Diagnosis and staging

DLBCL is diagnosed through tissue examination obtained by surgical biopsy. For patients presenting with DLBCL, the extent of the disease is evaluated by staging, which is crucial to determine the best therapeutic option and predict prognosis. The Ann Arbor Staging Classification is used routinely to classify the extent of disease on the basis of the distribution and number of involved sites, as well as the presence or absence of extranodal involvement and constitutional symptoms [5,9]. The stages and definition are shown in Table 1.

Table 1: Ann Arbor Staging Classification

Stage	Definition
I	Involvement of a single lymphatic region (I) or localised involvement of single extralymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localised involvement of a single extralymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without lymphatic involvement

5.1.3 Prognosis and risk factors

Prognosis of patients with aggressive NHL is most commonly predicted using the International Prognostic Index (IPI). IPI is based on five risk factors obtained at diagnosis that are independent predictors of DLBCL survival and progression-free survival [5,9]:

- Age (≤ 60 vs > 60 years) (not used for aaIPI)
- Serum lactate dehydrogenase (normal vs elevated) level
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) (0 or 1 vs 2–4)
- Ann Arbor stage (I or II vs III or IV)
- Number of extranodal sites (0 or 1 vs 2–4) (not used for aaIPI)

On the basis of the number of negative prognostic features present at the time of diagnosis, four discrete outcome groups are identified (risk groups) that predict survival rates. IPI comprises all five of the above risk factors (age > 60 years, elevated serum lactate dehydrogenase, ECOG PS ≥ 2, stage III/IV disease, > 1 extranodal sites of disease) (Table 2). While IPI was developed prior to rituximab being adopted as the standard of care [10], IPI still continues to be an effective prognostic factor in DLBCL with rituximab-based therapy [11-13]. A more simple index is the age-adjusted IPI, which can be used when comparing patients within an age group (i.e. age ≤ 60 vs > 60 years) and comprises three of the five risk factors (elevated serum lactate dehydrogenase, ECOG PS ≥ 2, stage III/IV disease) (Table 2). The aaIPI is used in the Danish clinical guideline [4]. Other factors that may affect prognosis and treatment strategies, including the maximum bulk of the disease, should also be assessed.

Table 2: The international Prognostic Index (IPI) and age-adjusted international Prognostic Index (aaIPI)

IPI			
Number of risk factors	Risk group	5-Year OS, % (without rituximab) [10,14]	3-Year OS, % (with rituximab) [14]
0-1	Low risk	73	91
2	Low-intermediate risk	51	81
3	Intermediate-high risk	43	65
4-5	High risk	26	59
aaIPI, patients aged ≤ 60			
Number of risk factors	Risk group	5-Year OS, % (without rituximab) [10,14]	3-Year OS, % (with rituximab) [14]
0	Low risk	83	95
1	Low-intermediate risk	69	91
2	Intermediate-high risk	46	69

3	High risk	32	-
aaIPI, patients aged > 60			
Number of risk factors	Risk group	5-Year OS, % (without rituximab) [10]	-
0	Low risk	56	-
1	Low-intermediate risk	44	-
2	Intermediate-high risk	37	-
3	High risk	21	-

Abbreviations: aaIPI - Age-adjusted International Prognostic Index (aaIPI); IPI - International Prognostic Index; OS - overall survival.

5.1.4 Patient populations relevant for this application

Polatuzumab vedotin (Pola) in combination with rituximab plus cyclophosphamide, doxorubicin and prednisone (R-CHP) is indicated for the treatment of adult patients with previously untreated DLBCL. The EMA approval is based on results from POLARIX, which included patients with IPI score 2-5 [1], corresponding to an aaIPI score of 1-3 in a Danish setting. Out of the full study population, 62% of patients had IPI score 3-5. The distinction between IPI score 2 vs 3-5 was one of the main stratification factors in the study.

According to Danish clinical experts there is a need for better treatment options for patients with poor prognosis, in particular older patients (> 60-65 years) with aaIPI 2-3 who are currently being treated with R-CHOP and who cannot receive an intensified treatment with the addition of etoposide [15]. Thus, these patients are considered to be the main candidates for Pola+R-CHP in the first-line setting and will be the scope of this application.

Figure 1 provides an overview of the DLBCL disease groups and current treatment landscape in first-line according to the clinical guideline by the Danish Lymphoma Group [4]. Patients are divided into two overall groups depending on age: patients aged 18-80 years and patients > 80 years. The patients aged 18-80 years are further split into disease groups depending on stage and aaIPI, and the patients > 80 are split into disease groups depending on their fitness (fit, frail, vulnerable) [4].

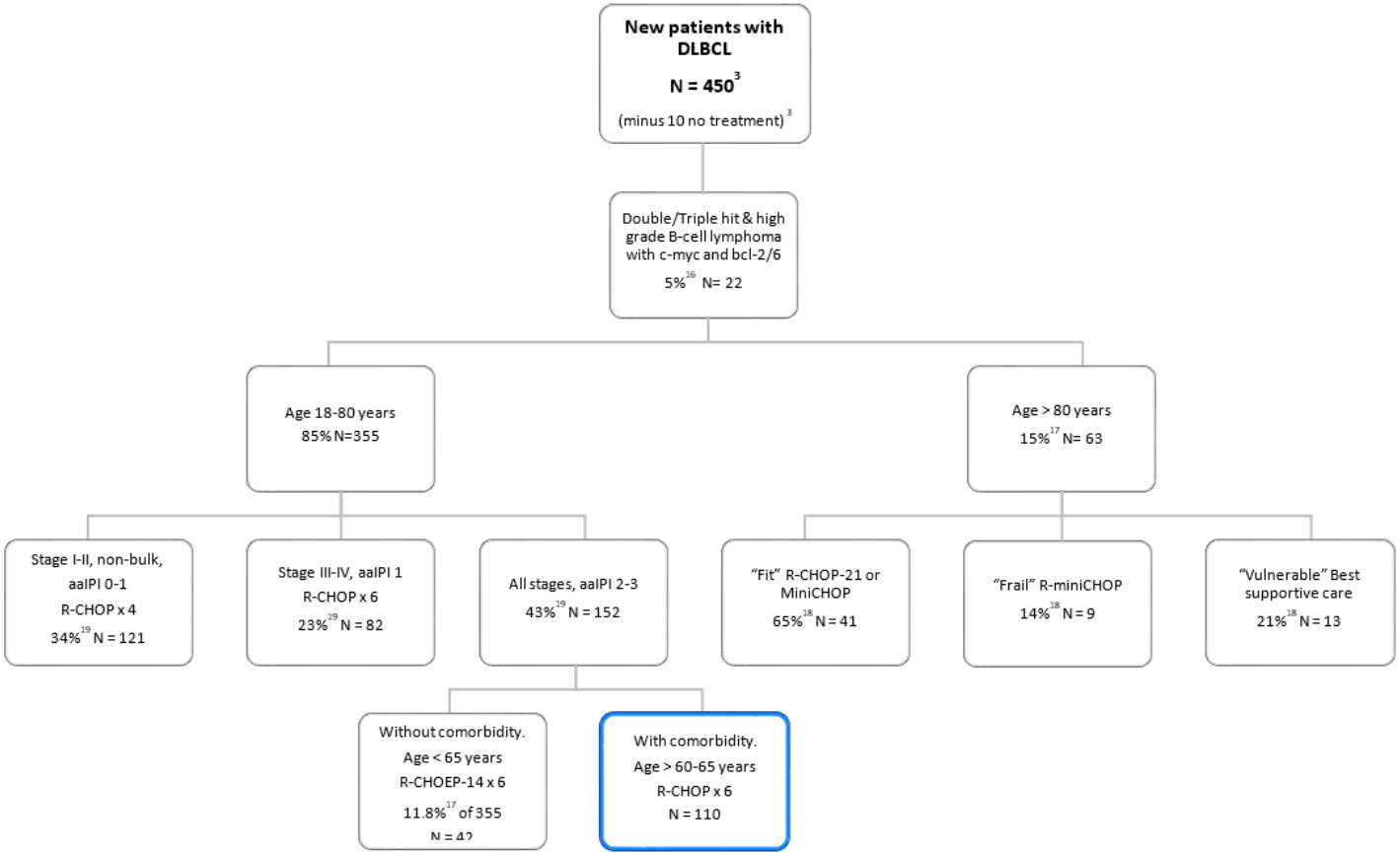


Figure 1: Overview of the Danish first-line DLBCL treatment algorithm

The figure gives an overview of disease groups, estimated patient numbers, current treatment options and eligibility for treatment with polatuzumab vedotin in combination with R-CHP according to clinical expert opinion. The patient group considered to be the main candidate for polatuzumab vedotin in combination R-CHP is marked with blue. Sources: [3,16-19] Abbreviations: IPI - International Prognostic Index; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone.

In the disease group with all stages and aaIPI score 2-3, patients aged > 60-65 years with co-morbidity will receive R-CHOP (14 or 21 day cycles), while younger patients aged up to 65 years without comorbidity will receive the intensified treatment R-CHOEP-14, which is R-CHOP and etoposide administered every 14 days [4]. Data from the Danish National Lymphoma Registry (LYFO) shows that patients receiving R-CHOEP-14 have a better outcome than patients receiving R-CHOP-14 (14 day cycles); the 4-year OS was 75% in the R-CHOEP-14 group compared to 62% in the R-CHOP-14 group [20]. Thus, the medical need is not as pronounced in the younger group who are candidates for treatment with R-CHOEP-14. Furthermore, polatuzumab has only been tested every 21 days in combination with R-CHP, and not in combination with etoposide nor in a dose dense regimen every 14 days. For these reasons, these patients are not considered candidates for Pola+R-CHP in this application.

Patients aged > 80 years that are fit can be offered either R-CHOP-21 (21 day cycles) or Mini-CHOP, in which the patients receive half the dose of the chemotherapy. Some of these patients may be candidates for treatment with Pola+R-CHP. An ongoing randomised clinical study in Denmark, POLAR BEAR (NCT04332822), is currently investigating the safety and efficacy of polatuzumab vedotin in combination with R-Mini-CHP versus R-Mini-CHOP in DLBCL patients aged > 80 years or frail patients aged > 75 years. Therefore, this patient group will not be considered in this application.

5.1.4.1 Incidence and prevalence

Based on numbers from 2016-2020 from the LYFO [3] an average of 450 DLBCL patients are diagnosed every year in Denmark. The incidence and prevalence in the past 5 years is presented in Table 3.

Table 3: Incidence and prevalence of DLBCL (all stages) in the past 5 years

Year	2016	2017	2018	2019	2020
Incidence in Denmark**[3,21]**	501	425	445	467	421
Prevalence in Denmark	-	-	-	-	4068 *

* Data for 2020 is extracted from the LYFO [22]. The prevalence is unknown for 2016-2019.

The number of Danish DLBCL patients eligible for first line treatment with Pola+R-CHP is estimated based on numbers extracted from the LYFO [3,17]. However, information on the frequency of double- and triple-hit and high grade B-cell lymphomas with c-myc and bcl-2 or bcl-6 translocation and the IPI score distribution in the DLBCL population is extracted elsewhere [16,19], as no Danish data is available.

Around ten of the 450 DLBCL patients do not qualify for treatment [3]. Of the remaining 440 patients, approximately 5% have double- and triple-hit lymphomas and high grade B-cell lymphoma with c-myc and bcl-2/bcl-6 translocation (22 patients) [16]. Of these, around 85% are aged 18-80 years (355 patients) and around 15% are aged > 80 years (63 patients) [17]. In the group aged 18-80 years, approximately 43% will be in the group of all stages and aaIPI 2-3, giving a total of 152 patients [19]. Of these, around 42 patients will receive R-CHOEP-14 (11.8% of patients in the

group aged 18-80 years [17]. Thus, a total of 110 patients will be eligible for treatment with Pola+R-CHP in the first-line setting. The estimated number of patients eligible for treatment in the next 5 years is presented in Table 4.

Table 4: Estimated number of patients eligible for treatment in the next 5 years

Year	2022	2023	2024	2025	2026
Number of patients in Denmark eligible for the pharmaceutical in the coming years	0	110	110	110	110

Patient numbers are estimated based on data from the LYFO and additional sources as described previously. The incidence of DLBCL has been relatively stable for many years, and based on this knowledge, the number of patients with aaIPI 2-3 (IPI 3-5) are expected to stay stable in the years after a recommendation.

5.2 Current treatment options and choice of comparator

5.2.1 Current treatment options

As described, the choice of treatment for previously untreated patients with DLBCL is based on age, stage and aaIPI score [4]. The current treatment option for each patient group in the first-line setting is illustrated in

Figure 1. For the majority of patients, R-CHOP and R-CHOP like regimes are the standard treatment options. A Danish study has shown that 88.2% of DLBCL-patients receive R-CHOP as standard therapy, while the remaining receive R-CHOEP-14 [17]. R-CHOP is also the current standard of care for patients considered the main candidates for treatment with Pola+R-CHP (

Figure 1, Table 5) [4].

Since the introduction of R-CHOP 20 years ago, there has been no advancement in treatment options for previously untreated DLBCL patients. In Denmark, about 60-70% of DLBCL patients treated in first-line remain progression-free after 5 years, while the remaining 30-40% relapse or are refractory to R-CHOP [17]. The majority of disease relapse occurs within the first 24 months after starting treatment. Patients who remain progression-free 24 months post initiation of first-line treatment have a survival that is comparable to the general population [15,23,24]. For patients who are not cured with first-line therapy, high-dose chemotherapy followed by autologous stem cell transplantation (ASCT) offers a second chance for cure [9,25]. However, this is only available for younger, fit patients who demonstrate chemosensitive disease [9].

Table 5: Current treatment option according to the clinical guideline by the Danish Lymphoma Group

Disease group	Treatment
Patient population aged 18-80 years	
All stages, aaIPI 2-3, with co-morbidity and age above 60-65 years.	R-CHOP x 6

Abbreviations: IPI - International Prognostic Index; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone

5.2.2 Choice of comparator

R-CHOP is the current standard of care for adult patients with previously untreated DLBCL aged > 60-65 years and baseline aaIPI score 2-3 (IPI score 3-5) (Table 5). Thus, introduction of Pola+R-CHP is expected to replace R-CHOP for the population in question.

R-CHOP has been the standard of care in Denmark for 20 years, and is therefore considered an established standard treatment practice. The treatment regimen has a documented effect on the patient population relevant for this application.

5.2.3 Description of the comparator

Each component of the R-CHOP regimen is described separately below.

5.2.3.1 Rituximab (L01XC02)

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. The antigen is expressed on >95% of all B cell NHLs. The Fab domain of rituximab binds to the CD20 antigen on B lymphocytes and the Fc domain can recruit immune effector functions to mediate B cell lysis. Possible mechanisms of effector-mediated cell lysis include complement-dependent cytotoxicity (CDC) resulting from C1q binding, and antibody-dependent cellular cytotoxicity (ADCC) mediated by one or more of the Fcγ receptors on the surface of granulocytes, macrophages and natural killer (NK) cells. Rituximab binding to CD 20 antigen on B lymphocytes has also been demonstrated to induce cell death via apoptosis.

Rituximab is a solution for intravenous (i.v.) infusion. It is supplied at a concentrate of 10 mg/mL in either 100 mg/mL or 500 mg/mL vials. It is administered every 21 days during 8 cycles, resulting in a treatment duration of 24 weeks. The recommended dosage is 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 6 cycles after i.v. infusion of the glucocorticoid component of the chemotherapy regimen. During cycle 7 and 8 rituximab is given as monotherapy. Premedication consisting of an antipyretic (paracetamol) and an antihistamine, should always be given before each administration of rituximab.

The recommended initial rate for infusion is 50 mg/h; after the first 30 minutes, it can be escalated in 50 mg/h increments every 30 minutes, to a maximum of 400 mg/h. Subsequent doses of rituximab can be infused at an initial rate of 100 mg/h, and increased by 100 mg/h increments at 30 minute intervals, to a maximum of 400 mg/h [13].

5.2.3.2 Cyclophosphamide (L01AA01)

Cyclophosphamide is an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide, phosphoramide mustard, alkylates, or binds, to DNA. Its cytotoxic effect is mainly due to cross-linking of strands of DNA and RNA, and to inhibition of protein synthesis.

Cyclophosphamide is a powder for solution for i.v. infusion. It is supplied in vials of 200 mg or 500 mg. The recommended dosage is 750 mg/m² body surface area. It is administered on day 1 every 21 days for 6 cycles (18 week treatment duration) [26].

5.2.3.3 Doxorubicin (L01DB01)

Doxorubicin (previously named hydroxydaunorubicin (H)) is an anthracycline that slows or stops the growth of cancer cells by blocking topoisomerase 2.

Doxorubicin is a powder for solution for i.v. infusion supplied in vials of 50 mg. The recommended dosage is 50 mg/m² body surface area. It is administered on day 1 every 21 days for 6 cycles (18 week treatment duration) [27].

5.2.3.4 Vincristine (L01CA02)

Vincristine (also named Oncovin (O)) binds to the microtubular proteins of the mitotic spindle, leading to crystallisation of the microtubule and mitotic arrest or cell death.

Vincristine is a powder for solution for i.v. infusion. It is supplied as solutions for injection at a concentrate of 1 mg/mL or 2 mg/mL in 1 mL and 2 mL vials, respectively. It is administered on day 1 every 21 days for 6 cycles (18 week treatment duration). The recommended dosage is 1.4 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 6 cycles [28].

5.2.3.5 Prednisone (S01CB02)

Prednisone/glucocorticoids induce apoptosis, or programmed cell death, in certain lymphoid cell populations. Despite an incomplete understanding of the mechanism of action of glucocorticoids, it is clear they are of great clinical value in the treatment of lymphoid neoplasms.

Prednisone comes as tablets containing 25 mg for oral administration. It is supplied in packs of 10, 25, or 100 tablets. The recommended dosage is 100 mg. It is administered on day 1 to 5 every 21 days for 6 cycles (18 week treatment duration) [29].

5.3 The intervention

The recommended dose of polatuzumab vedotin is 1.8 mg/kg, given as i.v. infusion every 21 days for 6 cycles (treatment duration of 18 weeks) followed by another two cycles of rituximab as monotherapy. Polatuzumab vedotin, rituximab, cyclophosphamide and doxorubicin can be administered in any order on Day 1 after the administration of prednisone. Prednisone is administered on Days 1-5 of each cycle [30].

The initial dose of polatuzumab vedotin should be administered as a 90 minute i.v. infusion. Patients should be monitored for IRRs/hypersensitivity reactions during the infusion and for at least 90 minutes following completion of the initial dose. If the prior infusion was well tolerated, the subsequent dose of polatuzumab vedotin may be administered as a 30 minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion [30].

Introduction of polatuzumab vedotin in first-line is not expected to change clinical practice in later lines. Polatuzumab vedotin in combination with bendamustine and rituximab is also approved for treatment of patients with relapsed/refractory DLBCL, however this indication is not recommended by the DMC [31].

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The clinical phase 3 study POLARIX directly compares polatuzumab vedotin plus R-CHP with the comparator relevant in Danish clinical practice, R-CHOP. The study provides sufficient documentation for efficacy and safety for both the intervention and comparator, and therefore, a literature search for additional evidence was not performed.

Results for the main study population in the trial are published in a peer-reviewed publication [1]. Data on certain outcomes in the subpopulation with baseline IPI score 3-5 is available in either Tilly et al. 2021 [1] and/or EMA's assessment report and SmPC for polatuzumab vedotin [2,3], while other outcomes are not yet published [4]. There is currently no plan for submission of these data.

6.2 List of relevant studies

The included study is listed in Table 6 below. For detailed information about the study refer to appendix B.

Table 6: Relevant study included in the assessment

Reference	Trial name	NCT number	Dates of study	Used in comparison of
Polatuzumab Vedotin in previously untreated diffuse large B-cell lymphoma, Tilly et al. N Engl J Med 2022;386:351-363 [1]	POLARIX	NCT03274492	Actual study start: Nov 16, 2017 Estimated primary completion: Jun 18, 2026 Estimated study completion: Jun 18, 2026	Polatuzumab vedotin plus R-CHP vs R-CHOP in adult patients with previously untreated DLBCL and baseline IPI score 2-5
				Polatuzumab vedotin plus R-CHP vs R-CHOP in adult patients with previously untreated DLBCL and baseline IPI score 3-5

7. Efficacy and safety

7.1 Efficacy and safety of polatuzumab vedotin plus R-CHP compared to R-CHOP for adult patients with previously untreated DLBCL and baseline aaIPI score of 2-3 (IPI score 3-5)

7.1.1 Relevant studies

In the following section, we provide a brief description of the study included in the assessment (Table 6). For detailed study characteristics refer to appendix B. For demographics and baseline characteristics of patients included in the study refer to appendix C.

7.1.1.1 POLARIX (NCT03274492)

The pivotal study POLARIX is a phase 3, multicentre, randomised, double-blind, placebo-controlled study designed to compare the efficacy, safety, pharmacokinetics and patient-reported outcomes of Pola+R-CHP with R-CHOP in patients with previously untreated DLBCL.

Patients were eligible for inclusion if they were 18 to 80 years of age, had cluster of differentiation 20 (CD20)-positive DLBCL, had not received previous treatment for lymphoma, had an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 to 2 (on a 5-point scale, with higher numbers indicating greater disability), had a baseline IPI score between 2 and 5 (on a 5-level prognostic scale, with higher numbers indicating a poorer prognosis).
A total of 879 patients underwent randomization. Patients were randomly assigned in a 1:1 ratio, using an interactive voice or web-based response system (IxRS), to receive polatuzumab vedotin 1.8 mg/kg plus R-CHP plus vincristine placebo every 21 days for 6 cycles (n=440) or R-CHOP plus polatuzumab vedotin placebo every 21 days for 6 cycles (n=439). Patients were stratified based on IPI score (2 vs. 3-5), bulky disease defined as at least one tumour mass with diameter of 7.5 cm or more (present or absent), and region (Western Europe, USA, Canada and Australia vs Asia vs rest of world) (

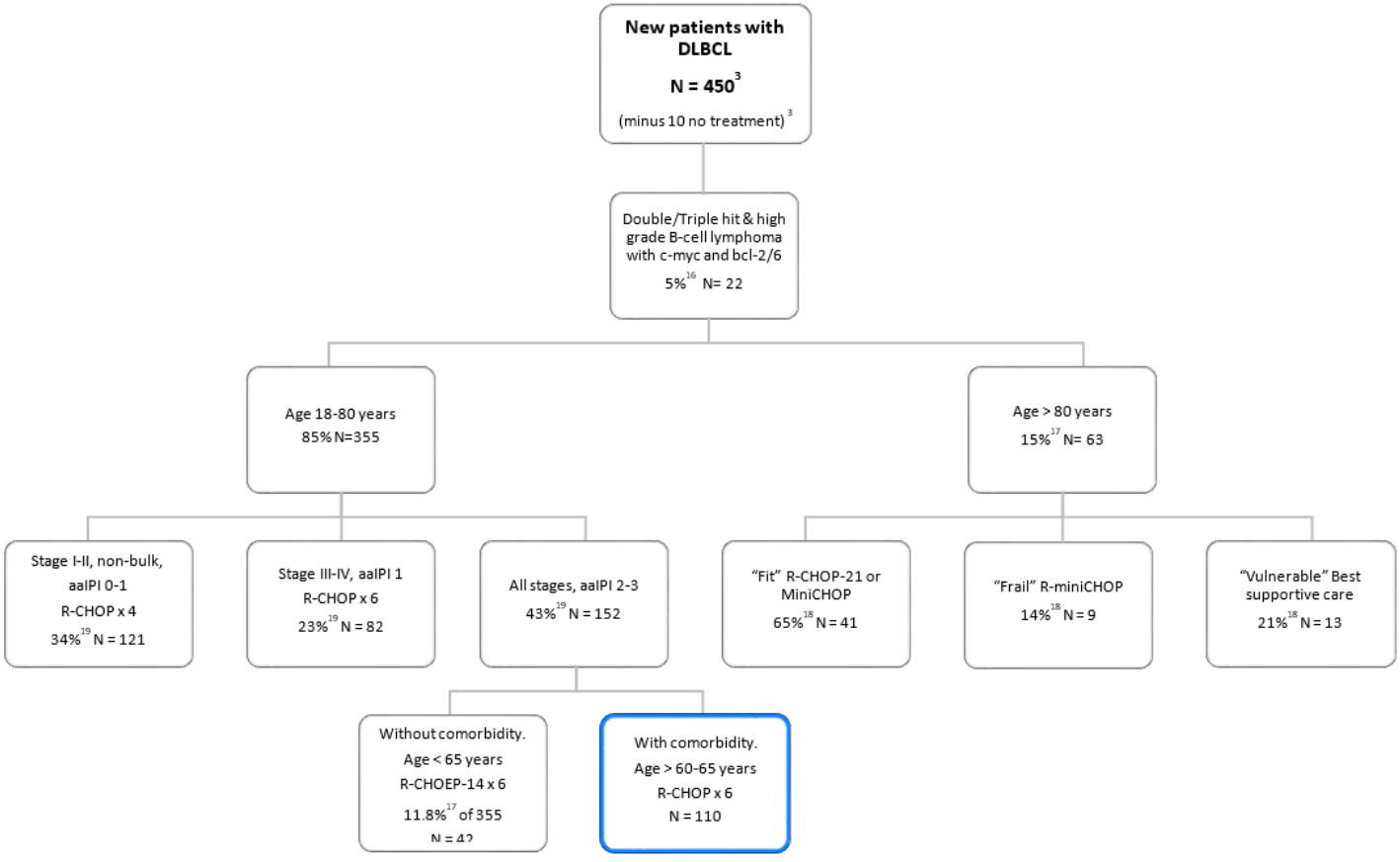


Figure 1). The patient demographics and baseline characteristics between the two treatment arms in the main study population were generally balanced and representative of a population of patients who had either intermediate-risk or high-risk disease, in which approximately one-third of the patients had ABC-like subtype DLBCL and almost two-thirds had a baseline IPI score between 3 and 5.

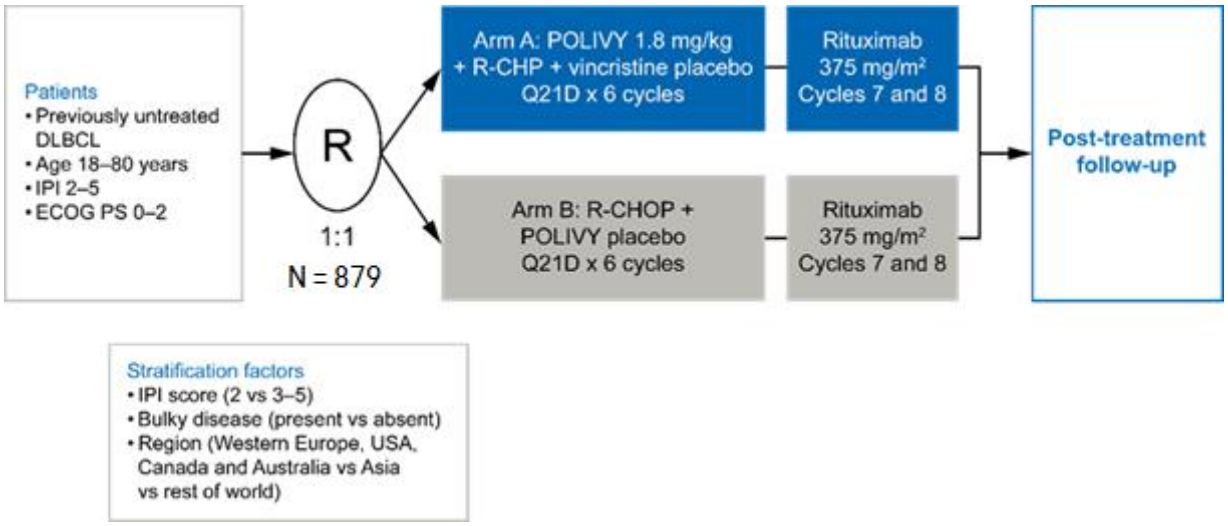


Figure 2: POLARIX study design

Abbreviations: DLBCL - diffuse large B-cell lymphoma; ECOG PS - Eastern Cooperative Oncology Group performance status; IPI - International Prognostic Index; Q21D - every 21 days; R - randomization; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone - R-CHP, rituximab plus cyclophosphamide, doxorubicin and prednisone.

The primary endpoint was PFS assessed by investigator. Key secondary efficacy endpoints included in the hierarchical testing procedure included event-free survival (EFS_{eff}) as determined by the investigator, complete response (CR) rate at end of treatment by FDG-PET as determined by blinded independent central review (BICR) and overall survival (OS) (Table 7). PFS was assessed by the investigator at a one-sided 0.025 level. If PFS was significant, EFS_{eff} was assessed by the investigator at a one-sided 0.025 level. If EFS_{eff} was significant, the one-sided 0.025 α was split between the EOT CR rate by BICR (α 0.005) and OS (α 0.02). If either endpoint was significant at its corresponding α level, the corresponding α was then recycled for the other endpoint so that the other endpoint could be tested again at a one-sided 0.025 level [1]. Additional secondary endpoints that were not adjusted for testing multiplicity included disease-free survival (DFS), best overall response (BOR) as determined by investigator and duration of response (DOR).

Table 7: A summary of data cut-offs for the primary and key secondary endpoints

CCOD	June 2021	February 2022	June 2022	Future
PFS	Primary/final analysis	Ad hoc	Ad hoc	Ad hoc
EFS_{eff}	Primary/final analysis	Ad hoc	Ad hoc	Ad hoc
CR	Primary/final analysis	Ad hoc	Ad hoc	Ad hoc
OS	Interim analysis	Interim analysis	Final analysis	Ad hoc

Ad hoc analyses are merely descriptive. Results from the second interim OS analysis are not presented in this application.
Abbreviations: CCOD - CR - complete response; EFS_{eff} - event-free survival; OS - overall survival; PFS - progression-free survival.

All efficacy analyses except for DFS were carried out in the intent-to-treat (ITT) population of 879 patients. The treatment effect on the primary endpoint of PFS was explored in exploratory subgroup analyses defined by demographics, baseline prognostic characteristics (including but not limited to IPI score) and *MYC* and *BCL2* and/or *BCL6* translocations by FISH (without adjusting for multiplicity) [1]. In addition, secondary efficacy endpoint data were analysed post hoc in the subpopulation with a baseline IPI score of 3-5. Analysed outcomes relevant for this assessment include EFS_{eff}, CR and OS. Patient-reported outcomes (PRO) analyses were carried out in all randomised patients who had a baseline and ≥1 post-baseline assessment. The ITT-population of 879 patients were included in the analysis. Safety was evaluated in all patients who received ≥1 dose of study treatment (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, vincristine or prednisone). A total of 873 patients were included in the safety-evaluable population.

7.1.2 Efficacy and safety – results per study

POLARIX provides a direct comparison between Pola+R-CHP and R-CHOP and the results can be used to address the clinical question. In the following section, we provide a summary of the key efficacy and safety findings in the study. Data on the following outcomes have been extracted:

- Progression-free survival
- Event-free survival
- Complete response rate
- Overall survival
- Health-related quality of life as assessed by EORTC QLQ-C30 and FACT-Lym LymS
- Safety
    - Incidence of adverse events (AEs) by severity, serious AEs (SAEs) and discontinuation due to AEs
    - Qualitative description of the safety profile of polatuzumab vedotin plus R-CHP

For the efficacy outcomes, we present data for the main study population with baseline IPI score 2-5 and the subpopulation with baseline IPI score 3-5. For health-related quality of life, we present data for the main study population only. For safety outcomes, we present data for the safety-evaluable population and the IPI score 3-5 subpopulation. The qualitative description of the safety profile of Pola+R-CHP is based on the safety-evaluable population. Efficacy and safety results presented are from the primary PFS analysis clinical cutoff date (CCOD) of June 28, 2021 after a median follow-up of 24.7 months (95% CI, 24.4 to 25.0) [32], and the final OS analysis CCOD of June 15, 2022 after a median follow-up of 30.8 months (95% CI, 30.7 to 31.0) for the IPI score 2-5 population and 30.9 months (95% CI, 30.7-31.3) for the IPI score 3-5 population. Health-related quality of life results are based on analyses at the primary CCOD. For detailed efficacy results, refer to appendix D and E.

In terms of subgroup analyses, it should be noted that POLARIX was not designed to show statistically significant differences in the subgroup. The subgroup analyses are exploratory or post hoc, they were not defined as part of the testing hierarchy and no nominal level of statistical significance for the subgroup analyses was defined. The study was not powered to show homogenous treatment effects across the subgroup nor powered to detect statistically significant differences.

7.1.2.1 Progression-free survival

The primary efficacy endpoint was investigator-assessed PFS as calculated in a time-to-event analysis, in which investigator-assessed disease progression and disease relapse or death from any cause were counted as events. The

primary (and final) analysis of PFS was conducted after approximately 228 PFS events had occurred in the ITT population and at least 24 months after the last patient was enrolled during the global enrolment phase, whichever occurred later. PFS at 24 months is a robust endpoint because most disease progression occurs within 24 months of initiation of therapy [23]. Patients were therefore followed up for at least 24 months, as this observation period would capture the vast majority of DLBCL disease progression/relapse. At the time of the primary PFS analysis, exploratory analyses of PFS were conducted in defined subgroups, including the subgroup with IPI score 3-5. No additional PFS analyses were planned, and thus analyses conducted at later time points are merely descriptive.

The Kaplan-Meier method was used to estimate PFS in each treatment group. Hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were estimated with the use of a stratified Cox proportional-hazards analysis. The stratification factors used for the analysis were geographical region, IPI score and bulky disease defined as one lesion ≥7.5 cm. Kaplan-Meier curves were constructed to provide a visual description of the difference between the treatment and control arms. 12- and 24-month milestone PFS rates were estimated by Kaplan-Meier methodology, and the corresponding 95% CIs were calculated based on the normal approximation with standard errors via the Greenwood method, and between-group differences were informally tested using the z-test, with standard errors computed via the Greenwood method. For patients who had not progressed, relapsed or died as of the clinical cut-off date for analysis, PFS was censored on the date of last disease assessment when the patient was known to be progression free. If no tumour assessments were performed after the baseline visit or all post-baseline tumour assessment results had overall responses of 'not evaluable', PFS was censored on the date of randomization. The proportional-hazards assumption for PFS was evaluated with the use of the method proposed by Grambsch and Therneau [33], and no evidence suggested violation of the proportionality assumption.

The data presented are based on PFS analyses at the primary data cut-off (CCOD of June 28, 2021). Both stratified and unstratified PFS HRs are available and will be presented. For both the ITT population and the IPI 3-5 subpopulation, main emphasis will be placed on the stratified HR.

IPI score 2-5 population

At the time of the primary analysis, 107 of 440 patients (24.3%) in the Pola+R-CHP arm and 134 of 439 patient (30.5%) in the R-CHOP arm had experienced disease progression, disease relapse or death; the stratified HR for PFS was 0.73 (95% CI, 0.57 to 0.95; p=0.0177), and thus the primary endpoint of the study was met [1,30,32]. The unstratified analysis showed results similar to the stratified analysis (HR: 0.76 (95% CI, 0.59 to 0.98; p=0.0326)) [34]; the differences between the HRs are small, the CIs overlap and do not include 1.

The Kaplan-Meier curves for investigator-assessed PFS began to separate at approximately 6 months after randomization in favour of Pola+R-CHP (Figure 3). Although PFS events were observed in less than 30%, the raw percentage of 30% is enough to achieve a robust median if enough patients are censored; thus, the PFS survival curve provides robust estimates until 28 months until 30% are still at risk. Given that PFS events were observed in less than 30% of patients in both arms, the median PFS times were not reached for either arm (the median PFS time estimation was not considered mature for either treatment arm at the CCOD) [32]. Because the majority of PFS events are known to occur within the first 24 months after starting therapy [24], a 2-year PFS event rate is considered more clinically meaningful than median PFS as a measurement of treatment effect.

In the Pola+R-CHP arm, a higher proportion of patients were alive and progression free at the 1- and 2-year milestones compared with R-CHOP. The PFS event-free rate at the 1-year milestone was 83.9% (95% CI, 80.4 to 87.4) and 79.8% (95% CI, 75.9 to 83.6) in the Pola+R-CHP and R-CHOP arms, respectively. The difference between treatment arms was 4.1% (95% CI, -1.1 to 9.3) [1,32]. The event-free rate at the 2-year milestone was 76.7% (95% C, 72.7 to 80.8) and

70.2% (95% CI, 65.8 to 74.6), respectively. The difference between treatment arms was 6.5% (95% CI, 0.5 to 12.5) [1,30,32].

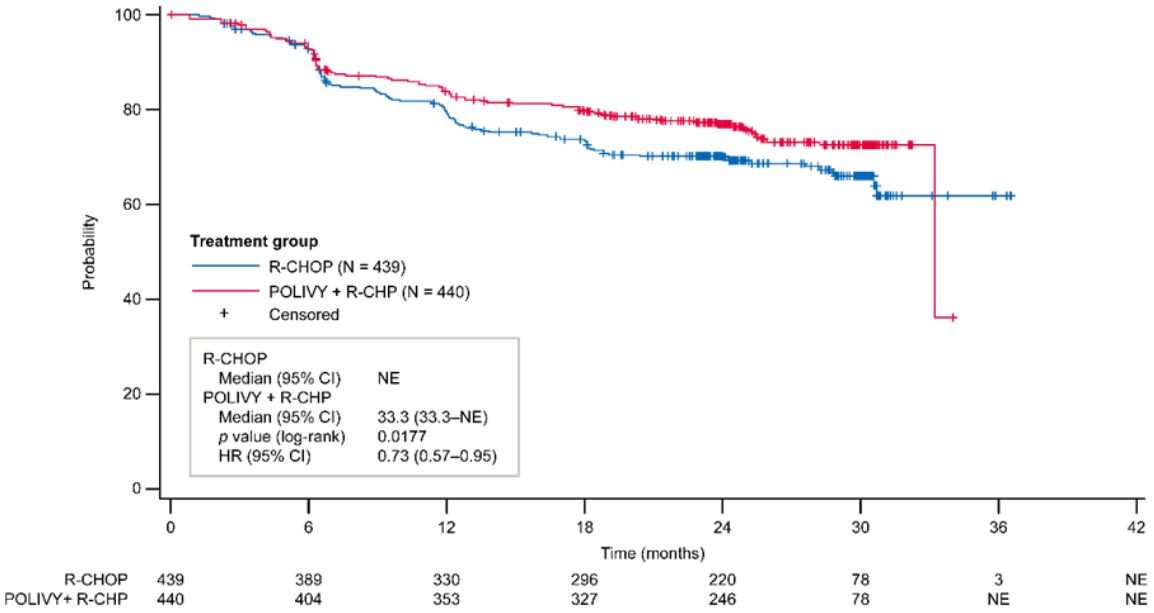


Figure 3: Kaplan-Meier plot of time to investigator-assessed PFS in the IPI score 2-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; IPI - international prognostic index; HR - hazard ratio; NE - not evaluable; PFS - progression-free survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is available in Tilly et al. 2021 and EMA's assessment report and SmPC [1,30,32].

At the time of the final OS analysis with an additional 12 months of follow-up, 20 PFS events had occurred (118 (26.8%) in the Pola+R-CHP arm and 143 (32.6%) in the R-CHOP arm). Overall, PFS remained stable, which is in line with the fact that most disease progression occurs within 24 months of initiation of therapy [23].

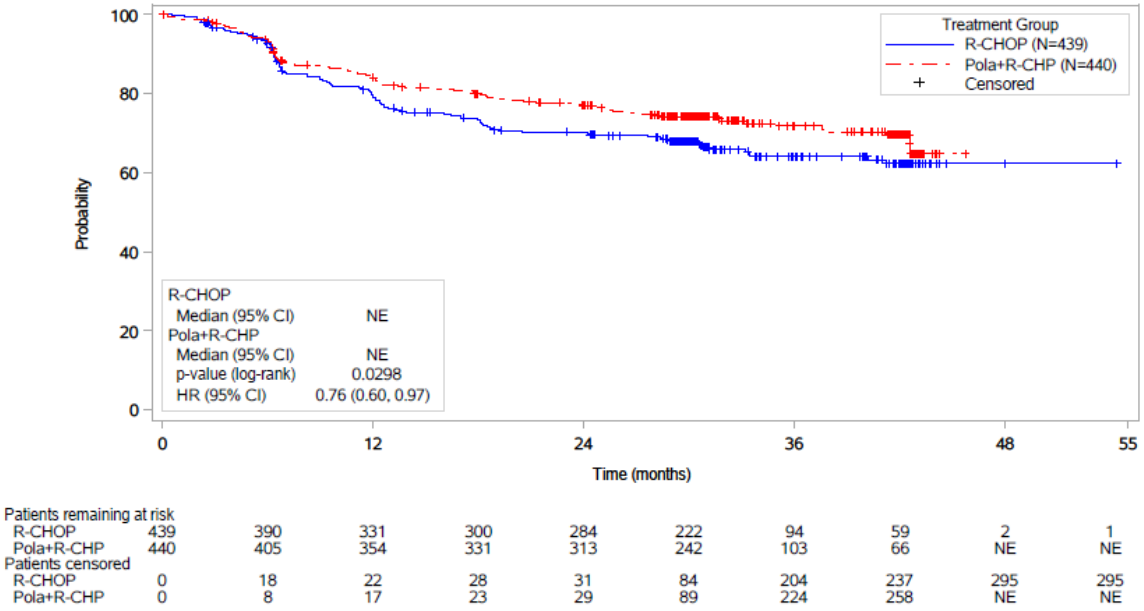


Figure 4: Kaplan-Meier plot of time to investigator-assessed PFS in the IPI score 2-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; IPI - international prognostic index; HR - hazard ratio; NE - not evaluable; PFS - progression-free survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

IPI score 3-5 population

At the time of the primary PFS analysis (CCOD June 2021), 70 of 273 patients (25.6%) in the Pola+R-CHP arm and 97 of 272 patients (35.7%) in the R-CHOP arm had experienced disease progression, relapse or death; the stratified HR for PFS was 0.65 (95% CI, 0.47 to 0.88; p=0.0053) [34]). The unstratified analysis showed results similar to the stratified analysis (HR: 0.67 (95% CI, 0.49 to 0.91; p=0.0106)) [1,32].

Median PFS was not reached for either arm [34]. As for the IPI 2-5 population, a higher proportion of patients were alive and progression free in the Pola+R-CHP arm compared with R-CHOP at the 1- and 2-year milestones. The PFS event-free rate at the 1-year milestone was 81.5% (95% CI, 76.9 to 86.2) and 76.2% (95% CI, 71.0 to 81.3) in Pola+R-CHP and R-CHOP arms, respectively. The difference between treatment arms was 5.4% (95% CI, -1.6 to 12.4) [34]. At the 2-year milestone, the event-free rate was 75.2% (95% CI, 69.9 to 80.4) and 65.1% (95% CI, 59.3 to 70.9), respectively. The difference between treatment arms was 10.1% (95% CI, 2.2 to 17.9) in favour of Pola+R-CHP [1,32,34].

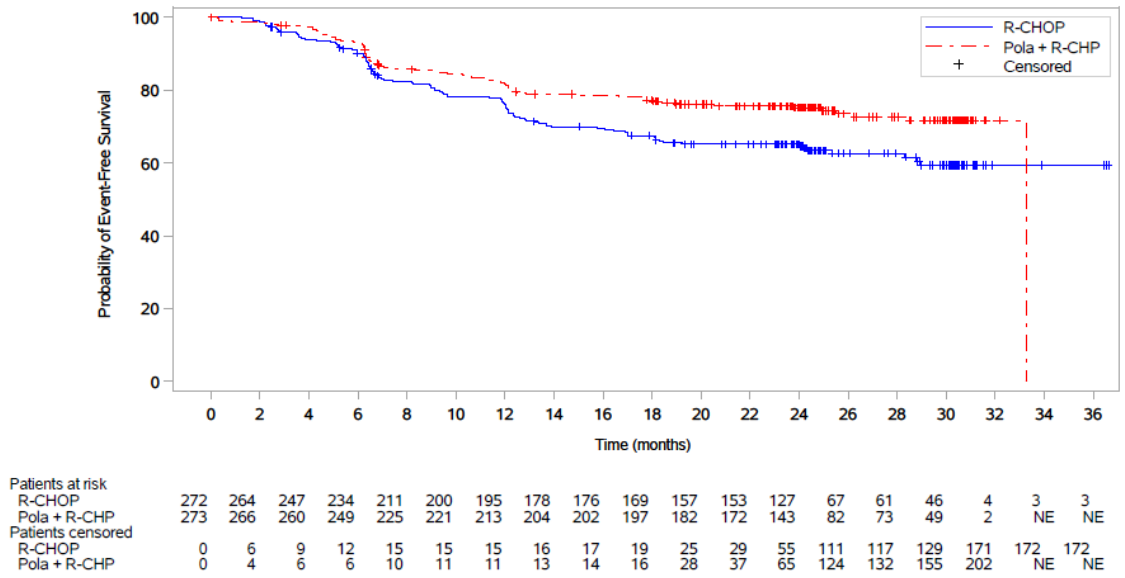


Figure 5: Kaplan-Meier plot of time to investigator-assessed PFS in the IPI score 3-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; IPI - international prognostic index; NE - not evaluable; PFS - progression-free survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

At the time of the final OS analysis, 15 additional PFS events had occurred (79 (28.9%) in the Pola+R-CHP arm and 103 (37.9%) in the R-CHOP arm). The stratified HR at the June CCOD 2022 is similar to the HR at the June 2021 CCOD 0.70 (95% CI, 0.52 to 0.93) [34]. The PFS event-free rate at the 1-year milestone was 81.6% (95% CI, 76.9 to 86.3) and 75.9% (95% CI, 70.7 to 81.1) in Pola+R-CHP and R-CHOP arms, respectively. The difference between treatment arms was 5.7% (95% CI, -1.3 to 12.7) [34]. At the 2-year milestone, the event-free rate was 75.4% (95% CI, 70.2 to 80.6) and 65.3% (95% CI, 59.5 to 71.1), respectively. The difference between treatment arms was 10.1% (95% CI, 2.3 to 17.88) in favour of Pola+R-CHP [1,2,32,34]. Thus, similar to the ITT population, PFS remained stable.

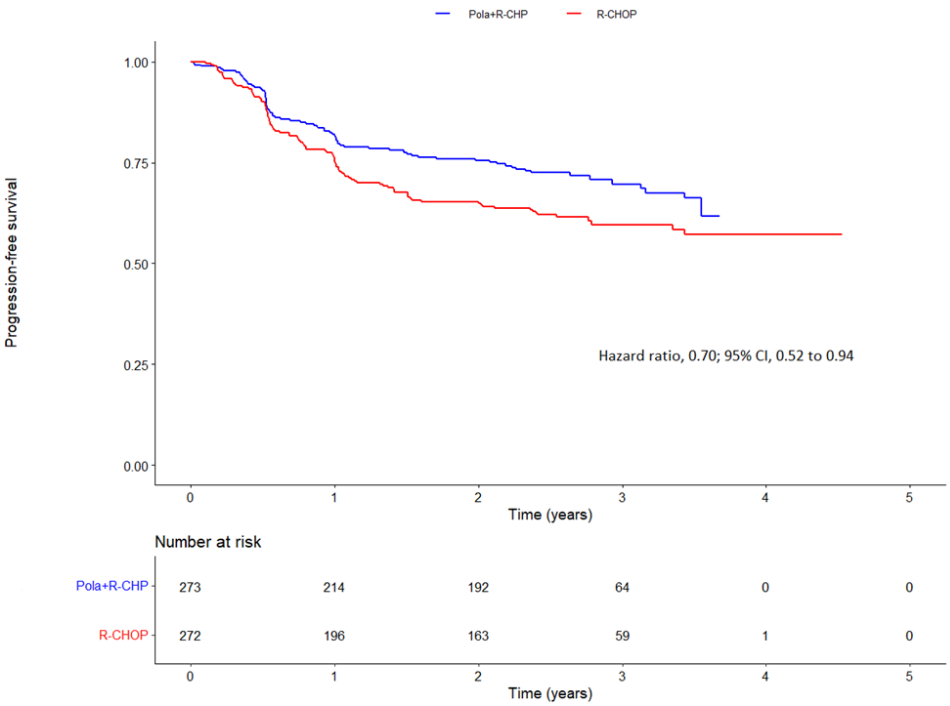


Figure 6: Kaplan-Meier plot of time to investigator-assessed PFS in the IPI score 3-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; IPI - international prognostic index; NE - not evaluable; PFS - progression-free survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

7.1.2.2 Event-free survival

Investigator-assessed EFS was a key secondary endpoint, which was included in the hierarchical testing procedure [1]. EFS was defined as the time from date of randomization to the earliest occurrence of any disease progression/relapse, death, new anti-lymphoma therapy resulting from an efficacy reason or objective evidence of disease (biopsy, clinical/imaging assessment).

Treatment comparisons were performed using the stratified log-rank test. Kaplan–Meier methodology was used to estimate the EFS distribution for each treatment arm and curves were constructed for the visual description of the difference between the treatment arms. HRs and corresponding 95% CIs were estimated with the use of a stratified Cox proportional-hazards analysis using the same stratification factors as in the primary analysis of PFS [1]. 12- and 24-month milestone EFS rates were estimated by Kaplan-Meier methodology.

The data presented are based on EFS analyses performed at the time of the primary PFS analysis (CCOD of June 28, 2021). Similar to the PFS analyses, no additional EFS analyses were planned, and thus analyses conducted at later time points are merely descriptive. In addition to the primary analysis population for EFS, additional post hoc EFS analyses based on the subpopulation with IPI score 3-5 were conducted. As for PFS, both stratified and unstratified EFS HRs are available, but main emphasis will be placed on the stratified HR.

IPI score 2-5 population

At the time of primary CCOD, 112 patients (25.5%) in the Pola+R-CHP arm and 138 patients (31.4%) in the R-CHOP arm had experienced an EFS event; the stratified HR was 0.75 (95% CI, 0.58 to 0.96; p=0.0244) [1,30,32]. Thus, results were statistically significant and highly consistent with results of the primary endpoint of investigator-assessed PFS and supportive of the clinical benefit for Pola+R-CHP compared with R-CHOP. The unstratified analysis showed results similar to the stratified analysis (HR: 0.77 (95% CI, 0.60 to 0.99; p=0.0441)) [34].

The Kaplan-Meier curves for EFS began to separate at approximately 6 months after randomisation in favour of Pola+R-CHP and the separation was maintained for the duration of follow-up. Median EFS estimates were not considered mature for either treatment arm as of the CCOD, given the low number of events [32]. On the basis of Kaplan-Meier estimates, treatment with Pola+R-CHP resulted in a higher proportion of patients alive and event free compared with R-CHOP at 1 and 2 years. The EFS event-free rate in the Pola+R-CHP and R-CHOP arms, respectively, was 82.5% (95% CI, 78.9 to 86.1) and 78.7% (95% CI, 74.8 to 82.6) at the 1-year milestone [32] and 75.6% (95% CI, 71.5 to 79.7) and 69.4% (95% CI, 65.0 to 73.8) at the 2-year milestone [1,32]. The difference between treatment arms was 3.9% (95% CI, -1.5 to 9.2) and 6.2% (95% CI, 0.1 to 12.2), respectively [32].

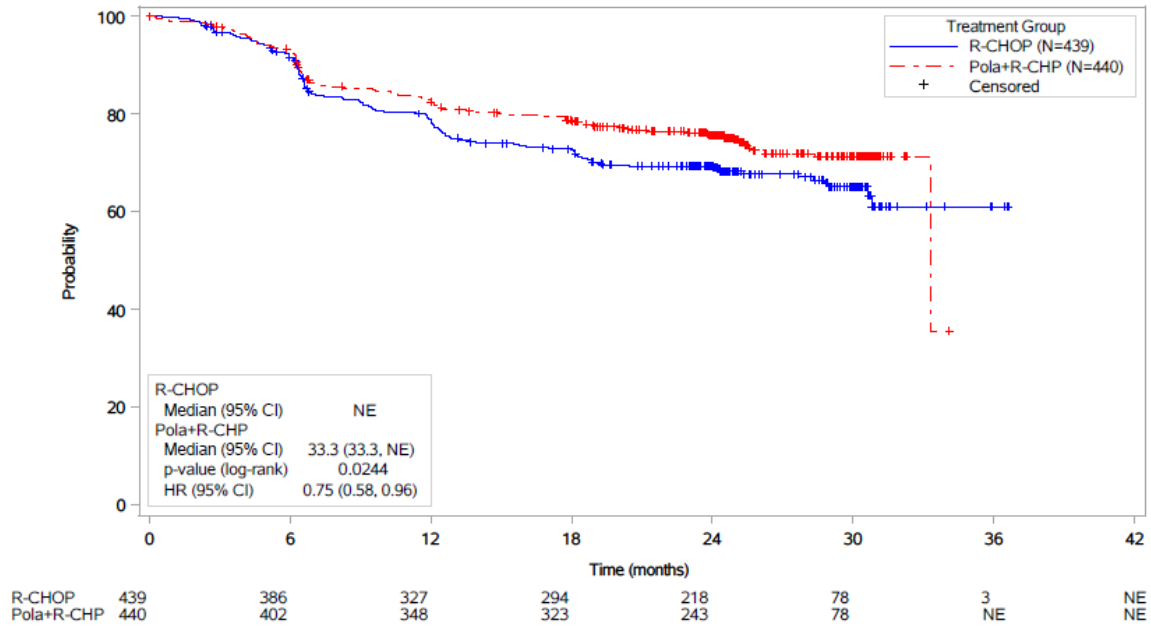


Figure 7: Kaplan-Meier plot of time to EFS in the IPI score 2-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; EFS - Event-free survival; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is available in Tilly et al. 2021 [1].

At the time of the final OS analysis, 12 additional EFS events had occurred in the Pola+R-CHP arm (124 (28.2%)) and 9 in the R-CHOP arm (147 (33.5%)) [34]. Thus, results are consistent with the results of PFS.

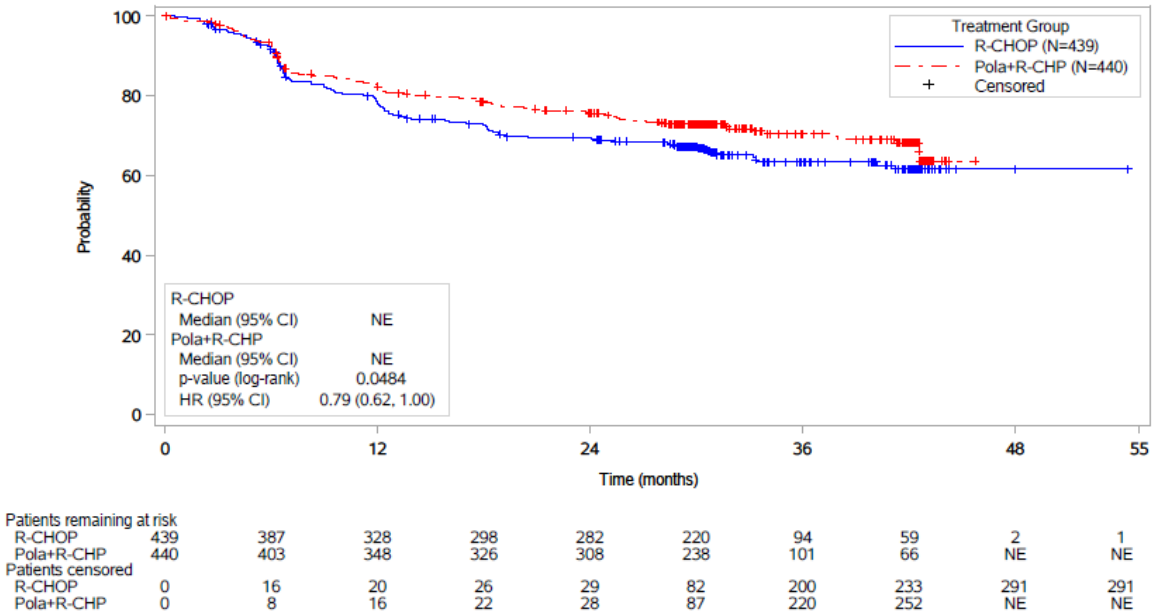


Figure 8: Kaplan-Meier plot of time to EFS in the IPI score 2-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; EFS - Event-free survival; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not yet publicly available [34].

IPI score 3-5 population

At the time of the CCOD June 2021, 73 patients (26.7%) in the Pola+R-CHP arm and 100 patients (36.8%) in the R-CHOP arm had experienced an EFS event; the stratified HR was 0.65 (95% CI, 0.48 to 0.88; p=0.0056)) [34]. The unstratified analysis showed results similar to the stratified analysis (HR: 0.68 (95% CI, 0.50 to 0.92; p=0.011)) [34].

Median EFS estimates were not considered mature for either treatment arm as of the CCOD, given the low number of events. Treatment with Pola+R-CHP resulted in a higher proportion of patients alive and event free compared with R-CHOP at 1 and 2 years. The EFS event-free rate in the Pola+R-CHP and R-CHOP arms, respectively, was 80.4 (95% CI, 75.7 to 85.2) and 74.3% (95% CI, 69.0 to 79.6) at the 1-year milestone and 74.1% (95% CI, 68.8 to 79.4) and 64.1% (95% CI, 58.3 to 70.0) at the 2-year milestone [34]. The difference between treatment arms was 6.1% (95% CI, -1.04 to 13.23) and 9.97% (95% CI, 2.06 to 17.87), respectively [34].

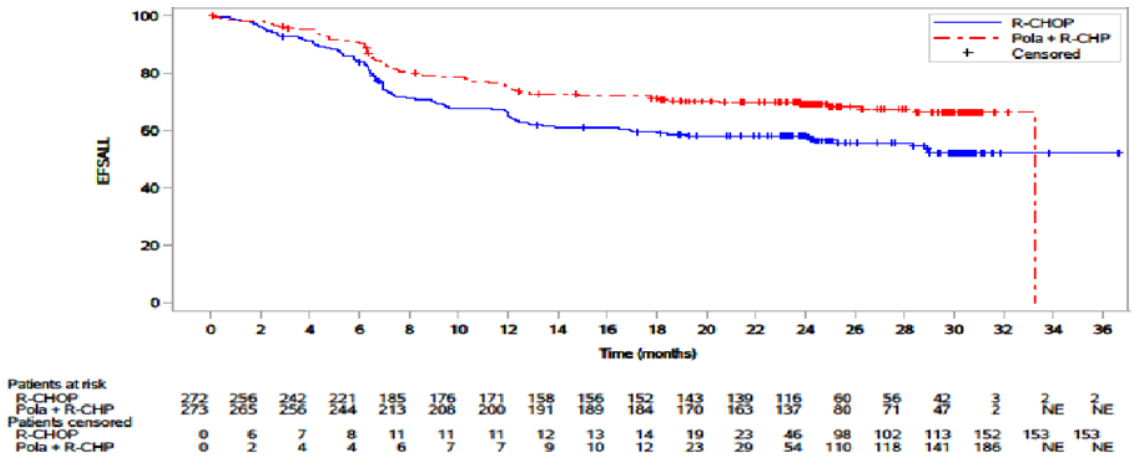


Figure 9: Kaplan-Meier plot of time to EFS in the IPI score 3-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; EFS - Event-free survival; IPI - international prognostic index; NE - not evaluable; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

At the time of the final analysis (CCOD June 2022) the HR showed results similar to the stratified HR from the CCOD June 2021 (HR: 0.71 (95% CI, 0.53 to 0.95). The EFS event-free rate in the Pola+R-CHP and R-CHOP arms, respectively, was 80.1 (95% CI, 75.4 to 84.9) and 74.1% (95% CI, 68.7 to 79.4) at the 1-year milestone and 74.0% (95% CI, 68.7 to 79.3) and 64.3% (95% CI, 58.5 to 70.2) at the 2-year milestone [34]. The difference between treatment arms was 6.07% (95% CI, -1.08 to 13.23) and 9.65% (95% CI, 1.78 to 17.51), respectively [34]

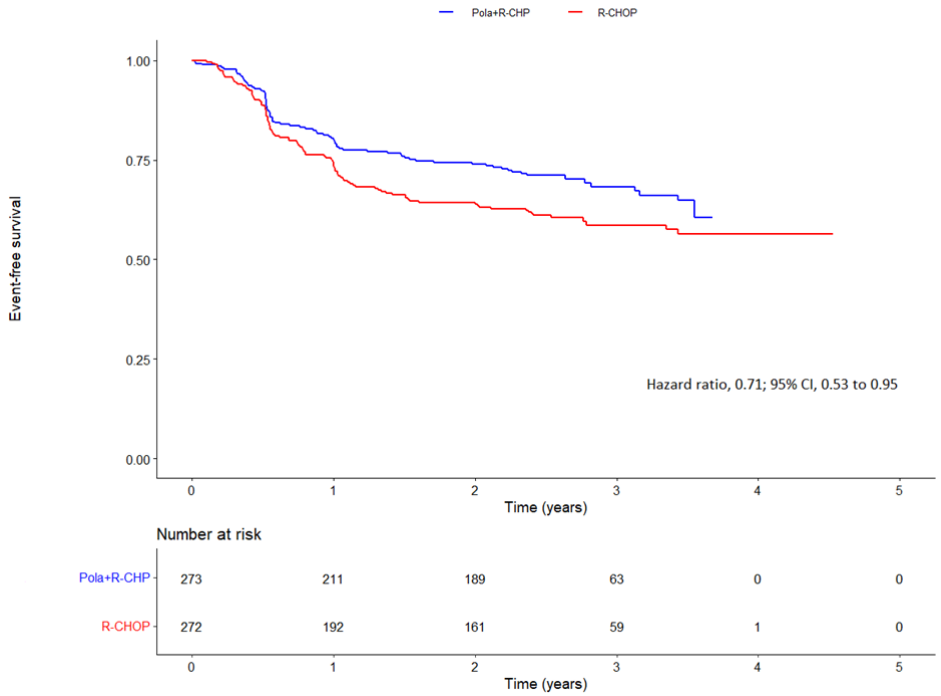


Figure 10: Kaplan-Meier plot of time to EFS in the IPI score 3-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; EFS - Event-free survival; IPI - international prognostic index; NE - not evaluable; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

7.1.2.3 Complete response rate

CR was a key secondary endpoint, which was included in the hierarchical testing procedure [1]. The CR rate is defined as the percentage of patients with CR at the end of treatment by PET-CT as determined by BICR.

An estimate of the CR rate and its 95% CI was calculated using the Clopper-Pearson method for each treatment arm. The 95% CIs for the difference in CR rate between the two treatment arms were computed using the Wilson method. The CR rate was compared between the two arms using the Cochran-Mantel-Haenszel test stratified by the same factors used in the primary analysis of PFS [1].

The data presented are based on CR analyses performed at the time of the primary PFS analysis (CCOD of June 28, 2021). In addition to the primary analysis population for CR, additional post hoc CR analyses based on the subpopulation with IPI score 3-5 were conducted.

IPI score 2-5 population

At the end of the treatment, BICR-assessed CR rate was high in both arms. A numerically higher proportion of patients treated with Pola+R-CHP had complete response at the end of treatment compared to patients treated with R-CHOP. The number of complete responders was 343 (78.0% (95% CI, 73.8 to 81.7)) in the Pola+R-CHP arm and 325 (74.0% (95% CI, 69.7 to 78.1)) in the R-CHOP arm [1,32]. The difference between treatments was 3.9% (95% CI, -1.9 to 9.7), which was not statistically significant (p=0.1557) [32].

IPI score 3-5 population

As for the IPI score 2-5 population, a numerically higher proportion of patients treated with Pola+R-CHP had complete response at the end of treatment compared to patients treated with R-CHOP. The number of complete responders was 205 (75.1% (95% CI, 69.5 to 80.1)) in the Pola+R-CHP arm and 189 (69.5% (95% CI, 63.6 to 74.9)) in the R-CHOP arm. The difference between treatments was 5.6% (95% CI, –2.2 to 13.3; p=0.1446) [34].

7.1.2.4 Overall survival

OS was a key secondary endpoint, which was included in the hierarchical testing procedure [1]. OS was defined as the time from date of randomization until the date of death from any cause. For patients who had not died at the clinical cutoff date for analysis, OS was censored on the last date when the patients were known to be alive, as documented by investigator. Patients who did not have post-baseline information were censored at the date of randomization. The same methodology used to analyse EFS was used to analyse OS.

Results from the interim analysis performed at the time of the primary PFS analysis (CCOD of June 28, 2021) and the final OS analysis (CCOD of June 15, 2022) are presented below. In addition to the primary analysis population for OS, additional post hoc OS analyses based on the subpopulation with IPI score 3-5 were conducted. As for PFS and EFS, both stratified and unstratified OS HRs are available, but main emphasis will be placed on the unstratified HR.

IPI score 2-5 population

As of the first CCOD, OS results were immature beyond 24 months and the event-to-patient ratio was low in both arms. At this time, 53 patients (12%) in the Pola+R-CHP arm and 57 patients (13%) in the R-CHOP arm had experienced an event; the stratified HR was 0.94 (95% CI, 0.65 to 1.37; p=0.7524) [1,30,32]. The unstratified analysis showed results similar to the stratified analysis (HR: 0.92 (95% CI, 0.63 to 1.34; p=0.6720)) [34].

Median OS was not reached for either arm [32]. A similar proportion of patients were alive at the 1- and 2-year milestones compared with R-CHOP. The OS rate at the 1-year milestone was 92.2% (95% CI, 89.6 to 94.7) and 94.6% (95% CI, 92.5 to 96.8) in the Pola+R-CHP and R-CHOP arms, respectively. The difference between treatment arms was -2.5% (95% CI, -5.8 to 0.9) [32]. The OS rate at the 2-year milestone was 88.7% (95% CI, 85.7 to 91.7) and 88.6% (95% CI, 85.6 to 91.6), respectively. The difference between treatment arms was 0.05% (95% CI, -4.2 to 4.3) [1,32].

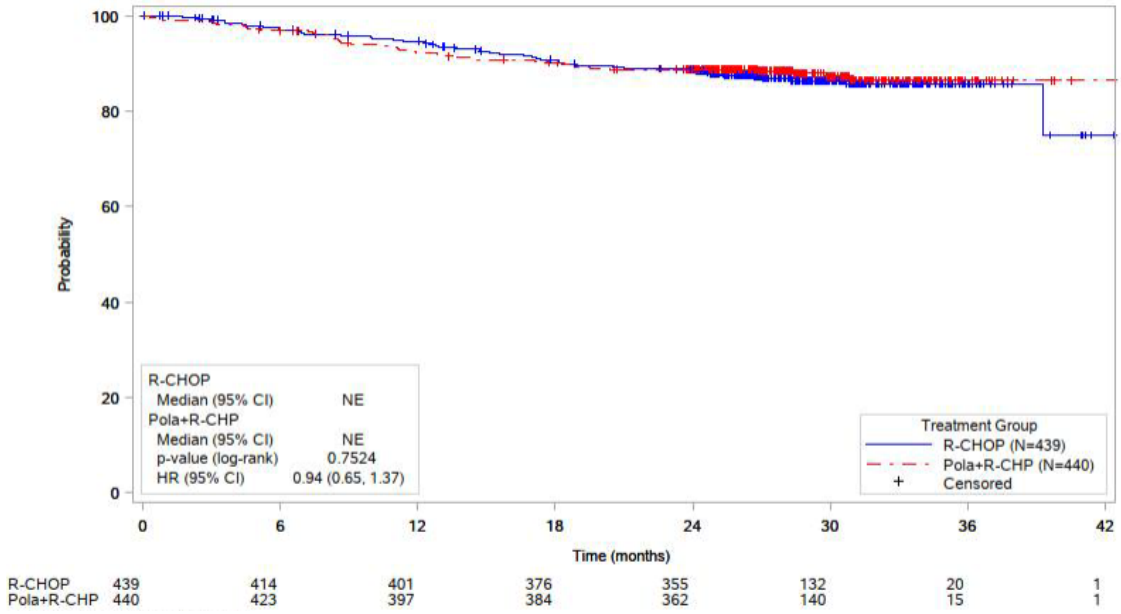
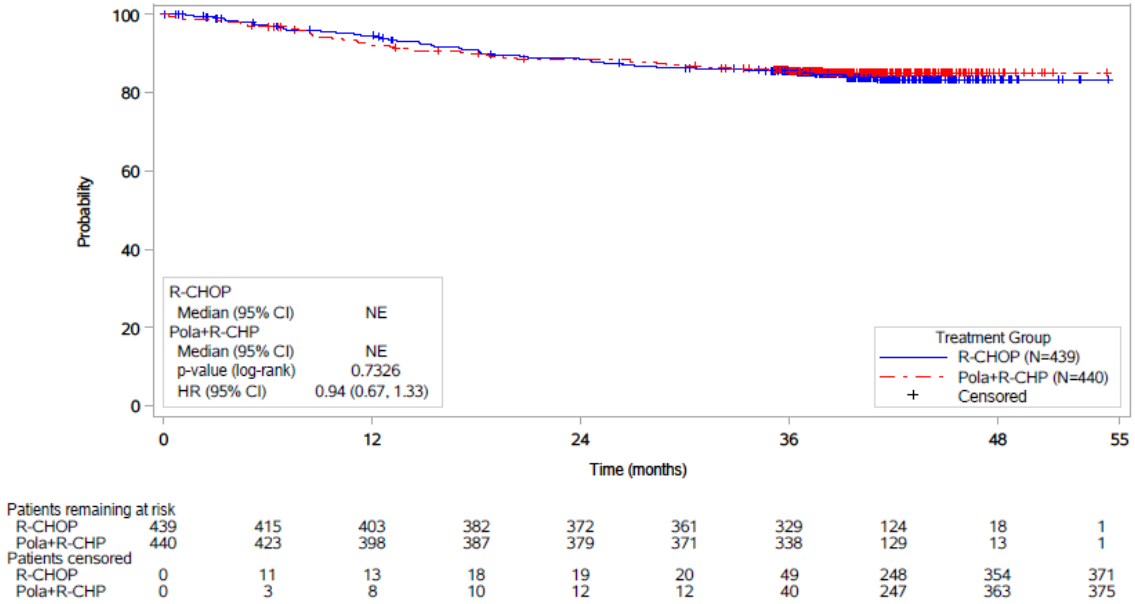


Figure 11: Kaplan-Meier plot of time to OS in the IPI score 2-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; OS - overall survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. Kaplan-Meier plot is available in Tilly et al. 2021 and EMA's assessment report [1,32].

Results from the final OS analysis were consistent with the results from the first interim OS analysis. OS remained immature with a low event rate of 14.5% and 15.3% in the Pola+R-CHP and R-CHOP arms, respectively. The stratified HR was 0.94 (95% CI, 0.67 to 1.33; p=0.7326), which was similar to the unstratified analysis (HR: 0.94, 0.67 to 1.33; p=0.7317) [34].

Median OS was not reached for either arm [34]. The OS event-free rate in the Pola+R-CHP and R-CHOP arms, respectively, was 92.2 (95 % CI, 89.7 to 94.7) and 94.6% (95% CI, 92.5 to 96.8) at the 1-year milestone and 88.7% (95% CI, 85.7 to 91.7) and 88.7% (95% CI, 85.7 to 91.7) at the 2-year milestone [34]. The difference between treatment arms was -2.5% (95% CI, -5.8 to 0.9) and -0.01% (95% CI, -4.3 to 4.2), respectively [34].



Patients remaining at risk										
R-CHOP	439	415	403	382	372	361	329	124	18	1
Pola+R-CHP	440	423	398	387	379	371	338	129	13	1
Patients censored										
R-CHOP	0	11	13	18	19	20	49	248	354	371
Pola+R-CHP	0	3	8	10	12	12	40	247	363	375

Figure 12: Kaplan-Meier plot of time to OS in the IPI score 2-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; OS - overall survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

IPI score 3-5 population

At the time of the primary PFS analysis, the frequency of deaths was low in both arms; 40 patients (15%) in the Pola+R-CHP arm and 43 patients (16%) in the R-CHOP arm had experienced an event. The stratified HR was 0.93 (95% CI, 0.60 to 1.43; p=0.7308) [34]. The unstratified analysis showed results similar to the stratified analysis (HR: 0.91 (95% CI, 0.59 to 1.41; p=0.686) [34]).

Median OS was not reached for either arm [34]. A similar proportion of patients were alive at the 1- and 2-year milestones compared with R-CHOP. The OS rate at the 1-year milestone was 90.4% (95% CI, 86.9 to 93.9) and 93.6% (95% CI, 90.6 to 96.5) in the Pola+R-CHP and R-CHOP arms, respectively. The difference between treatment arms was -3.18% (95% CI, -7.78 to 1.42) [34]. The OS rate at the 2-year milestone was 86.6% (95% CI, 82.6 to 90.7) and 85.4% (95% CI, 81.1 to 89.7), respectively. The difference between treatment arms was 1.24% (95% CI, -4.67 to 7.16) [34].

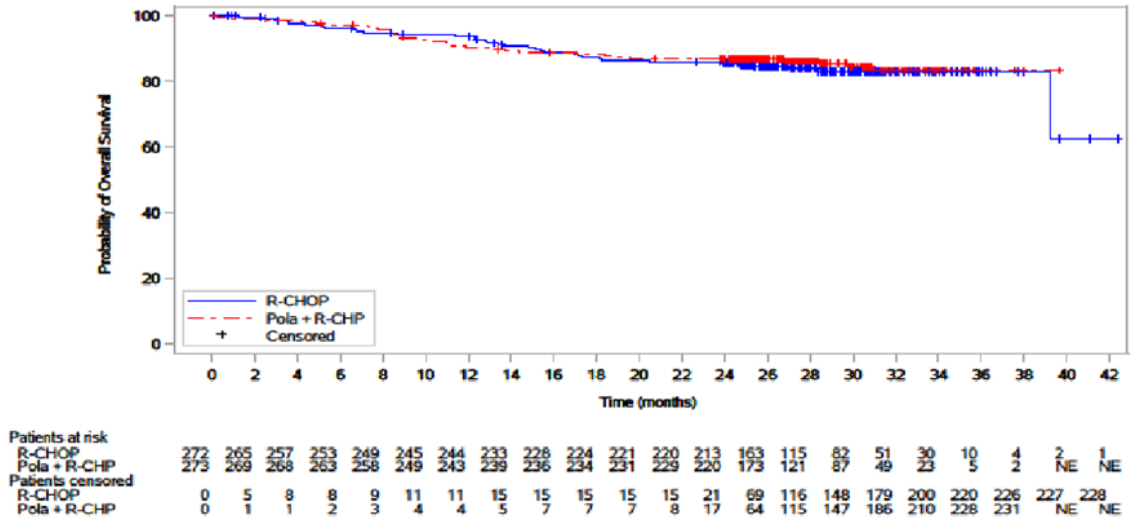
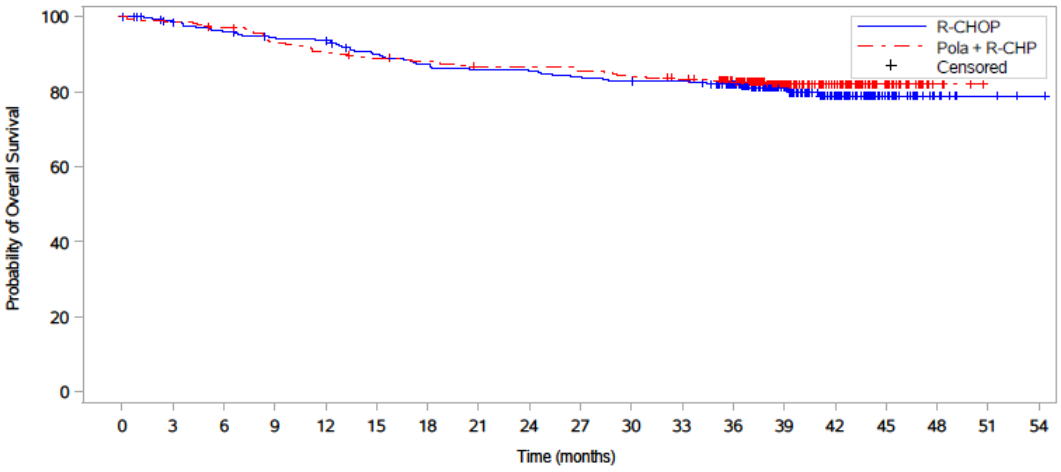


Figure 13: Kaplan-Meier plot of time to OS in the IPI score 3-5 population; CCOD: June 28, 2021

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; OS - overall survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

Results from the final OS analysis were consistent with the results from the first interim OS analysis. OS remained immature with a low event rate of 17.6% in the Pola+R-CHP and 19.1% in the R-CHOP arm. The stratified HR was 0.90 (95%, 0.61 to 1.34; p=0.61) [34]. The unstratified analysis showed results similar to the stratified analysis (HR: 0.90 (95%, 0.61 to 1.33; p=0.5859) [34].

Median OS was not reached for either arm [34]. The OS event-free rate in the Pola+R-CHP and R-CHOP arms, respectively, was 90.4% (95% CI, 86.9 to 93.9) and 93.6% (95% CI, 90.6 to 96.5) at the 1-year milestone and 86.7% (95% CI, 82.6 to 90.7) and 85.5% (95% CI, 81.2 to 89.8) at the 2-year milestone [34]. The difference between treatment arms was -3.2% (95% CI, -7.8 to 1.4) and 1.2% (95% CI, -4.7 to 7.0), respectively [34].



Patients at risk																			
R-CHOP	272	262	254	248	246	234	227	223	222	218	215	214	195	121	75	31	8	3	1
Pola + R-CHP	273	268	263	251	244	239	236	231	231	228	224	220	201	128	78	32	4	NE	NE
Patients censored																			
R-CHOP	0	6	7	9	9	12	12	12	12	12	12	13	30	102	145	189	212	217	219
Pola + R-CHP	0	1	2	3	3	4	5	6	6	6	6	8	26	97	147	193	221	NE	NE

Figure 14: Kaplan-Meier plot of time to OS in the IPI score 3-5 population; CCOD: June 15, 2022

Abbreviations: CCOD - clinical cut-off date; CI - confidence interval; HR - hazard ratio; ITT - intent-to-treat; NE - not evaluable; OS - overall survival; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone. The Kaplan-Meier plot is not publicly available [34].

7.1.2.5 Health-related quality of life

PROs were measured using the following instruments: the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30), the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS), the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity questionnaire (FACT/GOG-NTX) and the 5-dimension 5-level EuroQol questionnaire (EQ-5D-5L). In the following, we present data on EORTC QLQ-C30 and FACT-Lym LymS.

The EORTC QLQ-C30 and FACT-Lym LymS were administered at cycle 1, day 1 (baseline); cycle 2, day 1; cycle 3, day 1; and cycle 5, day 1. Patients completed both PRO measures at treatment discontinuation and at specified planned post-treatment visits thereafter until the close of the study (every 6 months for the first 2 years after the treatment completion visit or early termination visit, and every 12 months for the following 3 years) [34].

7.1.2.5.1 EORTC QLQ-C30

For EORTC QLQ-C30 a responder analysis is performed. The responder analysis is based on the number and proportion of patients with a clinically meaningful improvement in EORTC physical functioning and fatigue and the FACT-Lym LymS. Clinically meaningful improvement in EORTC for physical functioning scale was defined as ≥7-point increase and for fatigue scale was defined as ≥9-point decrease (Cocks et al. 2012). For FACT-Lym LymS, clinically meaningful improvement was defined as a ≥3-point increase (Carter et al. 2008, Hlubocky et al. 2013). Below results of these subdomains of EORTC QLQ-C30 are presented together with the Global Health Status.

Responder improvement analysis showed that a higher proportion of patients in the Pola+R-CHP arm (42.4% (95% CI, 37.6 to 47.3)) experienced an improvement in the EORTC QLQ-C30 measure of physical functioning, compared with

the R-CHOP arm (39.6% (95% CI, 34.8 to 44.5)). Median time to deterioration in physical functioning was not estimable (NE) (18.9-NE) in the Pola+R-CHP arm and was 25.4 months (17.6-NE) in the R-CHOP arm; HR was 0.97 (95% CI, 0.79 to 1.19) [34].

Responder improvement analysis revealed that a greater number of patients in the Pola+R-CHP arm experienced an improvement in fatigue compared with the R-CHOP arm (74.8% (95% CI, 70.3 to 78.9) and 68.2% (95%, 63.5 to 72.7), respectively). Treatment with Pola+R-CHP resulted in a slower median time to deterioration in fatigue, as measured by the EORTC QLQ-C30 score, compared with R-CHOP (Pola+R-CHP, 6.7 months; R-CHOP, 3.0 months), although the difference between treatment arms was not significant; HR was 0.94 (95% CI, 0.78 to 1.13) [34].

QoL at baseline and QoL at the following cycles measured by EORTC QLQ-C30 is illustrated below both for the ITT-population and patients with IPI 3-5. It is clear from the illustrations that QoL is not significantly different between Pola+R-CHP and R-CHOP. For this reason the utilities applied in the health economic model is pooled for Pola+R-CHP and R-CHP.

The timing and number of patients answering EORTC QoL-C30 is presented in appendix I.

7.1.2.5.2 FACT-Lym LymS

The proportion of patients with an improvement in the FACT Lym LymS scale was high in both treatment arms (Pola+R-CHP: 82.3% (95% CI, 78.3 to 85.9); R-CHOP: 81.3% (95% CI, 77.2 to 85.0)). Median time to deterioration in lymphoma-specific symptoms was not estimable in either treatment arm; HR was 1.03 (95% CI, 0.81 to 1.30) [34].

QoL at baseline and QoL at the following cycles measured by FACT-Lym LymS is illustrated below both for the ITT-population and patients with IPI 3-5. It is clear from the illustrations that QoL is not significantly different between Pola+R-CHP and R-CHOP. For this reason the utilities applied in the health economic model is pooled for Pola+R-CHP and R-CHP.

The timing and number of patients answering FACT-Lym Lyms is presented in appendix I.

7.1.2.5.3 EQ-5D-VAS

QoL at baseline and QoL at the following cycles measured by EQ-5D-VAS is illustrated below both for the ITT-population and patients with IPI 3-5. It is clear from the illustrations that QoL is not significantly different between Pola+R-CHP and R-CHOP. For this reason the utilities applied in the health economic model is pooled for Pola+R-CHP and R-CHP.

The timing and number of patients answering EQ-5D-VAS is presented in appendix I.

7.1.2.6 Safety

The primary safety objective in POLARIX was to compare the incidence of AEs in the two treatment groups. The incidence, nature and severity of AEs and rates of peripheral neuropathy were recorded by the investigator. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0.

In the following safety data will be presented in two parts:

- Incidence of AEs by severity, SAEs and discontinuation due to AEs
- Qualitative description of the safety profiles of the intervention and comparator

Safety results will be presented for the safety-evaluable population, including all patients who received ≥ 1 dose of study treatment (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, vincristine or prednisone) (n=873), and the IPI score 3-5 subpopulation (n=540).

The overall safety profile Included treatment-emergent AEs during an AE reporting period, which was defined as new or worsening AE from the first dose of any study drug through 90 days after the last dose of any study drug or prior to any new anti-lymphoma therapy (NALT), whichever is earlier. Patients in the Pola+R-CHP arm received a median of 6 cycles of pola (range 1-6) and patients in the R-CHOP arm received a median of 6 cycles of vincristine (range 1-6), both corresponding to a median treatment duration of 3.5 months. Patients in both the treatment arms also received a median of 8 cycles of rituximab (range 1-8), corresponding to a median treatment duration of 4.9 months [32].

7.1.2.6.1 Incidence of AEs by severity, SAEs and discontinuation due to AEs

The incidence of AEs of any grade, AEs of grade 3-5, SAEs, AE leading to study discontinuation and AEs leading to any study treatment dose discontinuations were comparable between the treatment arms in both populations and across populations (Table 8).

Table 8: Incidence of safety outcomes in the IPI score 2-5 and IPI score 3-5 population

Safety parameter	IPI score 2-5 population [1,2,3,4]		IPI score 3-5 population [2,4]	
	Pola+R-CHP n=435	R-CHOP n=438	Pola+R-CHP n=269	R-CHOP n=271
Any AE, n (%)	426 (97.9)	431 (98.4)	264 (98.1)	266 (98.2)
Grade 3-4 AEs	251 (57.7)	253 (57.7)	168 (62.5)	165 (60.9)
Grade 5 AEs	13 (3.0)	10 (2.3)	7 (2.6)	9 (3.3)
Treatment-related AE, n (%)				
Grade 3-4 treatment-related AEs	[redacted]			
Grade 5 treatment-related AEs				
Any SAE, n (%)	148 (34.0)	134 (30.6)	94 (34.9)	98 (36.2)
Treatment-related SAE	[redacted]			
AE leading to study discontinuation, n (%)	13 (3.0)	10 (2.3)	7 (2.6)	9 (3.3)
AE leading to any study treatment dose discontinuation, n (%)	27 (6.2)	29 (6.6)	19 (7.1)	21 (7.7)

CCOD: June 28, 2021. All safety outcomes except the treatment-related events for the IPI score 2-5 population are available in Tilly et al. 2021 [1] and EMA's assessment report [32]. All treatment-related outcomes are not publicly available [34]. All safety outcomes for the IPI score 3-5 population are not yet publicly available [34]. Abbreviations: CCOD - clinical cut-off date; AE - adverse event; n - number of patients; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone; SAE - serious adverse event.

7.1.2.6.2 Qualitative description of the safety profiles

In POLARIX, the proportion of patients with at least one AE was comparable between the two treatment arms [32] (Table 8). AEs by preferred term (PT) reported by ≥20% of patients in either the Pola+R-CHP or the R-CHOP arm were nausea (41.6% vs. 36.8%), neutropenia (30.8% vs. 32.6%), diarrhoea (30.8% vs. 20.1%), constipation (28.7% vs. 29.0%), anaemia (28.7% vs. 26.0%), fatigue (25.7% vs. 26.5%), alopecia (24.4% vs. 24.0%), peripheral neuropathy (24.1% vs. 22.6%), and peripheral sensory neuropathy (19.5% vs. 21.5%) [1,32] (Table 9).

The proportion of patients with AEs of grade 1-2 and AEs of grade 3-4 was comparable between treatment arms [32]. Grade 1-2 AEs were reported in 37.2% of patients in the Pola+R-CHP arm and 38.4% of patients in the R-CHOP arm, and grade 3-4 AEs were reported in 57.7% and 57.7% of patients, respectively [32]. The most common grade 3-4 AEs were neutropenia (Pola+R-CHP, 28.3%; R-CHOP, 30.8%), febrile neutropenia (Pola+R-CHP, 13.8%; R-CHOP, 8.0%), and anaemia (Pola+R-CHP, 12.0%; R-CHOP, 8.4%) [1,32] (Table 9).The rate of febrile neutropenia was higher in the Pola+R-CHP arm compared with the R-CHOP arm, however, this did not result in higher rates of infection (AE by System Organ

Class (SOC)), with the percentages of patients who had infections of grade 3-4 being comparable between the two arms (14.0% and 11.2% in the Pola+R-CHP and R-CHOP arms, respectively) [32]. Also, the proportion of patients discontinuing at least one of the drugs in the trial regimen (2.1% vs. 2.3%) or having dose reductions (1.8% vs. 2.5%) because of either infections or neutropenia were similar between treatment arms [1]. AEs that resulted in death (grade 5 AEs) were reported in 13 patients (3.0%) in the Pola+R-CHP group and in 10 patients (2.3%) in the R-CHOP group [1,32] (Table 8). These events were primarily related to infections (pneumonia in 4 patients and sepsis in 1 patient in the Pola+R-CHP arm; pneumonia in 3 patients, septic shock in 2 patients and sepsis in 1 patient in the R-CHOP arm) [32].

The proportion of patients with at least one serious AE (SAE) was comparable between the treatment arms (Pola+R-CHP, 34.0%; R-CHOP, 30.6%) [1,32] (Table 8). The most common SAE was febrile neutropenia, occurring in 9.9% and 6.4% of the Pola+R-CHP and R-CHOP arms, respectively [32].

The proportion of patients who experienced AEs leading discontinuation of at least one of the drugs in the trial regimen was similar in Pola+R-CHP and R-CHOP arms (6.2% and 6.6%, respectively; (Table 9)) [1,32]. Among these patients, 4.4% in the Pola+R-CHP group discontinued polatuzumab vedotin because of adverse events, and 5.0% in the R-CHOP group discontinued vincristine because of adverse events [1,32]. AEs leading to study discontinuation was 3.0% and 2.3% in Pola+R-CHP and R-CHOP arms, respectively [32].

The incidence of peripheral neuropathy of any grade was similar between the treatment arms. The proportion of patients who experienced peripheral neuropathy of any grade was 52.9% in the Pola+R-CHP arm and 53.9% in the R-CHOP arm [1,32]. The majority of patients experienced low-grade peripheral neuropathy. Events of grade 3 were reported in 7 patients (1.6%) in the Pola+R-CHP arm and 5 patients (1.1%) in the R-CHOP arm. No patients in either arm experienced grade 4 or 5 events [32]. The median time to the onset of any neuropathy was 2.3 months (range, 0.0 to 6.7) in the Pola+R-CHP arm and 1.9 months (range, 0.0 to 8.1) in the R-CHOP arm; the median time to resolution of any neuropathy was 4.0 (range 0.0 to 36) months and 4.6 months (range, 0.0 to 34.9), respectively [1,32]. Resolution of peripheral neuropathy was reported in the majority of patients at the time of CCOD (Pola+R-CHP, 57.8%; R-CHOP, 66.9%). The later time to onset of peripheral neuropathy events in the Pola+R-CHP arm compared with the R-CHOP arm likely contributed to more patients with unresolved peripheral neuropathy in the Pola+R-CHP arm at the time of CCOD [32]. Very few patients discontinued any treatment dose because of peripheral neuropathy (Pola+R-CHP, 0.7%; R-CHOP: 2.3%) [32]. The percentage of patients who had peripheral neuropathy that led to dose reduction was lower among those who received polatuzumab vedotin than among those who received vincristine (4.6% vs. 8.2%) [32].

Similarly, for neutropenia events, the proportion of patients who experienced neutropenia (including febrile neutropenia) in the Pola+R-CHP arm (46.0%) was generally comparable with the R-CHOP arm (42.7%) [32]. The majority of patients experienced neutropenia events of grade 3-4. The most common grade 3-4 AE was neutropenia (Pola+R-CHP, 28.3%; R-CHOP, 30.8%) Table 9. No patients in either arm experienced grade 5 events [32]. The median time to the onset of any neutropenia was 0.49 months (range, 0.1 to 7.2) in the Pola+R-CHP arm and 0.43 months (range, 0.1 to 6.4) in the R-CHOP arm; the median time to resolution was 0.23 (range 0.0 to 16.5) months and 0.26 months (range, 0.0 to 18.5), respectively. Neutropenia was reported as resolved in 98.0% of patients in the Pola+R-CHP arm and 97.9% in the R-CHOP arm at the time of CCOD [32].

Table 9: Incidence of grade 3-4 AEs by PT occurring in ≥2% of patients in the IPI score 2-5 and IPI score 3-5 populations

Adverse event during the treatment period	IPI score 2-5 population [1,32]	IPI score 3-5 population [34]

Grade 3-4 AEs	Pola+R-CHP n=435	R-CHOP n=438	Pola+R-CHP n=271	R-CHOP n=269
Neutropenia	123 (28.3)	135 (30.8)	82 (30.5)	82 (30.3)
Febrile neutropenia	60 (13.8)	35 (8.0)	42 (15.6)	25 (9.2)
Anaemia	52 (12.0)	37 (8.4)	42 (15.6)	26 (9.6)
Neutrophil count decreased	30 (6.9)	28 (6.4)	22 (8.2)	19 (7.0)
Leukopenia	25 (5.7)	30 (6.8)	20 (7.4)	18 (6.6)
Thrombocytopenia	14 (3.2)	19 (4.3)	12 (4.5)	13 (4.8)
White blood cell count decreased	18 (4.1)	14 (3.2)	13 (4.8)	8 (3.0)
Pneumonia	14 (3.2)	17 (3.9)	14 (5.2)	13 (4.8)
Lymphocyte count decreased	13 (3.0)	15 (3.4)	9 (3.3)	5 (1.8)
Diarrhoea	17 (3.9)	8 (1.8)	16 (5.9)	3 (1.1)
Lymphopenia	7 (1.6)	10 (2.3)	-	-
Syncope	8 (1.8)	9 (2.1)	-	-
Hypertension	6 (1.4)	10 (2.3)	-	-
Hyponatraemia	6 (1.4)	9 (2.1)	4 (1.5)	8 (3.0)
Fatigue	4 (0.9)	11 (2.5)	-	-
Platelet count decreased	9 (2.1)	3 (0.7)	9 (3.3)	3 (1.1)
Hypokalaemia	-	-	7 (2.6)	6 (2.2)
Hypophosphataemia	-	-	6 (2.2)	5 (1.8)
Sepsis	-	-	3 (1.1)	7 (2.6)
Asthenia	-	-	6 (2.2)	2 (0.7)

CCOD: June 28, 2021. Reported AEs for the IPI score 2-5 population are available in Tilly et al 2021 [1] and/or EMA's assessment report [32]. Reported AEs for the IPI score 3-5 population are not yet publicly available [34]. Abbreviations: CCOD - clinical cut-off date; AE - adverse event; n - number of patients; pola - polatuzumab vedotin; PT - preferred term; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone; SAE - serious adverse event.

7.1.2.6.3 Conclusion

The safety profile of the Pola+R-CHP regimen was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease. Toxicities were manageable. The incidence of AEs of any grade, AEs of grade 3-5, SAEs and AEs leading to any treatment discontinuations were comparable in the two groups. Although the incidence of febrile neutropenia was higher among patients who received Pola+R-CHP than among those who received R-CHOP, this finding did not translate into a higher overall incidence of infection, treatment discontinuation or dose reductions and was similar to the percentages reported in recent R-CHOP trials (9.0% to 15.2%) [35-37]. The proportion of patients who experienced peripheral neuropathy in the Pola+R-CHP arm was comparable with the R-CHOP arm and the majority of cases of peripheral neuropathy were grade 1.

7.1.3 Comparative analyses of efficacy and safety

POLARIX provides a direct comparison between Pola+R-CHP and R-CHOP and the results can be used to address the clinical question. Results are presented in Section 7.1.2.

8. Health economic analysis

8.1 Model

8.1.1 Model structure

A three-health state partitioned survival model is used to perform the cost-effectiveness analysis and estimate long-term costs and health benefits.

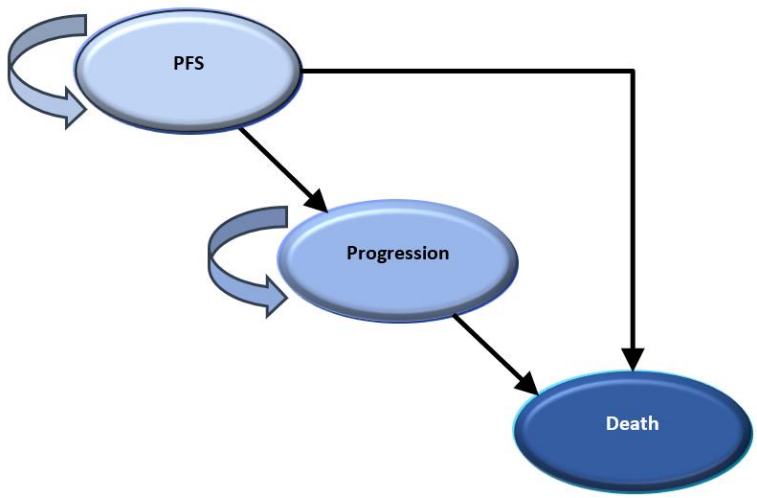
Partitioned survival models are often used in economic evaluations of oncology drugs, and have been commonly used in DLBCL submission to the DMC [38]. For the previous assessment of Pola+BR for R/R DLBCL patients in the DMC, a mixture cure rate model approach was selected. However, this was not accepted due to the lack of clinically plausibility. We had also assessed the use of a mixture cure model and came to the same conclusion. Consequently, a partitioned survival model was used with log-normal distributions to extrapolate PFS and OS in the previous assessment of Pola+BR for R/R patients [38].

The model schematic (Figure 21) aligns with previous DLBCL models submitted to the DMC. [38-40] Patients must be in any one of the three mutually exclusive health states at the end of each seven-day model cycle. The three health states are: pre-progression, post-progression, and death.

Based on this structure, to estimate the percentage of patients in each health state at each model cycle, survival distributions for PFS and OS were used. This enables the estimation of treatment costs, health state costs, and health state utility values to accrue quality-adjusted life years (QALY) and costs over the model time horizon. All patients are progression-free at the start of the model. At each cycle, state membership is calculated based on the PFS and OS curves, the PFS distribution is used to calculate the percentage of patients' remaining progression-free while the OS distributions is used to calculate the percentage of patients dead. The percentage of patients progressed will be inferred from the percentage difference between the patients alive and the progression-free patients.

The model structure is in line with previous models used in the DLBCL setting. The use of a pre-progression, post-progression and death health state is the same as in the Yescarta, polatuzumab + bendamustine and rituximab (Pola+BR), and Kymriah assessments. The structure for these three assessments were deemed appropriate and considered acceptable by both AMGROS and the DMC [38-40].

Figure 21. Model structure



Note: PFS, Progression-free survival

8.1.2 Health states

Progression free survival

Progression-free survival is the initial state in which all patients enter the model. Transitions out of this state are determined by the progression-free survival (PFS) curves estimated based on the POLARIX trial data. The PFS curves indicate for each point in time the proportion of patients who have not progressed and not died yet.

Post-progression state

The post-progression state accommodates all patients who have experienced disease progression but have not died yet. The proportion of all patients in this state was calculated as the difference between the proportion of patients who were alive and those who are progression-free. The transitions into and out of the post-progression health state were thus not modelled explicitly but as a residual proportion of patients, see Figure 21.

Death state

Death is as an absorbing state meaning that all patients eventually enter this state and cannot leave it. The transitions of patients from the progression-free and post-progression health states into the death state were determined by the overall survival curves derived from the POLARIX trial. Overall survival curves indicate the proportion of patients who are alive at a given point in time or, equivalently, the proportion of patients who die during a model cycle dependent on the time since treatment initiation.

8.1.3 Time horizon

The DMC method guideline states that the selected time horizon should be long enough to reflect all important differences in costs and efficacy between the technologies being compared [41].

The model uses a lifetime horizon of 40 years, considered to represent a lifetime horizon for patients. Given the mean age of 64 years in the POLARIX for the subgroup population with the inventory performance index (IPI) of 3-5, 40 years was considered a fair approximation of a lifetime time horizon [2,41].

8.1.4 Perspective

The perspective of the economic model is a restricted Danish societal perspective, which includes costs related to drug acquisition, drug administration, monitoring, adverse events, patient time, and transportation. Indirect costs are not included in line with the DMC's guidelines [41].

8.1.5 Cycle length, discounting, and half-cycle correction

Cycle length

A weekly cycle length was used in the model. By applying a relatively short cycle length of weekly cycle, the difference between the actual transition time and the model predicted transition time is reduced. This allows for more accurate estimation of the length of time patients remain in the health states and more flexibility and accuracy in in relation to costing. Furthermore, this cycle length was consistent with the cycle length used in a previous assessment of the Pola+BR for treatment of relapsed or refractory (R/R) DLBCL [38].

Discounting

A discount rate of 3.5% until year 35 and 2.5% from year 35-70 was applied to costs and efficacy, as defined by the Danish Ministry of Finance and in the DMC guidelines [41,42].

Half-cycle correction

It was assumed that transitions from one health state to another occur at the beginning of each cycle. However, state transitions are a continuous process, which may occur at any time during the cycle. The half-cycle correction was thus applied in the model to account for mid-cycle transitions. This assumes that state transitions occur, on average, halfway through the cycle. Due to the short cycle length of one week, the half-cycle correction was not expected to have a large impact on the results, but it was included in the model for completeness.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

8.2.1 Presentation of input data used in the model and how they were obtained

Table 10 below presents some of the key parameters used in the health economic model and how these have been obtained.

Table 10. Input data used in the model

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Progression-free survival (PFS) Pola+R-CHP, mean in years	See section 8.3	9.0	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Progression-free survival (PFS) R-CHOP, mean in years	See section 8.3	5.9	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Overall survival (OS) Pola+R-CHP, mean in years	See section 8.3	16.6	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Overall survival (OS) R-CHOP, mean in years	See section 8.3	15.4	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Polatuzumab (Pola+R-CHP), mean in months	See section 8.3	3.6	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Rituximab (Pola-R+CHP), mean in months	See section 8.3	4.9	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Time to off treatment (TTOT), Cyclophosphamide (Pola+R-CHP), mean in months	See section 8.3	3.6	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Doxorubicin (Pola+R-CHP), mean in months	See section 8.3	3.6	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Prednisone (Pola+R-CHP), mean in months	See section 8.3	3.7	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Rituximab (R-CHOP), mean in months	See section 8.3	4.6	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Cyclophosphamide (R-CHOP), mean in months	See section 8.3	3.5	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Doxorubicin (R-CHOP), mean in months	See section 8.3	3.5	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Vincristine (R-CHOP), mean in months	See section 8.3	3.4	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Time to off treatment (TTOT), Prednisone (R-CHOP), mean in months	See section 8.3	3.5	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
HSUV PFS	See section 8.4	0.862	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
HSUV PD	See section 8.4	0.832	Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].
Costs	See section 8.5		Medicinpriser.dk, interaktivdrg.dk, labportalen.dk [43-45]

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Adverse events	See section 8.2.2.5		Based on the POLARIX trial, for patients with CD20-positive DLBCL, IPI 3-5 [1,2].

Note: PFS, Progression-free survival; OS, Overall survival; TTOT, Time to off treatment; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; HSUV, Health-state utility value; PPS, Post-progression survival

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

Table 11 summarizes the patient population as expected in Danish clinical practice, in relation to the trial data, and the cost-effectiveness model.

The patient population of interest in Danish clinical practice is previously untreated adult patients with DLBCL with a IPI 3-5 score. This is in line with the label assigned by EMA.

Data regarding the patient population in the health economic model submitted uses the main documentation and subpopulation characteristics of patients previously untreated for DLBCL with a IPI 3-5 score from the POLARIX trial. As stated in section 8.1.3, patients entering the model at an average age of 64 years informed by the POLARIX trial for the subpopulation. The Danish DLBCL guideline is providing a median age of 67 for all patients in Denmark [11]. Additional patients' characteristics for the average Danish patient with DLBCL IPI 3-5 is not available in the DLBCL guideline developed by the DMCG and the Regions' Clinical Quality Development Programme (RKKP). Where data are available, it can be concluded that the POLARIX trial broadly reflects patients in Danish clinical practice.

Table 11. Patient population

Important baseline characteristics	Clinical documentation / indirect comparison etc. [1,2]	Used in the model	Danish clinical practice
Age mean	64	64	67 (median) [46]
Gender (% male)	55.41%	55.41%	A little more prevalent in men [47]
Weight (kg)	75.92	75.92	NA
Height (cm)	167.97	167.97	NA
Body Surface Area (m^2)	1.86	1.86	NA

Important baseline characteristics	Clinical documentation / indirect comparison etc. [1,2]	Used in the model	Danish clinical practice
Patient population	Adult patients with CD20-positive DLBCL, previously untreated, with an IPI score of 3-5	Adult patients with CD20-positive DLBCL, previously untreated, with an IPI score of 3-5	Adult patients with CD20-positive DLBCL, previously untreated, with an IPI score of 3-5

Note: DLBCL, Diffuse large B-cell lymphoma; kg, kilogram; cm, centimetres

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice: refer to section 5.3. Inputs regarding polatuzumab in the model are informed by the clinical trial POLARIX most recent data-cut from June 2022 [1,2].

Polatuzumab is approved by the EMA as a combination therapy with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola+R-CHP) for previously untreated patients with DLBCL [48].

Polatuzumab is intravenously (IV) administered at a recommended dose of 1.8 mg/kg every 21 days in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone for 6 cycles. Cycles 7 and 8 consists of rituximab monotherapy [1,48].

In POLARIX, polatuzumab is used in line with the label, which is 1.8 mg/kg every 21 days in combination with rituximab 375 mg/m^2 IV, cyclophosphamide 750 mg/m^2 IV, and doxorubicin 50 mg/m^2 IV each given on Day 1 and prednisone 100 mg/day orally (PO) given on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m^2 IV will be given as monotherapy in Cycles 7 and 8. However, a Danish clinical expert within DLBCL stated that prednisone is administrated subcutaneously (SC), 100 mg on day 1-5 every 21 day [49]. This is difference in practices is not expected to affect the efficacy if the intervention.

Table 12. Intervention

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice [49]
Posology	*Polatuzumab:* 1.8 mg/kg every 21 days, IV [1,48] *Rituximab*: 375 mg/m^2, IV [1,50] *Cyclophosphamide*: 750 mg/m^2, IV [1] *Doxorubicin*: 50 mg/m^2, IV [1] *Prednisone*: 100 mg, Oral [1]	*Polatuzumab:* 1.8 mg/kg every 21 days, IV *Rituximab*: 375 mg/m^2, IV *Cyclophosphamide*: 750 mg/m^2, IV *Doxorubicin*: 50 mg/m^2, IV *Prednisone*: 100 mg, SC	*Polatuzumab:* 1.8 mg/kg every 21 days, IV *Rituximab*: 375 mg/m^2, IV *Cyclophosphamide*: 750 mg/m^2, IV *Doxorubicin*: 50 mg/m^2, IV *Prednisone*: 100 mg, SC
Length of treatment (time on treatment) (mean/median)	6 cycles [1,48] Rituximab 8 cycles [1,50]	6 cycles Rituximab 8 cycles	6 cycles Rituximab 8 cycles

Intervention	Clinical documentation	Used in the model	Expected Danish clinical practice [49]
Criteria for discontinuation	Consider end of treatment if unacceptable toxicity [48]	Consider end of treatment if unacceptable toxicity	Consider end of treatment if unacceptable toxicity
The pharmaceutical's position in Danish clinical practice	NA	1L	1L

Note: IV, Intravenous; mg, milligram; SC, Subcutaneously

8.2.2.3 Comparators

In current Danish clinical practice, the combination therapy of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) is recommended for patients aged ≥ 65 with comorbidity with DLBCL by the DMCG, and the practice was confirmed by a a Danish clinical expert within DLBCL [49,51]. Consequently R-CHOP is considered relevant treatment alternative [51].

The POLARIX trial is a head-to-head trial, comparing Pola+R-CHP with R-CHOP in previously untreated DLBCL patients [1]. As the POLARIX study is considered representative to danish clinical practice, the combination treatment of R-CHOP is used as the comparator to Pola+R-CHP in this economic analysis.

Table 13. Comparator

Comparator	Clinical documentation (including source) [49,51]	Used in the model (number/value including source)	Expected Danish clinical practice (including source) [49]
Posology	*Rituximab*: 375 mg/m^2, IV [1,49-51] *Cyclophosphamide*: 750 mg/m^2, IV [1,49,51] *Vincristine*: 1.4 mg/ m^2, IV [1,49,51] *Doxorubicin*: 50 mg/m^2, IV [1,49,51] *Prednisone*: 100 mg, Oral [1,51]	*Rituximab*: 375 mg/m^2, IV *Cyclophosphamide*: 750 mg/m^2, IV *Vincristine*: 1.4 mg/ m^2, IV *Doxorubicin*: 50 mg/m^2, IV *Prednisone*: 100 mg, SC	*Rituximab*: 375 mg/m^2, IV *Cyclophosphamide*: 750 mg/m^2, IV *Vincristine*: 1.4 mg/ m^2, IV *Doxorubicin*: 50 mg/m^2, IV *Prednisone*: 100 mg, SC
Length of treatment (time on treatment) (mean/median)	6 cycles Rituximab 8 cycles [1,49-51]	6 cycles Rituximab 8 cycles	6 cycles Rituximab 8 cycles [49,51]
The pharmaceutical's position in Danish clinical practice	1L, standard of care [51]	1L	1L [49,51]

Note: mg, milligrams; m^2, square meters; 1L, First-line; IV, Intravenous; SC, Subcutaneously

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes are summarized in section 7. A head to head trial is available for Pola+R-CHP vs. R-CHOP and relative efficacy outcomes for PFS and OS as well as safety have been estimated directly from POLARIX [1].

Consequently, we consider that the included efficacy outcomes are highly relevant to determine the cost-effectiveness of Pola+R-CHP in 1L treatment of DLBCL, see Table 14 and Table 15.

Table 14. Value

Clinical efficacy outcome	Clinical documentation [1]	Used in the model (value)
Progression-free survival (PFS)	POLARIX trial	See Table 10
Overall Survival (OS)	POLARIX trial	See Table 10

Note: PFS, Progression-free survival; OS, Overall survival

Table 15. Relevance

Clinical efficacy outcome	Clinical documentation (measurement method) [1]	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Progression-free survival (PFS)	See section 7, POLARIX trial	Traditionally used in evaluations of drugs in oncology	Traditionally used in evaluations of drugs in oncology
Overall Survival (OS)	See section 7, POLARIX trial	Traditionally used in evaluations of drugs in oncology	Traditionally used in evaluations of drugs in oncology

Note: PFS, Progression-free survival; OS, Overall survival

8.2.2.5 Adverse reaction outcomes

The AE reaction outcomes in the health economic model is based on the safety population from the POLARIX trial consisting of 435 patients in the Pola+R-CHP arm and 438 in the R-CHOP arm. All grade 3, 4 or 5 adverse events which are serious or leading to any action have been included. The number of occurrences, the number of patients with at least one occurrence and the standard deviation of this are included on the sheet “Adverse Events” for each treatment arm. The frequencies were obtained from the POLARIX trial [1]. By default all AEs with an incidence of more than 2% in any of the arms of the trials were considered. The AEs included in the cost-effectiveness model are listed in Table 16.

Table 16. Adverse reaction outcomes [1]

AEs	Grade	% AE, Pola + R-CHP	% AEs, R-CHOP
Anaemia	3	11.49%	6.62%

Diarrhoea	3	3.68%	0.91%
Febrile neutropenia	3	14.02%	5.48%
Febrile neutropenia	4	3.91%	2.51%
Neutropenia	3	10.11%	13.01%
Neutropenia	4	23.68%	26.94%
Neutrophil count decreased	3	2.53%	1.83%
Neutrophil count decreased	4	8.05%	5.71%
Pneumonia	3	2.99%	3.65%

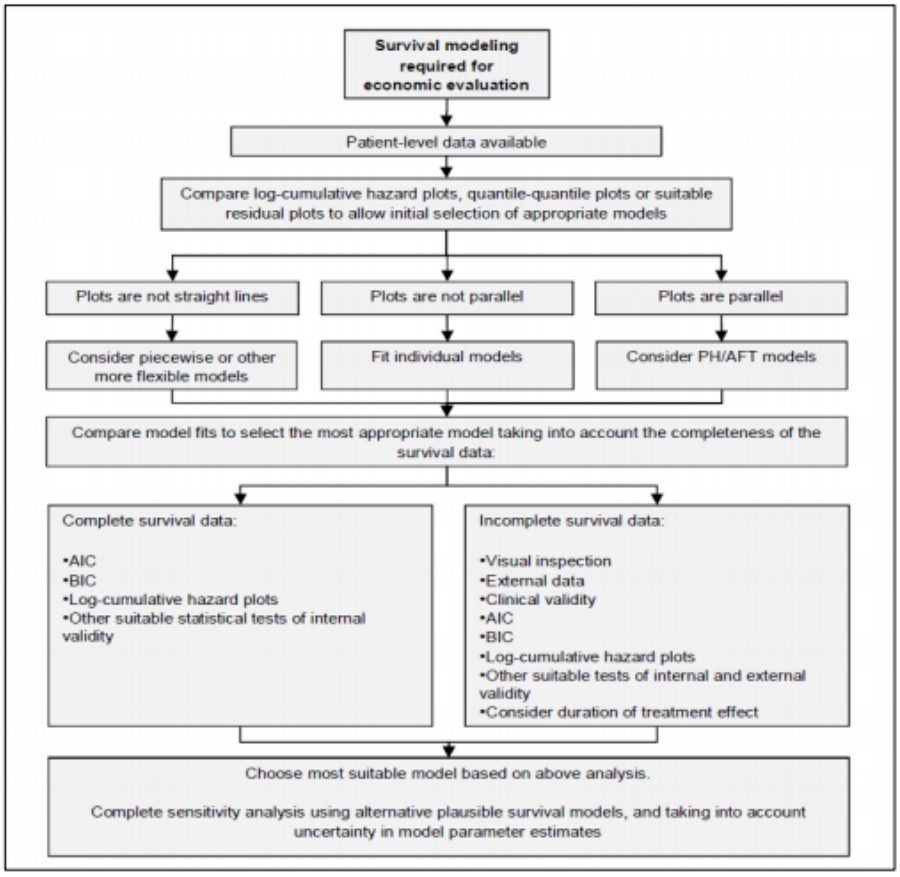
Note: AE, Adverse event; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

8.3 Extrapolation of relative efficacy

Consistent with recommendations in the NICE DSU technical support document 14 [52], the selection of base case parametric functions for PFS and OS were informed by:

Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection to assess the concordance between predicted and observed PFS and OS curves within the trial period; and clinical plausibility of long-term extrapolations beyond the trial period, which was evaluated based on smoothed hazard plots and biological plausibility.

Figure 22. Survival Model Selection Process Algorithm by NICE DSU [53]



Abbreviations: AFT: Accelerated failure time; AIC: Akaike information criterion; BIC: Bayesian information criterion; PH: Proportional hazards Source.

In order to extrapolate beyond the POLARIX clinical follow-up period, individual curve fitting (as per the NICE model selection process) was performed by using the following parametric distributions to the observed data.

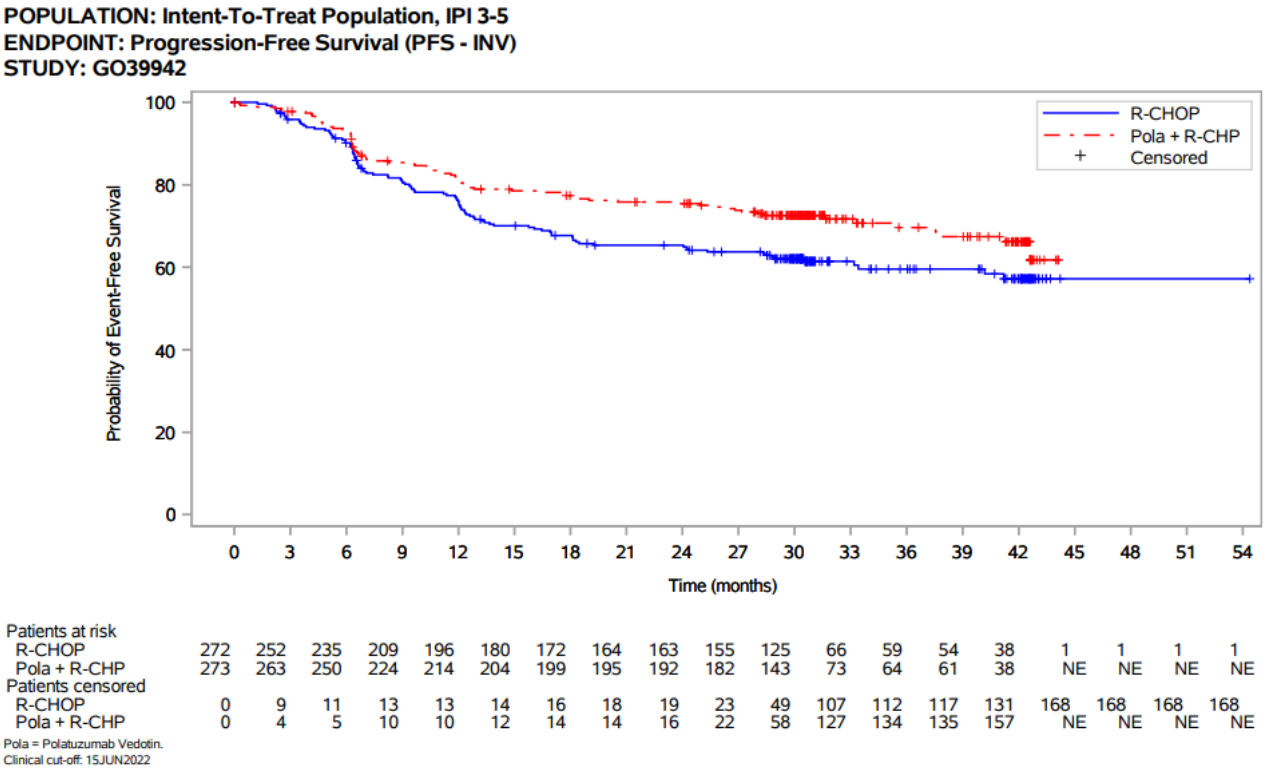
- Exponential
- Weibull
- Log-normal
- Generalized Gamma
- Log-logistic
- Gompertz
- Gamma

To keep the mortality risk of eligible patients, equivalent to or greater than the general population in all model cycles, all outcomes (OS, PFS) were capped by general mortality using Danish life tables.

8.3.1 Progression-free survival

PFS-data from POLARIX is applied for the IPI 3-5 subpopulation. Pola+R-CHP demonstrated a statistically significant PFS improvement compared to R-CHOP (hazard ratio [HR]: 0.70; 95% CI: 0.52-0.94).

Figure 23. KM PFS IPI 3-5 from POLARIX June 2022 DCO



Note: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; IPI, Inventory Performance Index; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

8.3.1.1 Choice of parametric distribution

Table 17. Parametric distribution selected for PFS for Pola+R-CHP and R-CHOP

PH-Assumption	PH assumption does not likely hold and therefore is not assumed, log-cumulative hazard plots are relatively parallel, but cross and converge in the centre. As such, individual modelling is preferred, as this does not require the PH assumption to be met
Distribution selected – Pola+R-CHP	Gamma
AIC-rank	6th
BIC-rank	7th
Distribution selected – R-CHOP	Gamma
AIC-rank	7th

BIC-rank	7th
Visual Inspection	Good visual fit of the extrapolated curves to the observed KM data
Smooth Hazards plot	Still immature, but demonstrates the behaviour of hazards that is expected (increase of hazards as those who don't respond die, change in mixture of patients as long-term responders/survivors now make up a larger proportion of the cohort, and hence the hazard decreases, and then an increase in hazards again as patients begin to get old), see Appendix G.
Clinically plausibility	Of the curves available, only gamma, exponential and Weibull provide estimates that avoid a sharp change in hazards when capped by background mortality. As demonstrated by the smooth hazards plots the exponential can be ruled out as hazards are not constant. Of the remaining curves, gamma gave a more likely estimate of a clinically plausible extrapolation.
Comments	Choosing Gamma distribution for extrapolation generates a realistic and clinical plausible result. AIC and BIC values were very similar between all of the curves (showing that there was almost no difference in statistical fit), additionally AIC and BIC only assess the fit to the observed period and therefore clinical plausibility (long term extrapolation and assumed hazard profile) must be used to determine the correct choice of curve.

Note: PH, Proportional Hazard; Pola, Polatuzumab; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Test of PH assumption

The log cumulative hazard plot (Figure 24) showed that the plots for Pola+R-CHP and R-CHOP remain separated and broadly parallel until the end of follow-up, but that they cross at the beginning and converge around in the centre. This suggests that the proportional hazard assumption may not hold, and as such individual fitting of curves is preferred.

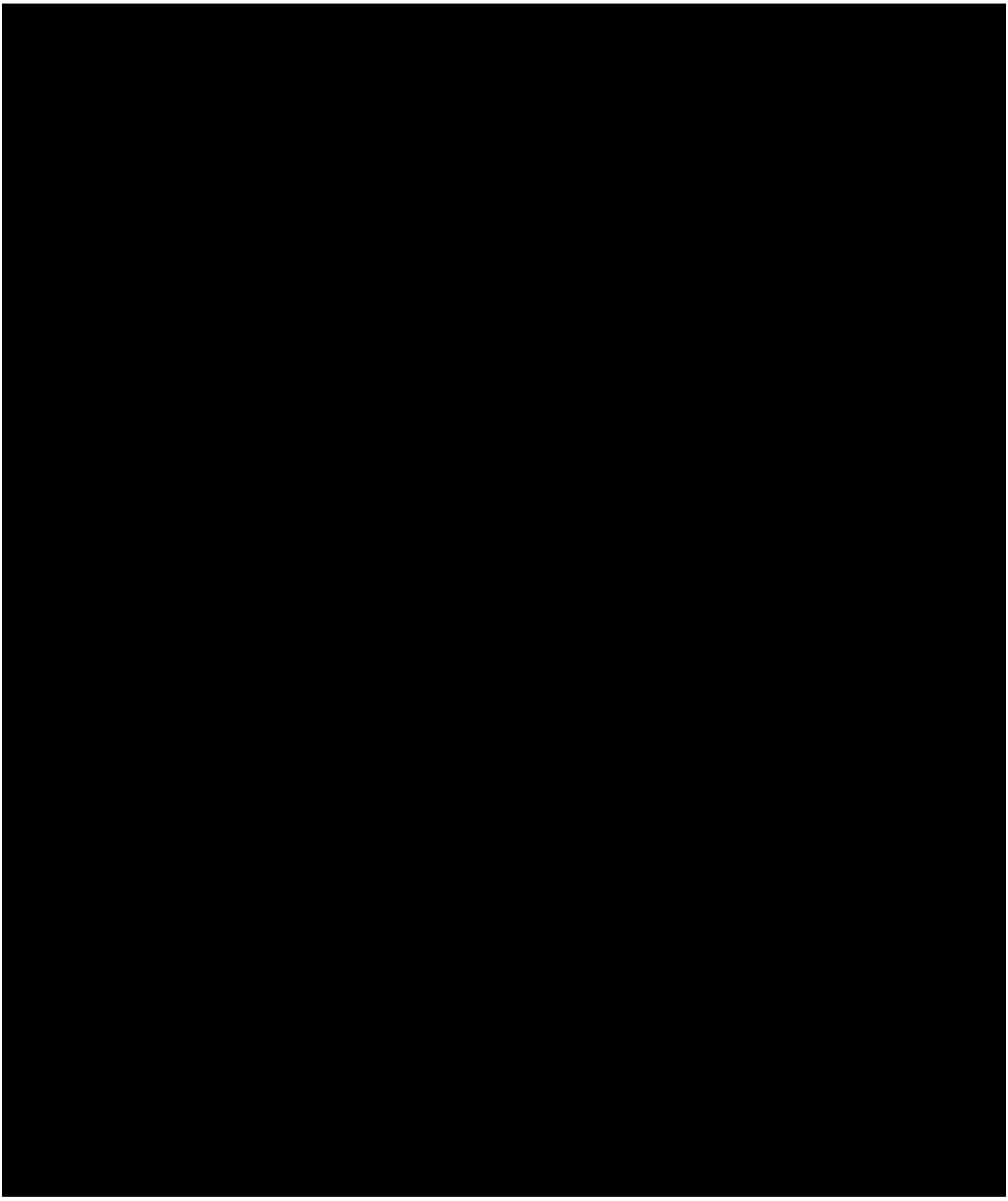
Goodness of fit

Fit statistics in form of AIC and BIC are presented for all curves in Table 18. AIC and BIC provide a summary of how well curves fit within the observed period, with BIC penalising curves that are more complex (i.e., have more parameters). Given the relative immaturity of the data, and that all values are relatively close to one another (<5 points apart), AIC and BIC should not be used as the main reason for curve selection, instead this should be done based on clinical plausibility of the long-term extrapolation and the underlying assumed hazard profile based on the curve chosen. Smoothed hazard plots are presented in Appendix G.

Table 18. AIC and BIC for PFS with ranks in brackets

Parametric distribution	Pola + R-CHP		R-CHOP	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	481,15 (7)	484,76 (4)	551,22 (6)	554,83 (5)
Weibull	480,01 (5)	487,23 (6)	550,22 (5)	557,43 (6)
Log-logistic	477,32 (4)	484,54 (3)	542,15 (4)	549,37 (4)
Log-normal	472,98 (1)	480,2 (1)	532,03 (2)	539,24 (2)
Gen Gamma	473,94 (3)	484,77 (5)	514,01 (1)	524,83 (1)
Gompertz	473,86 (2)	481,08 (2)	534,42 (3)	541,63 (3)
Gamma	480,76 (6)	487,98 (7)	551,68 (7)	558,89 (7)

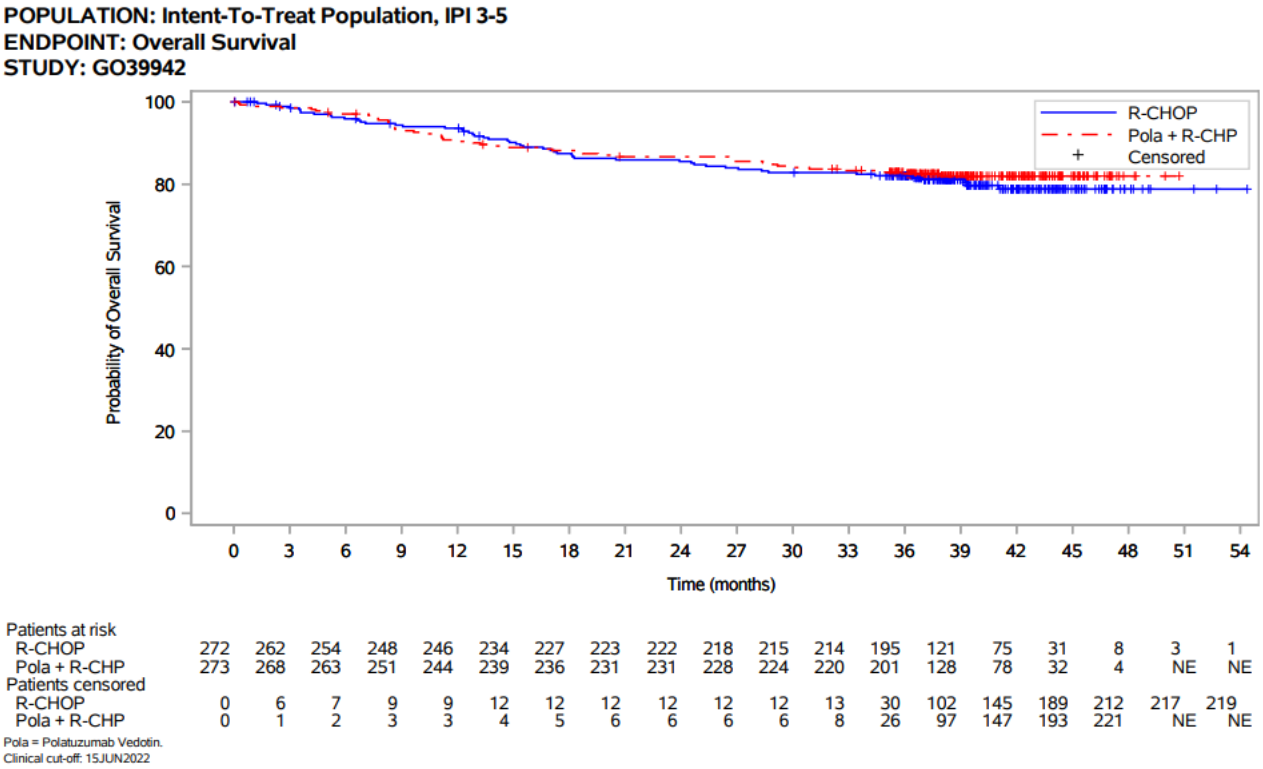
Note: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone



8.3.2 Overall survival

OS-data from POLARIX is applied for the IPI 3-5 subpopulation. Pola+R-CHP has not demonstrated a statistically significant OS improvement compared to R-CHOP (hazard ratio [HR]: 0.90; 95% CI: 0.61-1.34).

Figure 27. KM OS IPI 3-5 from POLARIX June 2022 DCO



Note: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; IPI, Inventory Performance Index; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

8.3.2.1 Choice of parametric distribution

Table 19. Parametric distribution selected for OS for Pola+R-CHP and R-CHOP

PH-Assumption	PH assumption does not likely hold and therefore is not assumed, log-cumulative hazard plots are relatively parallel, but cross. However, individual modelling is preferred, as this does not require the PH assumption to be met
Distribution selected – Pola+R-CHP	Log-normal
AIC-rank	2nd
BIC-rank	3rd
Distribution selected – R-CHOP	Log-normal

AIC-rank	2nd
BIC-rank	2nd
Visual Inspection	Good visual fit of the extrapolated curves to the observed KM data
Smooth Hazards plot	Have turning point, as expected, see Appendix G
Clinically plausibility	All curves give good visual fit and similar extrapolations in the long term, there are no sharp hazard changes and all curves end with almost all patients dead by the end of the time horizon. From the smoothed hazard plot and from what we expect clinically, the hazard of death is not constant, but instead will have at least one turning point. Log-normal provides the best statistically fitting curve, once exponential is excluded.
Comments	Choosing log-normal for extrapolation generates a realistic and clinical plausible result, taking into account the expected hazard profile and statistical fit.

Note: PH, Proportional Hazard; Pola, Polatuzumab; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Test of PH assumption

The log cumulative hazard plot (Figure 28) showed that the plots for Pola+R-CHP and R-CHOP are not parallel and cross many times. This suggests that the proportional hazard assumption does not hold, and as such individual fitting of curves is preferred.

Figure 28. Visual check of PH assumption - log-cumulative hazard for OS IPI 3-5

Goodness of fit

Fit statistics in form of AIC and BIC are presented for all curves in Table 20. AIC and BIC provide a summary of how well curves fit within the observed period, with BIC penalising curves that are more complex (i.e., have more parameters). Given the relative immaturity of the data, and that all values are relatively close to one another (<5 points apart), AIC and BIC should not be used as the main reason for curve selection, instead this should be done based on clinical plausibility of the long-term extrapolation and the underlying assumed hazard profile based on the curve chosen. Smoothed hazard plots are presented in Appendix G. The smoothed hazard plots begin to exhibit the expected behaviour: increase of hazards as those who don't respond progress/die, change in mixture of patients as long-term responders/survivors now make up a larger proportion of the cohort, and hence the hazard decreases, and then an increase in hazards again as patients begin to get old) [this last change in hazards is not yet observed in the Polivy arm, but is included in the model via the capping of general background mortality].

Table 20. AIC and BIC for OS with ranks in brackets – Pola R-CHP arm

Parametric distribution	Pola + R-CHP		R-CHOP	
	AIC (rank)	BIC (rank)	AIC (rank)	BIC (rank)
Exponential	368,46 (7)	372,07 (2)	387,70 (4)	391,31 (1)
Weibull	367,40 (5)	374,62 (5)	389,22 (6)	396,43 (6)
Log-logistic	366,63 (3)	373,85 (4)	388,24 (5)	395,45 (4)
Log-normal	365,25 (2)	372,47 (3)	385,12 (2)	392,33 (2)
Gen Gamma	367,22 (4)	378,05 (7)	384,89 (1)	395,71 (5)
Gompertz	363,32 (1)	370,54 (1)	386,68 (3)	393,89 (3)
Gamma	367,71 (6)	374,93 (6)	389,38 (7)	396,59 (7)

Note: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

8.3.3 Treatment duration

Extrapolation of Treatment duration

All patients in the POLARIX trial had completed their treatment, hence there is no need for any extrapolation.

In the POLARIX trial all treatments were given with a fixed treatment duration and all patients had either completed the full treatment cycle or discontinued treatment at the last data-cut. Hence only the Kaplan-Meier estimate was used to estimate the treatment duration in the cost-effectiveness model. The uncertainty around the treatment duration is captured in the probabilistic sensitivity analysis (PSA).

8.4 Documentation of health-related quality of life (HRQoL)

8.4.1 Overview of health state utility values (HSUV)

Within the cost-effectiveness model, there are three sets of utility values that can be applied, see Table 21. The base case is using the POLARIX utility values, as these are based on the clinical trial data observed in patients treated with Pola+R-CHP and R-CHOP, respectively.

To validate the utility values, a UK advisory board with clinical experts were conducted. Here, the consensus was that the utility values from the GOYA trial were more plausible compared to the POLARIX trial [1,2,54]. According to the clinical experts, the utility values from POLARIX trial were considered too high and Haematological Malignancy

Research Network (HMRN) too low for DLBCL patients [55]. The utility values from the GOYA for PFS and PD are also considered plausible for the following reasons:

1. The definition of disease progression was identical to that of POLARIX, and the time to disease progression in the adjusted and non-adjusted populations were equivalent.
2. The IPD data could be used for reweighting the GOYA data to match with POLARIX clinical prognostic factors as well as baseline patient reported outcomes.

For this reason, a scenario analysis is performed using the utility values from the GOYA trial to investigate the utilities impact on the results [54].

Table 21. Set of utility value in the model

Source	PFS	PD
POLARIX trial IPI 3-5 (5L)	0.86 [0.85-0.88]	0.83 [0.80-0.86]
GOYA subset IPI 3-5 (weighted)	0.82 [0.80-0.84]	0.73 [0.68-0.78]
HMRN EQ-5D-5L	0.83 [NR-NR]	0.66 [NR-NR]

Note: NR, Not reported; PFS, Progression-free survival; PD, Progressed disease; 3L, three-level; 5L, five-level; IPI, International Prognostic Index; HMRN, Haematological Malignancy Research Network

8.4.2 Health state utility values used in the health economic model

HRQoL is used based on the POLARIX trial. Utility values were applied to each health state in the model to capture the quality of life associated with treatment and disease outcomes.

The utility values are derived from the analysis of EuroQoL Five-Dimension Five-Level (EQ-5D-5L) data from the POLARIX trial. Even though the UK clinical advisory board recommended using utility data from the GOYA trial. Trial data is preferred as a source of utility inputs given that this allows the use of utility and efficacy data from the exact population from which efficacy data is derived. Consequently, the utilities from the POLARIX trial is applied to the model and mapped to Danish utility weights to follow the method guideline from the DMC [41]. The utility values are estimated using a “Least Squares Means”-model. The number of observations from EQ-5D-5L are used to estimate these utilities are shown i Table 45.

The state utilities applied in the model were age-adjusted according to the methodology prescribed by the DMC in section 7.3 of the guideline [41,56]. The HSUV used in the model is shown in Table 22. Treatment specific utilities is also shown.

When calculating utilities and PRO-results, missing data is not imputed, but just treated as missing.

Table 22. Summary of the HSUV used in the model

Health state	HSUV	[95% CI] SE	Tariff	Source
Progression-free survival	[redacted]	[redacted]	Danish EQ-5D-5L utility weights	EQ-5D-5L, POLARIX trial [1,2]
Progressive disease	[redacted]	[redacted]	Danish EQ-5D-5L utility weights	EQ-5D-5L, POLARIX trial [1,2]

Health state			HSUV	[95% CI] SE	Tariff	Source
			Treatment specific utilities			
IPI 2-5	PFS	Pola-R-CHP	[redacted]		Danish EQ-5D-5L utility weights	EQ-5D-5L, POLARIX trial [1,2]
IPI 2-5	PD	Pola-R-CHP				
IPI 2-5	PFS	R-CHOP				
IPI 2-5	PD	R-CHOP				
IPI 3-5	PFS	Pola-R-CHP				
IPI 3-5	PD	Pola-R-CHP				
IPI 3-5	PFS	R-CHOP				
IPI 3-5	PFS	R-CHOP				

Note: HSUV, Health state utility values; CI, confidence [redacted] EuroQoL Five-Dimension Five-Level

8.5 Resource use and costs

Costs and resource use vary depending on the administered treatment and health states. The model includes drug costs, administration costs, subsequent therapy costs, supportive care costs, and AE costs, as well as patients' time and transport costs spent on treatment. The costs included are consistent with the limited societal perspective as described in the DMC guidelines [41,57]. Table 23 presents the cost components for consideration in the model. Drug costs are estimated from Medicinpriser.dk, where administration costs, supportive care costs, and AE costs are based on the Danish diagnose relative group (DRG) tariffs 2022 and labportalen.dk [43-45,57]. Patient time and transportation costs are estimated based on the DMC catalogue for the valuation of unit costs [57].

Table 23. Cost categories and frequency

Cost category	Frequency	Health state(s)
Drug acquisition costs	Per administration (every 3rd cycle, 21 days)	Progression-free survival
Drug administration costs	Per administration (every 3rd cycle, 21 days)	Progression-free survival
Subsequent therapy costs	One-off cost (proportion of new cases in every cycle)	Progressed disease
Supportive care costs	Per cycle	Progression-free survival & Progressed disease
AE costs	One-off cost	Progression-free survival
Travel costs	Per cycle	Progression-free survival & Progressed disease

Patient time costs	Per cycle	Progression-free survival & Progressed disease

Note: AE, Adverse events

8.5.1 Drug acquisition cost

For all pharmaceuticals administered in the model, pharmacy purchase prices (PPP) have been used. Drug acquisition costs are applied to patients in the health state of PFS and PD in the cost-effectiveness model. The drug acquisition cost of the different drug components for patients in the PFS health state on treatment are shown in Table 24. For patients in the PD health state the costs of the different treatment components are shown in section 8.5.4, Table 27. Patients in the health state of PFS will either receive polatuzumab in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola+R-CHP) or rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP). This is in line with the Danish guidelines, which recommend patients with DLBCL receive R-CHOP as 1L treatment.

Table 24. Drug acquisition cost

Drug	Small vial (mg)	Small vial (cost)	Large vial (mg)	Large vial (cost)	Source [43]
Polatuzumab	30	15,583.70 DKK	140	72,723.93 DKK	Medcinpriser.dk (2022)
Rituximab	100	3,277.84 DKK	500	8,194.58 DKK	Medcinpriser.dk (2022)
Cyclophosphamide	500	180.00 DKK	1,000	330.00 DKK	Medcinpriser.dk (2022)
Doxorubicin	10	150.00 DKK	200	360.00 DKK	Medcinpriser.dk (2022)
Prednisone	31	310.00 DKK	NA	NA	Medcinpriser.dk (2022)
Vincristine	1	390.00 DKK	2	645.00 DKK	Medcinpriser.dk (2022)
Gemcitabine	1,200	310.00 DKK	2.200	420.00 DKK	Medcinpriser.dk (2022)
Oxaliplatin	50	41.18 DKK	100	68.80 DKK	Medcinpriser.dk (2022)
Carboplatin	150	84.00 DKK	450	203.00 DKK	Medcinpriser.dk (2022)
Etoposide	100	71.37 DKK	500	278,72 DKK	Medcinpriser.dk (2022)
Ifosfamide	1,000	380.00 DKK	NA	NA	Medcinpriser.dk (2022)
Cytarabine	1.000	150.00 DKK	2,000	200.00 DKK	Medcinpriser.dk (2022)
Cisplatin	50	100.00 DKK	100	200.00 DKK	Medcinpriser.dk (2022)
Bendamustine	125	300.00 DKK	500	1,100.00 DKK	Medcinpriser.dk (2022)

Note: mg, milligram

8.5.2 Administration costs

The costs of treatment administration for Pola+R-CHP and R-CHOP are shown in Table 25. The unit costs for the mode of administration were obtained from DRG tariffs 2022 and are applied to the administration cost in the model [45]. Polatuzumab, rituximab, cyclophosphamide, doxorubicin, and vincristine are administrated IV, and each incurs an administration cost of 3,225.00 DKK, in line with the administration cost from the previous DMC assessment of Pola+BR for R/R DLBCL patients [38]. Prednisolone is administered orally in the POLARIX trial on day 1 to 5. However, according to Danish clinical experts' prednisolone is given SC. Hence, the administration cost of 3,225.00 DKK for a subcutaneous injection of prednisolone is included in both treatment regimens to reflect Danish clinical practice. Consequently, the administration cost for both Pola+R-CHP and R-CHOP is 29,025 DKK per treatment administration.

Table 25. Administration costs

Administration form	Unit cost	Source
Intravenous	3,225.00 DKK	DRG 2022, 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnose: DC833: Diffust storcellet B-celle lymfom, Procedure: BWAA: Medicingivning intravenøst
Subcutaneous	3,225.00 DKK	DRG 2022, 17MA98 MDC17 1-dagsgruppe, pat. mindst 7 år, Diagnose: DC833: Diffust storcellet B-celle lymfom, Procedure: BWAA31: Medicingivning ved subkutan injektion
Cost per administration of each regime		
Pola+R-CHP	29,025.00 DKK	Polatuzumab, rituximab, cyclophosphamide, & doxorubicin: IV, Prednisolone: SC
R-CHOP	29,025.00 DKK	Rituximab, cyclophosphamide, doxorubicin, & vincristine: IV, Prednisolone: SC

Note: Pola+R-CHP, Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

8.5.3 Subsequent therapy costs

Patients progressing to the PD health state will receive second line (2L) treatment. Danish clinical experts and guidelines state that patients will be treated with either Rituximab + Dexamethasone, Cytarabine, and Cisplatin (R-DHAP), Rituximab + Ifosfamide, Carboplatin, and Etoposide (R-ICE), Rituximab + Gemcitabine, Cisplatin, and Dexamethasone (R-GDP), Rituximab + Gemcitabine and Oxaliplatin (R-GemOx), Rituximab + Bendamustine (R-Benda) or autologous stem cell transplantation (ASCT). The drug cost of the different treatment components is presented in Table 26.

Table 26. Drug acquisition cost, subsequent therapy

Drug	Small vial (mg)	Small vial (cost)	Large vial (mg)	Large vial (cost)	Source [43]
Rituximab	100	3,277.84 DKK	500	8,194.58 DKK	Medcinpriser.dk (2022)
Gemcitabine	1,200	310.00 DKK	2.200	420.00 DKK	Medcinpriser.dk (2022)
Oxaliplatin	50	41.18 DKK	100	68.80 DKK	Medcinpriser.dk (2022)
Carboplatin	150	84.00 DKK	450	203.00 DKK	Medcinpriser.dk (2022)
Etoposide	100	71.37 DKK	500	278,72 DKK	Medcinpriser.dk (2022)

Drug	Small vial (mg)	Small vial (cost)	Large vial (mg)	Large vial (cost)	Source [43]
Ifosfamide	1,000	380.00 DKK	NA	NA	Medcinpriser.dk (2022)
Cytarabine	1.000	150.00 DKK	2,000	200.00 DKK	Medcinpriser.dk (2022)
Cisplatin	50	100.00 DKK	100	200.00 DKK	Medcinpriser.dk (2022)
Bendamustine	125	300.00 DKK	500	1,100.00 DKK	Medcinpriser.dk (2022)
Autologous stem cell transplant	NA	111,255.00 DKK	NA	NA	DRG 2022, 26MP24, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (BOQF0) Autolog knoglemarvstransplantation [27]

Note: mg, milligram; NA, Not applicable

The clinical trial POLARIX found that an average of patients would receive 1.78 treatments and 1.95 treatments after 1L treatment with Pola+R-CHP and R-CHOP, respectively. However, this is difficult apprise if it would be clinical plausible in Denmark. A Danish DLBCL specialist estimated that patients progressing to the PD state will receive on average 1.22 treatments after 1L treatment in Denmark based on patients treated with R-CHOP [58]. Consequently, it is assumed in the base case that patients in both treatment arms in the PD state will receive an average of 1.22 treatments after 1L treatment. Data found in the trial will be explored in a scenario analysis.

The proportion of patients receiving the different subsequent treatments are presented in Table 27. These are estimated by Danish clinical experts specialised within DLBCL and Danish clinical guidelines for patients treated with R-CHOP in 1L [46,58]. It has not been possible for the expert to estimate the proportion for patients treated with Pola+R-CHP. Consequently, it was assumed that the same proportion was used in the Pola+R-CHP arm. All the different treatment regimens are administrated IV for 3,225 DKK per component using the DRG tariff 17MA98 2022, see Table 25. Both drug costs and administration costs are applied as a one-off cost in the model taking the proportion of new patients in the PD state in every cycle, see Table 27.

Table 27. Subsequent treatment costs

Subsequent treatment	One-off drug cost in model	One-off administration cost in model	% Pola+R-CHP	% R-CHOP	Source
Autologous stem cell transplant	111,255.00 DKK	NA	18.60%	18.60%	DRG 2022, 26MP24, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (BOQF0) Autolog knoglemarvstransplantation [45] & Danish clinical experts [58]

R-DHAP	68,178.93 DKK	32,991.57 DKK	16.33%	16.33%	Medicinpriser.dk (2022) [43] & Danish clinical experts [58]
R-ICE	75,402.19 DKK	32,991.57 DKK	16.33%	16.33%	Medicinpriser.dk (2022) [43] & Danish clinical experts [58]
R-GDP	55,597.55 DKK	24,743.68 DKK	16.33%	16.33%	Medicinpriser.dk (2022) [43] & Danish clinical experts [58]
R-GemOx	50,328.10 DKK	24,743.68 DKK	10.00%	10.00%	Medicinpriser.dk (2022) [43] & Danish clinical experts [58]
R-Benda	97,190.43 DKK	49,487.35 DKK	12.00%	12.00%	Medicinpriser.dk (2022) [43] & Danish clinical experts [58]

Note: Pola+R-CHP, Polatuzumab + Rituximab-Cyclophosphamide, Doxorubicin, and Prednisone; R-CHOP, Rituximab-Cyclophosphamide, Doxorubicin, Vincristine and Prednisone; NA, Not applicable; R-DHAP, Rituximab + Dexamethasone, Cytarabine, and Cisplatin; R-ICE, Rituximab + Ifosfamide, Carboplatin, and Etoposide; R-GDP, Rituximab + Gemcitabine, Cisplatin, and Dexamethasone; R-GemOx, Rituximab + Gemcitabine and Oxaliplatin; R-Benda, Rituximab + Bendamustine

The percentage of subsequent treatment is adding up to 89.59%. It has not been possible to identify and estimate a realistic estimate scenario for the last 10.41% of subsequent treatment. Consequently, it is chosen to use the numbers based on the expert statement and guidelines reflecting the best possible estimate for Danish clinical practice.

8.5.4 Supportive care costs

Table 28 presents the details of the health state costs. Costs are separated based upon patients' disease status (progression-free on treatment/progression-free off treatment/post-progression). A micro-costing approach is applied for specialist and nurse resource use based on the average duration of each visit, while officially available tariffs were applied for the remaining procedures. The resource use for the PFS on/off treatment health states are estimated in collaboration with Danish clinical experts within DLBCL. Where resource use for the PD state is based on the PFS state in the previous application for polatuzumab in combination with bendamustine and rituximab for relapsed or refractory (R/R) DLBCL patients [38]. A micro-costing approach is chosen for supportive care to avoid double counting of resources since a tariff-based approach are used for the administration costs, where additional costs are often included in the tariff. A tariff-based approach will require the bundling of several of the elements, which will necessitate further assumptions.

Patients on treatment will according to Danish specialists go to the hospital one day before each treatment administration for blood samples (Haemoglobin, Platelets, Neutrophilocytes, ALAT, LDH, Liver function (bilirubin + fosfatase), Renal function, Immunoglobulin, Creatinine and Calcium phosphate) at a cost of 1,154 DKK resulting in a total cost of 9,232 DKK for the full treatment period in both treatments arms. Danish clinical experts estimated that the treatment administration is containing one hour of consultation with an oncologist and five hours with a nurse during administration, resulting in a total cost of 3,225 DKK for patients treated with R-CHOP. Both treatments, Pola+R-CHP and R-CHOP, is a combination therapy containing five drug components. The treatment with polatuzumab requires 90 minutes of administration and monitoring at first administration and 30 minutes in the following administration compared to the treatment with R-CHOP. Consequently, we assume that treatment administration

with Pola+R-CHP will take 8.5 hours including one-hour clinical consultation and 7.5 hours with the nurse at the first administration and 6.5 hours (one-hour clinical consultation and 5.5 hours with the nurse) during the following administrations at a cost of 4,356.5 DKK and 3,474.5 DKK, respectively. Both Pola+R-CHP and R-CHOP are given over 6 cycles and additional 2 cycles with rituximab monotherapy for 1,931 DKK per administration (60 minutes of administration and 60 minutes post-monitoring). This is leading to 8 hours of clinical consultation with an oncologist for patients in both treatment arms for the whole treatment period and 39 hours of nurse time and 34 hours of nurse time when getting treated with Pola+R-CHP and R-CHOP during the treatment period, see Table 28 [46,49].

After treatment cessation patients in the PFS health state will according to the DMCG guidelines and Danish experts be followed for three years. The first-year patients will go to the hospital every third month for a check with a specialist and get blood samples taken [46,49]. Furthermore, Danish clinical experts estimate that patients will receive one additional PET-CT/CT scan after treatment cessation. Based on Danish clinical experts statements, we assume that 50% of patients in PFS will get a PET-CT as the additional scan and the other 50% will have a CT scan at a cost of 3,225 DKK and 2,411 DKK, respectively [49]. Danish clinical experts estimated that 20% of all patients would get additional radiotherapy after treatment with Pola+R-CHP and R-CHOP, respectively. Consequently, a one-off cost of 2,733 DKK was applied for 20% of patients in the PFS health state, see Table 28 [49].

Patients in the PD state are estimated to have four examinations with an oncologist, four blood samples and two PET-CT scans every year. This is based on the Danish experts within DLBCL and the previous assessment for polatuzumab in combination with bendamustine and rituximab for relapsed or refractory (R/R) DLBCL patients [38,49]. Additionally, Danish clinical experts state that 90% of all patients will get a bone marrow biopsy to see if they are candidates for autologous stem cell transplantation [49]. Consequently, a one-off cost of 12,984.00 DKK is assigned for 90% of patients entering the PD health state [45].

Table 28. Supportive care costs

Supportive care	Number of units per year PFS on treatment		Number of units year 1 PFS	Number of units year 2 and 3 PFS	Number of units per year PD	Unit Cost	Source
	Pola+R-CHP	R-CHOP					
Oncologist (visit)	8		4	2	4	1,049.00 DKK	Værdisætning af enhedsomkostninger [25]
Nurse (visit)	39	34	NA	NA	NA	441.00 DKK	Værdisætning af enhedsomkostninger [57]
Haemoglobin	8		4	2	4	17.00 DKK	Labportalen.dk [44]
Platelets	8		4	2	4	720.00 DKK	Labportalen.dk [44]
Neutrophilocytes	8		4	2	4	13.00 DKK	Labportalen.dk [44]
ALAT	8		4	2	4	13.00 DKK	Labportalen.dk [44]
LDH	8		4	2	4	29.00 DKK	Labportalen.dk [44]

Supportive care	Number of units per year PFS on treatment	Number of units year 1 PFS	Number of units year 2 and 3 PFS	Number of units per year PD	Unit Cost	Source
Liver function (bilirubin + phosphatase)	8	4	2	4	87.00 DKK	Labportalen.dk [44]
Renal function	8	4	2	4	95.00 DKK	Labportalen.dk [44]
Immunoglobulin	8	4	2	4	29.00 DKK	Labportalen.dk [44]
Creatinine	8	4	2	4	29.00 DKK	Labportalen.dk [44]
Calcium phosphate	8	4	2	4	122.00 DKK	Labportalen.dk [44]
PET-CT	1	1*	NA	2	3,225.00 DKK	DRG 2022, 17MA98, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (WDTCPXYXX) CT-scanning, PET/CT, uspecificeret isotop [45]
CT-scan	NA	1*	NA	NA	2,411.00 DKK	DRG 2022, 30PR06, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (UXCF00) CT-skanning af hel overekstremitet, (UXCF00) CT-skanning af hel underekstremitet
One-off costs	**Proportion of patients requiring the service**					
Bone marrow biopsy	NA	NA		90%	12,984.00 DKK	DRG 2022, 17PR01, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (KTNE25A) Knoglemarvsbiopsi fra crista iliaca [45]
Radiotherapy	NA	20%		NA	2,733.00 DKK	DRG 2022, 27MP10, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (BWGC1) Konventionel ekstern strålebehandling [45]

Note: PFS, Progression-free survival; PD, Progressed disease; PET-CT, Positron Emissions Tomography – Computerized Tomography;
* 50% of patients will receive PET-CT and 50% will receive CT in PFS

8.5.5 Adverse event costs

The model captures the costs associated with the management of treatment-related AEs with Common Terminology Criteria (CTC) grade of 3, 4 or 5. This happened independent of the time of onset and the time since the last dose of the drug was received. The number of occurrences, the number of patients with at least one occurrence and the standard deviation of this are included on the sheet "Adverse Events" for each treatment arm. The frequencies were obtained from the POLARIX trial. By default, all AEs with an incidence of more than 2% in any of the arms of the trials were considered. AEs were applied in the model as one-off costs per treatment arm considering the rate of occurrence (listed in section 8.2.2.5) of AEs during treatment and unit cost per AE. Estimated unit costs per AE are shown in Table 29.

Table 29. Adverse event costs

AEs	Grade	Unit cost	Source [45]
Anaemia	3	3,176.00 DKK	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD649: Anæmi UNS
Diarrhoea	3	6,756.00 DKK	DRG 2022, 06MA11: Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, Diagnosis: DK529B: Ikke-infektiøs diaré UNS
Febrile neutropenia	3	38,408.00 DKK	DRG 2022, 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Febrile neutropenia	4	38,408.00 DKK	DRG 2022, 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Neutropenia	3	3,176.00 DKK	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Neutropenia	4	3,176.00 DKK	DRG 2022, 16MA98: MDC16 1-dagsgruppe, pat. mindst 7 år, Diagnosis: DD709: Neutropeni UNS
Neutrophil count decreased	3	38,408.00 DKK	DRG 2022, 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Neutrophil count decreased	4	38,408.00 DKK	DRG 2022, 16MA03: Granulo- og trombocytopeni, Diagnosis: DD709A: Neutropeni og agranulocytose forårsaget af lægemiddel
Pneumonia	3	40,070.00 DKK	DRG 2022, 04MA13: Lungebetændelse og pleurit, pat. mindst 60 år, Diagnosis: DJ189: Pneumoni UNS

8.5.6 Patient time and travel costs

Patient and transportation costs are included in the model in line with the DMC method guidelines [41]. The unit cost per patient hour was estimated to be 181 DKK and the transportation cost was estimated to be 3.51 DKK per km with the assumption of an average distance to the hospital of 40 km (roundtrip) in line with the DMC guidelines, see Table 30 [41,57]. It is further assumed that patients would spend 30 minutes on transportation per visit (roundtrip).

Table 30. Patient and transportation cost per unit

	Costs	Source
Patient cost per hour	181 DKK	Danish method guidelines [41,57]
Transport cost per visit	140 DKK	Danish method guidelines [41,57]

Patient time and transportation costs are separated into the health states of PFS on/off treatment and PD for both treatment arms. Patient time is based on Danish clinical experts' estimates and summary of product characteristics (SmPC) for the different treatment components [48-50,59-62]. The time associated with treatment in the PD health state is not taken into consideration. Consequently, the patient time and transportation costs for PD state are underestimated. Table 31 shows the administration time found in the SmPC.

Table 31. Drug components administration time from SmPC

Drug components	Administration time (minutes)	Monitoring (minutes)	Source
Polatuzumab	90 minutes (1st admin) 30 minutes (main)	90 minutes (1st admin) 30 minutes (main)	[48]
Rituximab	60 minutes	60 minutes	[50]
Cyclophosphamide	120 minutes	NA	[59]
Doxorubicin	10 minutes	NA	[60]
Vincristine	10 minutes	NA	[62]
Prednisone	NA	NA	

As described in section 8.5.4, Danish clinical experts estimate that patients treated with R-CHOP will spend six hours per treatment administration and patients treated with Pola+R-CHP will spend 8.5 hours at the first administration and 6.5 hours at the following treatment administration. This is resulting in a patient time cost of 1,086 DKK, 1,538.5 DKK, and 1,176.5 DKK per treatment administration, respectively.

In section 8.5.4 it is described that patients will have blood samples taken one day before each treatment for both treatment arms. Blood samples are assumed to take 30 minutes (90.5 DKK). Furthermore, Danish clinical experts and DLBCL guidelines prescribe that patients will have a PET-CT after 3-4 administration and one after treatment cessation. The time used for a PET-CT is based on information from the webpage cancer.dk, estimating a PET-CT to take two hours for the full visit for the patient at a cost of 362 DKK, see Table 32 [63]. After treatment cessation patients in the health state of PFS are followed for three years according to the DMCG guidelines and Danish experts [46,49]. The first-year patients will go to the hospital four times for a one-hour control check by a specialist and blood samples. In the following two years, patients will go to the hospital two times for control visits and blood samples.

Table 32. Patient time and cost

Patient time	Usage (hours)	Resource use PFS on treatment	Resource use year 1 PFS	Resource use year 2 and 3 PFS	Resource use (PD)	Costs (per usage)
Pola+R-CHP						
1st Administration	7.5	1	NA	NA	NA	1,357.50 DKK
Administration	5.5	5	NA	NA	NA	995.50 DKK
R-CHOP						
Administration	5.0	6	NA	NA	NA	905.00 DKK

Both Pola+R-CHP and R-CHOP						
Administration rituximab	2	2	NA	NA	NA	362.00 DKK
Outpatient consultation	1	8	4	2	4	181.00 DKK
Blood samples	0.5	8	4	2	4	90.50 DKK
PET-CT	2	1	1	NA	2	362.00 DKK
CT	2	NA	1	NA	NA	362.00 DKK
Transportation roundtrip	0.5	16	8	4	8	90.50 DKK

Note: NA, Not applicable; PD, Progressed Disease; PFS, Progression-free survival

The transportation cost in both treatment arms is based on the Danish Medicine Councils' guidelines and Danish clinical experts' estimates.

Patients on treatment are going to the hospital for blood samples and treatment administration in a total of sixteen times. It is assumed that the PET-CT after 3-4 treatment administrations will be done during one of these visits resulting in a transportation cost of 2,240 DKK over the total treatment period. After treatment cessation, patients in the PFS will then go to the hospital for blood samples four times a year the day before the clinical examination leading to eight hospital visits in year 1 (1,120 DKK). In the following 2 years, patients will go for two blood samples and consultations leading to a transportation cost of 560 DKK. Patients in the PD health state will primarily have the same transportation costs as patients in the PFS health state in the first year, resulting in a transportation cost of 1,120 DKK, see Table 33.

Table 33. Transportation cost

Transportation	Resource use PFS on treatment	Resource use year 1 PFS	Resource use year 2 and 3 PFS	Resource use PD	Source
Transportation units	16	8	4	8	DMC methods guideline [41]
Total transportation cost	2,240.00 DKK	1,120.00 DKK	560.00 DKK	1,120.00 DKK	DMC methods guideline [41]

Note: PD, Progressed Disease; PFS, Progression-free survival

8.6 Results

8.6.1 Base case overview

Table 34. Base case overview

Parameter	Value	Rationale
General model parameters		
Time horizon	40 years	Life-time horizon
Discount rate – efficacy	3.5% until year 35 then 2.5%	DMC methods guideline [41]
Discount rate – costs	3.5% until year 35 then 2.5%	DMC methods guideline [41]
Data source	POLARIX	POLARIX, in line with relevant population in Denmark
Intervention	Pola+R-CHP	POLARIX
Comparator	R-CHOP	POLARIX
Population parameters		
Age	64 years	POLARIX average age IPI 3-5 subgroup
Body weight	76 kg	POLARIX
Height	168 cm	POLARIX
Body surface area	1.86 m^2	POLARIX
Efficacy and treatment duration		
Mean TTOT – Polatuzumab (Pola+R-CHP)	3.6 months, as observed in trial	POLARIX
Mean TTOT – Rituximab (Pola+R-CHP)	4.9 months, as observed in trial	POLARIX
Mean TTOT – Cyclophosphamide (Pola+R-CHP)	3.6 months, as observed in trial	POLARIX
Mean TTOT – Doxorubicin (Pola+R-CHP)	3.6 months, as observed in trial	POLARIX
Mean TTOT – Prednisone (Pola+R-CHP)	3.7 months, as observed in trial	POLARIX
Mean TTOT – Rituximab (R-CHOP)	4.6 months, as observed in trial	POLARIX
Mean TTOT – Cyclophosphamide (R-CHOP)	3.5 months, as observed in trial	POLARIX
Mean TTOT – Doxorubicin (R-CHOP)	3.5 months, as observed in trial	POLARIX
Mean TTOT – Prednisone (R-CHOP)	3.5 months, as observed in trial	POLARIX
Mean TTOT – Vincristine (R-CHOP)	3.4 months, as observed in trial	POLARIX
PFS – Pola+R-CHP arm and R-CHOP arm	Gamma	See section 8.3.1
OS – Pola+R-CHP and R-CHOP arm	Log-normal	See section 8.3.2
PFS – Pola+R-CHP and R-CHOP arm	0.86	POLARIX, Danish EQ-5D-5L weight, IPI 3-5
PD – Pola+R-CHP and R-CHOP arm	0.83	POLARIX, Danish EQ-5D-5L weight, IPI 3-5
Cost variables		
Drug cost	1L therapy applied to reflect the real administration	Reflects the drug costs accrued over the patient´s course of treatment
Administration cost	1L treatment applied to reflect the real administration, following lines is applied as a monthly cost for both treatment arms.	Reflects the administration costs accrued over the patient´s course of treatment

Subsequent treatment cost	One-time cost for new PD incidence cases per cycle	Reflecting number and cost of treatments patients receives after 1L treatment
AE management cost	One-time cost in the first model cycle for adjuvant treatment (PFS health state)	Reflects the AE management costs accrued during treatment
Supportive care cost	Applied as monthly costs for both treatment arms. Monthly follow-up costs are not assumed to differ between treatment arms.	Reflects the follow-up costs accrued over the patient's lifetime
Patient and transportation cost	Applied as a monthly cost for both treatment arms.	DMC methods guideline [41]

8.6.2 Base case results

Base-case results of the economic model with the parameters as discussed and presented in the sections above are presented below, versus R-CHOP

Table 35. Base case results provides a summary of the base case results using known list-prices for the various medicines. The analysis is based on pricing based on official PPP from medicinpriser.dk, no discounts included. The intervention is costlier than the comparator for patients in the PFS health states but saves costs in comparison for patients in the following health state PD. This can be explained by the significantly higher proportion of patients remaining in the PFS health state in the Pola+R-CHP arm versus the R-CHOP arm, underlining the new intervention's

[redacted]

Table 35. Base case results

Per patient	[redacted]
Life years gained	
Total life years gained	
PFS	
PD	
QALYs	
Total QALYs	
PFS	
PD	
Costs	
Total costs	

Total PFS cost	[redacted]
Polatuzumab	
Rituximab	
Cyclophosphamide	
Doxorubicin	
Prednisone	
Vincristine	
Administration cost	
AE management cost	
Supportive care	
Travel cost	
Patient time cost	
Total PD cost	
Drug cost	
Administration cost	
Supportive care	
Travel cost	
Patient time cost	
Incremental results	
ICER (per QALY)	
ICER (per life year gained)	

8.7 Sensitivity analyses

To identify key model drivers and the influence of parameter uncertainty, one-way deterministic sensitivity analyses (DSA) are conducted using alternate values for model parameters. To test the impact of applying different assumption, scenario analyses are conducted for the key model parameters.

To test the robustness of results with respect to uncertainty in the model input parameters, a PSA is performed using a second-order Monte Carlo simulation. In this analysis, each parameter subject to parameter uncertainty is assigned a probability distribution, and cost-effectiveness results associated with the simultaneous selection of random values from the distribution of each of these parameters were generated. The process was repeated for 1,000 iterations and results of the PSA were plotted on the cost-effectiveness plane (or scatter plot) and were used to calculate cost-effectiveness acceptability curves (CEACs), highlighting the probability of cost-effectiveness over various willingness to pay thresholds.

8.7.1 Deterministic sensitivity analyses

Impact on the ICER of the range of some key parameters is presented in Figure 31 below. The tornado diagram presents the relative impact some key influential model parameters have on the list-price ICER (703,952 DKK per QALY).

[redacted]

8.7.2 Scenario analysis

[redacted]

Table 36. Scenario analyses exploring changes to key parameters

Parameter	Inc. cost per QALY Pola+R-CHP vs R-CHOP average	DKK Δ ICER vs base case
Base case	[redacted]	
Assumptions		
Time horizon: 10 years		
Time horizon: 15 years		
Time horizon: 20 years		
Time horizon: 25 years		
Time horizon: 30 years		
Time horizon: 35 years		
Average number of treatments after 1L Pola+R-CHP & R-CHOP, POLARIX		
PFS distribution		
Pola+R-CHP	[redacted]	
Exponential		

Weibull	[redacted]
Log-normal	
Generalized Gamma	
Log-logistic	
Gompert**z**	
R-CHOP	
Exponential	
Weibull	
Log-normal	
Generalized Gamma	
Log-logistic	
Gompertz	
OS distribution	
Pola+R-CHP	
Exponential	
Weibull	
Generalized Gamma	
Log-logistic	
Gompertz	
Gamma	
R-CHOP	
Exponential	
Weibull	
Generalized Gamma	
Log-logistic	
Gompertz	
Gamma	
Treatment effect	
PFS	
Effect is limited in time	
OS	
Effect is limited in time	
Utility	
GOYA IPI 3-5, PFS and PD	

8.7.3 Probabilistic sensitivity analyses

The cost-effectiveness plane and incremental cost-effectiveness plane, illustrating the QALYs and costs and the incremental QALYs and costs, respectively, are presented in Figure 32 and Figure 33 below using list prices. This represents the joint distribution of costs and effect for the intervention (Pola+R-CHP), and the comparator included in the model (R-CHOP) and the incremental results between these. The majority of simulated ICERs are located in the NE quadrant, indicating the intervention to be costlier and more effective than the comparator.

[redacted]

9. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending Pola+R-CHP as a treatment option in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model.

The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC.

The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where Pola+R-CHP is recommended as a standard treatment and the scenario where Pola+R-CHP is not recommended as a standard treatment. The total budget impact per year is the difference between the two scenarios

9.1 Market shares and number of patients

As described in section 5.1.1 approximately 110 patients are expected to be eligible for treatment with Pola+R-CHP the first year. For the budget impact analysis, 110 new patients have been assumed in every year for 5 years, see Table 37.

Future market shares depend on multiple factors such as developments in the treatment landscape, and available physical and economic resources. The estimate is an assumption and is associated with uncertainty. The potential market share for Pola+R-CHP with or without a recommendation is reported in Table 37.

[redacted]

[redacted]

9.2 Budget impact result

Based on the base case assumptions, the estimated budget impact of recommending Pola+R-CHP as a possible standard treatment in Denmark for patients with previous untreated DLBCL [redacted] year 5, shown in Table 38.

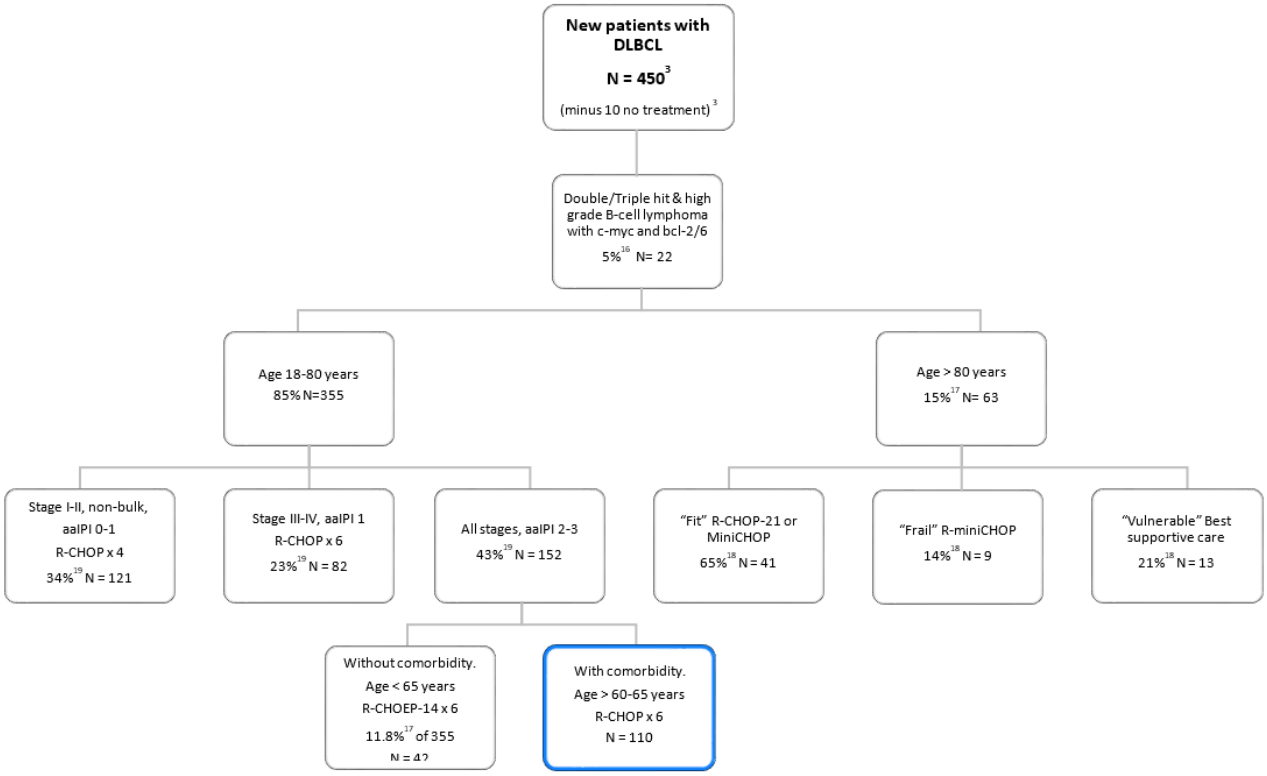
Table 38. Expected budget impact of recommending Pola+R-CHP as standard treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Without recommendation	[redacted]				
With recommendation					
Budget impact of recommendation					

10. Discussion on the submitted documentation

Clinical assessment

The clinical efficacy and safety of Pola+R-CHP are assessed using direct evidence from the phase 3 study, POLARIX. POLARIX is a large multicentre, randomized, double-blind, placebo-controlled trial comparing the efficacy and safety of Pola+R-CHP versus R-CHOP in 879 patients with previously untreated DLBCL. Patients were stratified based on IPI score (2 vs. 3-5), bulky disease defined as at least one tumour mass with diameter of 7.5 cm or more (present or absent), and region (Western Europe, USA, Canada and Australia vs Asia vs rest of world). The patient demographics and baseline characteristics between the two treatment arms were generally balanced and representative of a population of patients who had either intermediate-risk or high-risk disease, in which almost two-thirds had a baseline IPI score between 3 and 5. Overal



l the patients included in POLARIX are found to be representative of a Danish patient population.

In this application, we present data for both the full study population and the subgroup with IPI score 3-5 as adult patients with previously untreated DLBCL aged > 60-65 years and baseline aaIPI score 2-3 (corresponding to IPI score 3-5) are considered the main candidates for Pola+R-CHP in the first-line setting in Danish clinical practise. These patients are currently treated with R-CHOP according to Danish guidelines.

POLARIX met its primary endpoint with a statistically significant and clinically meaningful improvement in PFS. At the time of the final OS analysis with an additional 12 months of follow-up, only few additional PFS events had occurred, which supports that the majority of disease relapse or progression occurs within 24 months of initiation of therapy. Consistent with the primary endpoint results, Pola+R-CHP showed a statistically significant improvement in the key secondary endpoint EFS_{eff}. Although not statistically significant, BICR-assessed CR rates by PET-CT at end of treatment were numerically higher in the Pola+R-CHP arm compared with R-CHOP. At the time of the final OS analysis, OS results remained immature with a low event rate in both arms. No difference was observed between treatment arms. The lower number of expected events and longer than expected survival post progression is likely to be explained by the advent of new, effective treatments for R/R DLBCL in recent years. Moreover, the distribution of subsequent therapies in the study is not controlled and may confound the OS analysis. There are more patients in the R-CHOP arm who have received more intensive therapies such as stem-cell transplantation and chimeric antigen receptor T-cell therapy.

The POLARIX study was not designed for detecting subgroup effects (i.e. no alpha level was specified for subgroup effects). It was powered to show homogenous treatment effects across the subgroups nor powered to detect statistically significant differences. However, subgroup analyses of PFS and EFS indicated an even greater improvement for Pola+R-CHP vs. R-CHOP in patients with IPI score 3-5. Similar to the full study population, only few additional PFS events and EFS events had occurred at the final CCOD. As for the full study population, a numerically

higher proportion of patients treated with Pola+R-CHP had complete response at the end of treatment compared to patients treated with R-CHOP and no difference in OS was observed.

The incidence of AEs of any grade, AEs of grade 3-5, SAEs, AE leading to study discontinuation and AEs leading to any study treatment dose discontinuations were comparable between the treatment arms in the safety-evaluable population and the IPI score 3-5 population and across populations. The safety profile of the Pola+R-CHP regimen was comparable to R-CHOP and in line with the known safety profiles of each individual component and the underlying disease.

Health economic assessment

For the cost-effectiveness analysis, the clinical efficacy and safety are assessed with direct evidence from one pivotal Phase III study, POLARIX. All clinical efficacy endpoints were directly taken from POLARIX. Results are compared to the current SoC in Denmark, R-CHOP, aligned with Danish guidelines and the comparator arm in the POLARIX trial.

[redacted]

Costs is applied in the model in line with the DMC process guide for assessing new pharmaceuticals [41]. However, the patient time and transportation costs in the PD health state in both treatment arms is excluded.This exclusion is resulting in an underestimation and uncertainty of the health state. Nonetheless, this exclusion is in favour of the R-CHOP arm as a result of a higher progression when receiving treatment with R-CHOP compared to Pola+R-CHP. Furthermore, the PD state is cheaper for patients in the Pola+R-CHP arm than the R-CHOP arm; [redacted] vs [redacted] Indicating that patients treated with Pola+R-CHP is at a lower risk of progressing than patients treated with R-CHOP. The PFS state is more expensive in the Pola+R-CHP arm compared to the R-CHOP arm, mainly caused by the price of polatuzumab. Costs such as administration cost, supportive care cost, patient time and transportation cost are similar between the two arms, indicating that the treatment with Pola+R-CHP is not associated with additional costs compared to R-CHOP, with the exception of the drug cost of polatuzumab.

11. List of experts

The following experts were consulted to gain input for the health economic analysis:

[redacted]

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Appendix A Literature search for efficacy and safety of intervention and comparator

The clinical phase 3 study POLARIX directly compares polatuzumab vedotin plus R-CHP with the comparator relevant in Danish clinical practice. The study provides sufficient documentation for efficacy and safety for both the intervention and comparator, and therefore, a literature search for additional evidence has not been performed.

Unpublished data

All unpublished data are derived from POLARIX. There is currently no plan for submission of these data.

Appendix B Main characteristics of included studies

Table 39: Main characteristics of POLARIX

Trial name: POLARIX	**NCT number: 03274492**
Objective	To compare the efficacy and safety of polatuzumab vedotin with R-CHP versus R-CHOP in participants with DLBCL.
Publications – title, author, journal, year	Polatuzumab Vedotin in previously untreated diffuse large B-cell lymphoma, Tilly et al. N Engl J Med 2022;386:351-363 [1]
Study type and design	Phase 3, randomised, double-blind, placebo-controlled study. A total of 879 patients were randomised in a 1:1 ratio to either Arm A or Arm B. Both patients and the investigator were blinded to the assigned active microtubule inhibitor (i.e., polatuzumab vedotin or vincristine) and placebo control. Study site personnel (with the exception of unblinded pharmacists) and patients were blinded to treatment assignment during the study. The Sponsor and its agents were also blinded to treatment assignment, with the exception of individuals who required access to patient treatment assignments to fulfil their job roles during a clinical trial. These roles included the unblinding group responsible, clinical supply chain managers, sample handling staff, operational assay group personnel, interactive voice or Web-based response system (IxRS) service provider, drug safety responsible, and iDMC members. The unblinded pharmacist provided the active agent and the placebo agent according to the patient's treatment assignment. The investigator remained blinded to the treatment assignment. POLARIX was stratified to ensure there was an equal spread of patients. Patients were randomised using the following stratification factors: ● International Prognostic Index IPI score (IPI 2 versus IPI 3–5) ● Bulky disease, defined as one lesion ≥ 7.5 cm (present versus absent) ● Geographical region (Western Europe, United States, Canada, and Australia versus Asia versus Rest of World [remaining countries]) No crossover to the investigational arm was allowed.
Sample size (n)	R-CHP plus placebo for vincristine plus polatuzumab vedotin, N=440 R-CHOP plus placebo for polatuzumab vedotin, N=439

Main inclusion and exclusion criteria	Inclusion Criteria ● Previously untreated participants with cluster of differentiation 20 (CD20)-positive DLBCL, including one of the following diagnoses by 2016 World Health Organization (WHO) classification of lymphoid neoplasms: DLBCL, not otherwise specified (NOS) including germinal center B-cell type, activated B-cell type; T-cell/histiocyte-rich large B-cell lymphoma; Epstein-Barr virus-positive DLBCL, NOS; anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma; human herpesvirus-8 (HHV8)-positive DLBCL, NOS; High-grade B-cell lymphoma with MYC and B-cell lymphoma 2 (BCL2) and/or B-cell lymphoma 6 (BCL6) rearrangements (double-hit or triple-hit lymphoma); High-grade B-cell lymphoma, NOS ● Availability of archival or freshly collected tumor tissue before study enrolment ● International Prognostic Index (IPI) score of 2-5 ● Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2 ● Life expectancy greater than or equal to (>/=)12 months ● Left ventricular ejection fraction (LVEF) >/= 50 percent (%) on cardiac multiple-gated acquisition (MUGA) scan or cardiac echocardiogram (ECHO) ● Adequate hematologic function ● Female participants: Agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods and refrain from donating eggs. ● Male participants: agreement to remain abstinent (refrain from heterosexual intercourse) or use a condom and agreement to refrain from donating sperm. Exclusion Criteria ● History of severe allergic or anaphylactic reactions to humanized or murine monoclonal antibodies or known sensitivity or allergy to murine products ● Contraindication to any of the individual components of CHOP, including prior receipt of anthracyclines ● Prior organ transplantation ● Current Grade greater than (>) 1 peripheral neuropathy by clinical examination ● Demyelinating form of Charcot-Marie-Tooth disease ● History of indolent lymphoma ● History of follicular lymphoma grade 3B ● B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma (grey-zone lymphoma) ● Primary mediastinal (thymic) large B-cell lymphoma ● Burkitt lymphoma ● Prior treatment with cytotoxic drugs within 5 years of screening for any condition (example [e.g.], cancer, rheumatoid arthritis) or prior use of any anti-CD20 antibody ● Prior use of any monoclonal antibody within 3 months of the start of Cycle 1 ● Prior therapy for DLBCL, with the exception of nodal biopsy ● Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than lymphoma symptom control ● Participants with central nervous system (CNS) lymphoma (primary or secondary involvement), primary effusion DLBCL, and primary cutaneous DLBCL ● Vaccination with live vaccines within 28 days prior to the start of Cycle 1 ● Any investigational therapy within 28 days prior to the start of Cycle 1 ● History of other malignancy that could affect compliance with the protocol or interpretation of results ● Evidence of significant, uncontrolled, concomitant diseases that could affect compliance with the protocol or interpretation of results, including significant cardiovascular disease or pulmonary disease

Trial name: POLARIX	NCT number: 03274492
	• Recent major surgery (within 4 weeks prior to the start of Cycle 1), other than for diagnosis • History or presence of an abnormal electrocardiogram (ECG) that is clinically significant in the investigator's opinion, including complete left bundle branch block, second- or third-degree heart block, or evidence of prior myocardial infarction • Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study enrollment or significant infections within 2 weeks before the start of Cycle 1 • Clinically significant liver disease, including active viral or other hepatitis, current alcohol abuse, or cirrhosis • Prior radiotherapy to the mediastinal/pericardial region • Participants with suspected active or latent tuberculosis • Positive test results for chronic hepatitis B and hepatitis C infection • Known history of human immunodeficiency virus (HIV) seropositive status • Positive results for the human T-lymphotrophic 1 virus (HTLV-1) • Participants with a history of progressive multifocal leukoencephalopathy
Intervention	R-CHP plus placebo for vincristine plus polatuzumab vedotin. Participants received polatuzumab vedotin 1.8 milligrams per kilogram (mg/kg) intravenously (IV), placebo for vincristine IV, rituximab 375 milligrams per square metre (mg/m²) IV, cyclophosphamide 750 mg/m² IV, and doxorubicin 50 mg/m² IV on Day 1 and prednisone 100 milligrams per day (mg/day) orally (PO) on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m² IV was administered as monotherapy in Cycles 7 and 8.
Comparator(s)	R-CHOP plus place for polatuzumab vedotin. Participants received placebo for polatuzumab vedotin, rituximab 375 mg/m² IV, cyclophosphamide 750 mg/m² IV, doxorubicin 50 mg/m² IV, and vincristine 1.4 mg/m² IV (maximum 2 milligrams per dose [mg/dose]) on Day 1 and prednisone 100 mg/day PO on Days 1-5 of every 21-day cycle for 6 cycles. Rituximab 375 mg/m² IV was administered as monotherapy in Cycles 7 and 8.
Follow-up time	Median follow-up at CCOD of June 28, 2021: 24.7 months (95% CI, 24.4 to 25.0) (both the IPI score 2-5 and IPI score 3-5 populations). Median follow-up at CCOD of June 15, 2022: 30.8 months (95% CI, 30.7 to 31.0) for the IPI score 2-5 population and 30.9 months (95% CI, 30.7-31.3) for the IPI score 3-5 population.
Is the study used in the health economic model?	Yes

Trial name: POLARIX	NCT number: 03274492
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** The primary endpoint was progression-free survival (PFS) as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma. Secondary endpoints were overall survival (OS), event-free survival-efficacy (EFS_{eff}), complete response (CR) as assessed by fluorodeoxyglucose positron emission tomography (FDG-PET) by blinded independent central review (BICR), health-related quality of life as assessed by EORTC QLQ-C30 and FACT-Lym LymS. Relevant safety objectives were incidence of adverse events (AEs), treatment-related AEs, serious AEs, serious treatment-related AEs, and discontinuations due to AEs. **Other endpoints:** CR as assessed by investigator, disease-free survival (DFS), duration of response and event-free survival-all causes (EFS_{all}) as assessed by investigator, using the Lugano Response Criteria for Malignant Lymphoma; functional assessment of cancer treatment/gynecologic oncology group-neurotoxicity (FACT/GOG-NTX) peripheral neuropathy score; serum concentration of total polatuzumab vedotin; plasma concentration of polatuzumab vedotin conjugate; plasma concentration of polatuzumab vedotin unconjugated MMAE; and percentage of participants with anti-drug antibody (ADA) to polatuzumab vedotin were included as secondary end points in the study, but results are not included in this application.
Method of analysis	With the exception of the analysis of investigator assessed disease-free survival (described above), the efficacy analyses were performed in the intention-to-treat population, which included all patients who underwent randomization. Safety was evaluated in all patients in the study who received ≥ 1 dose of study treatment (safety evaluable population) and PRO was evaluated in all randomized patients in the study who had a baseline and ≥ 1 post-baseline assessment. To control the overall type I error rate at a one-sided 0.025 level of significance, a hierarchical testing procedure including possible α recycling was used to adjust for multiple statistical testing of the primary and key secondary efficacy endpoints. If the primary endpoint hypothesis was positive, key secondary endpoints (i.e., event-free survival [EFS], CR rate at the end of treatment by blinded independent central review, and overall survival were hierarchically tested. The remaining secondary endpoints, CR rate at end of treatment by PET-computed tomography by the investigator, overall response rate at end of treatment, best overall response, disease-free survival, duration of response, and patient-reported outcomes were tested without adjusting for multiplicity. Kaplan–Meier methodology was used to estimate progression-free survival in each treatment group. Estimates of the treatment effect were expressed as hazard ratios and corresponding 95% confidence intervals and were derived with the use of a stratified Cox proportional-hazards analysis. The proportional-hazards assumption for progression-free survival was evaluated with the use of the method proposed by Grambsch and Therneau [33]. The 12- and 24-month PFS rate was calculated using the Kaplan–Meier method. Corresponding 95% CIs were calculated based on the normal approximation with standard errors via the Greenwood method, and between-group differences were informally tested using the z-test, with standard errors computed via the Greenwood method. Treatment comparisons for EFS_{eff} were performed using the stratified log-rank test. Kaplan–Meier methodology was used to estimate the EFS_{eff} distribution for each treatment arm and construct curves for the visual description of the difference between the treatment arms. Estimates of the treatment effect were expressed as hazard ratios using a stratified Cox proportional-hazards analysis, including 95% confidence intervals. OS was analysed with the same methodologies as $EFSe_{ff}$. Estimates of complete, objective and best overall response rates and their accompanying 95% confidence interval (CI) were calculated with the Clopper–Pearson method, with 95% CI for the differences between treatment arms calculated using the Wilson method.

Trial name: POLARIX	NCT number: 03274492
Subgroup analyses	The effects of baseline characteristics and tumour subtype on investigator-assessed PFS were investigated using stratified and unstratified HRs estimated from Cox proportional hazards models. Kaplan–Meier estimates comparing PFS between treatment arms were produced for each level of the categorical variables.
Other relevant information	NA

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table 40: Baseline characteristics of patients in the study included for the comparative analysis of efficacy and safety

	POLARIX			
	IPI score 2-5 population [1,32]		**IPI score 3-5 population [34]**	
	R-CHOP n=439	Pola+R-CHP n=440	R-CHOP n=272	Pola+R-CHP n=273
Age, years				
Median	66	65	67	67
18-60, n (%)	131 (29.8)	140 (31.8)	59 (21.7)	70 (25.6)
>60, n (%)	308 (70.2)	300 (68.2)	213 (78.3)	203 (74.4)
Sex, n (%)				
Female	205 (46.7)	201 (45.7)	116 (42.6)	127 (46.5)
Male	234 (53.3)	239 (54.3)	156 (57.4)	146 (53.5)
Ethnicity, n (%)				
Hispanic or Latino	30 (6.8)	18 (4.1)	18 (6.6)	9 (3.3)
Not Hispanic or Latino	306 (69.7)	317 (72.0)	183 (67.3)	197 (72.2)
Not stated	49 (11.2)	66 (15.0)	32 (11.8)	42 (15.4)
Unknown	54 (12.3)	39 (8.9)	39 (14.3)	25 (9.2)
ECOG PS at Baseline, n (%)				
0	173 (39.5)	175 (39.8)	87 (32.0)	88 (32.2)
1	190 (43.4)	199 (45.2)	128 (47.1)	136 (49.8)
2	75 (17.1)	66 (15.0)	57 (21.0)	49 (17.9)
Lactate dehydrogenase level – no (%)				
Normal	154 (35.1)	146 (33.2)	68 (25.1)	54 (19.9)
Evevated	284 (64.7)	291 (66.1)	203 (74.9)	217 (80.1)
Ann Arbor Stage, n (%)				
I	9 (2.1)	2 (0.5)	1 (0.4)	0 (0.0)
II	43 (9.8)	45 (10.2)	2 (0.7)	3 (1.1)
III	108 (24.6)	124 (28.2)	62 (22.8)	65 (23.8)
IV	279 (63.6)	269 (61.1)	207 (76.1)	205 (75.1)
No. of extranodal sites – no (%)				
0 or 1	226 (51.5)	227 (51.6)	88 (32.4)	92 (33.7)
≥ 2	213 (48.5)	213 (48.4)	184 (67.6)	181 (66.3)
Stratification – IPI Score (IxRS), n (%)				

IPI 2	167 (38.0)	167 (38.0)	0	0
IPI 3-5	272 (62.0)	273 (62.0)	272 (100)	273 (100)
Double-expressor lymphoma – no./total no.				
	151/366 (41.3)	139/362 (38.4)	99/222 (44.6)	96/230 (41.7)
Double-hit or triple-hit lymphoma — no./total no.				
	19/334 (5.7)	26/331 (7.9)	11/203 (5.4)	18/216 (8.3)
Stratification – Bulky Disease (IxRS), n (%)				
Absent	247 (56.3)	247 (56.1)	138 (50.7)	139 (50.9)
Present	192 (43.7)	193 (43.9)	134 (49.3)	134 (49.1)
Stratification – Geographical Region (IxRS), n (%)				
Western Europe, United States, Canada and Australia	301 (68.6)	302 (68.6)	186 (68.4)	187 (68.5)
Asia	79 (18.0)	81 (18.4)	50 (18.4)	50 (18.3)
Rest of World	59 (13.4)	57 (13.0)	36 (13.2)	36 (13.2)

Abbreviations: ECOG PS - Eastern Cooperative Oncology Group performance status; IxRS - Interactive Voice or Web-Based Response System; pola - polatuzumab vedotin; R-CHOP - rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone; R-CHP - rituximab plus cyclophosphamide, doxorubicin and prednisone.

Comparability of patients across studies

Only one study, POLARIX, is included in the application. In the ITT population (IPI score 2-5) and the IPI score 3-5 population, respectively, treatment arms were generally well-balanced with respect to demographic (age, sex, race, height, weight, geographic region) and baseline characteristics (ECOG performance status, Ann Arbor stage, IPI Score, presence of Bulky disease or not, bone marrow involvement, number of extranodal sites and NHL histologic diagnosis).

Comparability of the study populations with Danish patients eligible for treatment

A Danish nationwide study describes the diagnostic clinicopathological characteristics of newly diagnosed Danish DLBCL-patients identified from the LYFO [17]. Patients included in this study (n=1446) were aged above 18 years, were treated with 6-8 cycles of R-CHOP or R-CHOEP as first-line treatment, were in CR/CR unconfirmed (CRu) after first-line treatment according to PET or CT-based response criteria, and were alive and relapse-free 90 days after the end of treatment response evaluation. Although this study only included patients in CR after R-CHOP and R-CHOP-like regimes, which is different from the POLARIX study, the data are the best available to assess comparability. Characteristics of Danish patients with IPI score 3-5 are not available, and therefore the comparison is based on the full study population. In POLARIX, 38% of patients had IPI score 2 and 62% of patients had IPI score 3-5. Low risk patients were not eligible for the study. This is comparable to what is reported in a study by Rupert et al. that evaluated 2124 DLBCL-patients treated from 1998 to 2009 with R-CHOP or a variant across seven multicentre randomized clinical trials. The distribution reported in this study is assumed to be comparable to the distribution in a Danish population. As mentioned previously the IPI distribution among Danish patients is reported for all NHLs (low risk: 28.7%; low-intermediate risk: 33.7%, high-intermediate risk: 23.2%; high risk: 12.3%), but not for DLBCL alone [3].

The study population in POLARIX and the Danish population in the registry study have similar characteristics in terms of age and gender. Median age in POLARIX was 66 years, which is similar to the Danish population [17]. In POLARIX, around 70% were aged above 60 years. This is comparable with the Danish population, where 22.5% were aged 18-55 years, 25.4%, were aged 56-65 years, 36.2% were aged 66-75 years and 15.0% were aged > 75 years. The distribution of females and males in POLARIX was 46.7% and 53.3%, which is similar to the Danish population (females: 44.2%; males: 55.2%) [17].

The POLARIX study population differ somewhat from the Danish population in terms of performance status (PS) and Ann Arbor stage. In POLARIX, 60.5% of patients had PS > 0 (PS 1: 34.4%; PS 2: 17.7%). In comparison, 45.6% of Danish patients had PS > 0 in the registry study [17]. In POLARIX, a total of 88.2% of the patients had Ann Arbor Stage III-IV (stage III: 24.6%; stage IV: 63.6%), and in the registry study 66.3% of patients had Ann Arbor Stage III-IV. Thus, patients in POLARIX had a slightly higher performance status and more widespread disease at diagnosis compared to the Danish population, which could result in the clinical trial population being more difficult to treat or more likely to experience AEs. However, the differences observed are likely to be a result of the differences in the inclusion criteria between the studies.

Overall the patients included in POLARIX are found to be representative of a Danish patient population.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 41: Definition, validity and clinical relevance of included outcome measures

Outcome measure	Definition	Validity	Clinical relevance
PFS	PFS is defined as the time from randomization to the first occurrence of disease progression or relapse as assessed by the investigator, using the Lugano Response Criteria for Malignant Lymphoma, or death from any cause, whichever occurs earlier [64].	PFS is a commonly used endpoint within oncology trials, and is an accepted primary endpoint in 1L DLBCL, as confirmed by the FDA and EMA in pre-phase meetings [65,66]. It is used to assess the time during which patients are alive without progressive disease. PFS is not affected by the impact of subsequent treatment and patient crossover between trial arms in the same manner as OS, and therefore serves as a relevant supplement to OS. See evidence on PFS surrogacy with OS in Table 42.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within DLBCL in second or later treatment lines, PFS has been defined as an important clinical endpoint.
EFS_{eff}	EFSeff is used to reflect EFS events that are primarily due to efficacy. It is defined as the time from date of randomization to the earliest occurrence of any disease progression/relapse, death, new anti-lymphoma therapy resulting from an efficacy reason or objective evidence of disease (biopsy, clinical/imaging assessment).	EFS is used to assess the time during which patients are alive without any disease progression/relapse, death or new anti-lymphoma therapy. EFS is not affected by the impact of subsequent treatment and patient crossover between trial arms in the same manner as OS, and therefore serves as a relevant supplement to OS. See evidence on EFS surrogacy with OS in Table 42.	To our knowledge, published information on minimal important differences is not available.
CR	Percentage of patients with CR at the end of treatment by PET-CT as determined by BICR or by investigator.	CR is an important endpoint to demonstrate the response to treatment.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within DLBCL in second or later treatment lines, CR has been defined as an important clinical endpoint.

Outcome measure	Definition	Validity	Clinical relevance
OS	OS is defined as the time from date of randomization until the date of death from any cause.	OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy or patient crossover between treatment arms in studies of early treatment.	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within DLBCL in second or later treatment lines, OS has been defined as the most important clinical endpoints (critical endpoint).
AEs	Incidence of AEs and treatment-related by severity, SAEs and treatment-related SAEs, and discontinuation due to AEs. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.0, and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0). Safety data is presented in accordance with section 4.2 in the Medicines Council guideline.	NA	To our knowledge, published information on minimal important differences is not available. In previous Medicines Council assessments within DLBCL in second or later treatment lines, AEs, specifically grade 3-4 AEs and discontinuations due to AEs, have been defined as an important clinical endpoint.
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) consists of 30 questions that assess five aspects of patient functioning (physical, emotional, role, cognitive, and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health/QoL, and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) with a recall period of the previous week Scale scores can be obtained for the multi-item scales. The first 28 items are scored on a 4-point scale that ranges from “not at all” to “very much,” and the last two items are scores on a 7-point scale that ranges from “very poor” to “excellent.” Higher scores indicate higher response levels (i.e., higher HRQoL, higher symptom severity).	EORTC QLQ-C30 is a validated, reliable self-report measure [67,68].	To our knowledge, published information on minimal important differences is not available.

Outcome measure	Definition	Validity	Clinical relevance
FACT-Lym LymS	Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) is a measure of HRQoL aspects relevant to lymphoma patients. The full measure consists of the FACT-G physical, social/family, emotional, and functional well-being scales (27 items), as well as a lymphoma-specific symptoms scale (15 items). For POLARIX, only the items that comprise the lymphoma-specific symptoms (LymS) scale were administered to patients. Each item is rated on a 5-point response scale that ranges from “not at all” to “very much,” with higher scores indicative of better HRQoL.	FACT-Lym is a validated, reliable self-report measure of HRQoL aspects relevant to lymphoma patients [69].	To our knowledge, published information on minimal important differences is not available.

Evidence on PFS and EFS surrogacy with OS

Several studies have assessed PFS and EFS surrogacy with OS in DLBCL. The evidence is derived from both RCTs and registries. The evidence that resulted from the randomized clinical trials (RCTs) has been fully covered by systematic reviews and meta-analysis; key assessments are included in Table 42. Relevant registry studies, identified based on an internal review, are also summarised in Table 42. Surrogacy validations require RCTs and preferably individual patient-level data to show that the treatment effect on the surrogate endpoint predicts the treatment effect on the true endpoint. Registry or real-world studies are focused on stating whether an early event is prognostic, though they cannot provide complete validation of surrogacy.

The most recent systematic review of RCTs by Zhu et al performed the classical meta-analytic surrogate endpoint validation, regressing the PFS and EFS HR with OS HR, and using the log transformed aggregate level results from 26 RCTs. The resulting correlation coefficients for log PFS HR (r, 0.772; 95% CI: 0.471 to 0.913) or log EFS HR (r, 0.838; 95% CI: 0.625 to 0.938) showed both a strong association with log OS HR, and, together with the various sensitivity analyses, confirmed that treatment gain in PFS or EFS can predict OS benefit at trial level with an acceptable consistency. The study also built prediction models between 1-, 2-, 3- and 5-year PFS or EFS rates, and 5-year OS rates that were first established using the RCTs, and then externally validated in the phase II and retrospective populations. The findings indicated that 1–3-year PFS or EFS rates were strongly associated with higher 5-year OS; however, they also mention that the predictive models may need reshaping due to more effective salvage treatments that are significantly

prolonging post-progression survival, which were not available at the time the selected studies were conducted. This surrogacy study at trial level and treatment arm level complemented previous evidence and strengthened the clinical use of PFS and EFS as early efficacy endpoints [70].

The most relevant work, from a methodological perspective, was the Surrogate Endpoints for Aggressive Lymphoma (SEAL) group's systematic review, as it pooled individual patient data. The SEAL group's systematic review also pooled data from 13 DLBCL RCTs published between 2002 and 2015 in order to evaluate PFS and PFS at 24 months (PFS24) as surrogate endpoints for OS in 1L DLBCL. Trial-level surrogacy for PFS was strong, whereas PFS24 was slightly less robust than PFS and did not meet the pre-specified surrogacy qualification criteria. The Surrogacy performance of PFS24 improved when the analysis was restricted to induction comparisons, and had the original study selection excluded maintenance studies had PFS24 met the predefined surrogacy criteria. At the patient level, the global objective response was 61.1 (95% CI: 52.6, 69.6), which suggested a higher odds of remaining alive beyond a particular time point for patients who were alive and disease-free at 24 months after treatment initiation. Although PFS24 was significantly correlated with longer OS at the patient-level analysis, this was considered a supportive but not sufficient condition for surrogacy validation. The study concludes that future analyses with additional trials should re-evaluate the role of PFS24 as a surrogate endpoint, focusing on the trial-level correlation with OS [71].

The work that is most often cited for DLBCL endpoint validations is based on Mayo clinic cohorts for EFS [24] and PFS SEAL [23]. These Mayo clinical cohorts analyses aimed to validate event-free survival at 12- months (EFS12) and 24 months (EFS24), and compared the subsequent survival with age-, sex- and calendar year-matched reference population data. The evaluation covered 767 patients with newly diagnosed DLBCL enrolled between 2002 and 2009. The study showed that patients achieving EFS24 had an overall survival equivalent to that of the age- and sex-matched general population (standardized mortality ratio [SMR], 1.18; P=0.25). This result was confirmed in 820 patients from the GELA study and registry in Lyon (SMR, 1.09; P=0.71) [24]. The former study repeated the analysis using clinical trial data pooled by the SEAL group, with PFS24 as the clinical early endpoint. Using the data from 5,853 rituximab-treated patients, the study showed that survival was marginally lower having achieved PFS24, but clinically indistinguishable from the age-, sex-, and country-matched background population.

Table 42: Studies on PFS and EFS Surrogacy with OS

Study name	Included studies/patients	Outcome	Reference
Zhu et al. (2020) Treatment level meta-analysis (2019 systematic search)*	All Phase 2 and 3L DLBCL studies (N=26)	Positive surrogacy of PFS, EFS and OS	Zhu et al. 2020 [70]

Study name	Included studies/patients	Outcome	Reference
SEAL	Meta-database of clinical trial data Phase 3 studies; 1L DLBCL (N=13)	Positive surrogacy of PFS and OS; suggestive PFS24 and OSa	Shi et al. 2018 [71]
EFS24 Mayo Clinic assessment	Mayo Clinic Specialized Programs of Research Excellence Molecular Epidemiology Resource (MER; N = 986) or the Lymphoma Study Association (LYSA) LNH-2003 clinical trials program (N = 1,444)	Patients achieving EFS24 had an overall survival equivalent to that of the age- and sex-matched general population	Maurer et al. 2014 [24]
SEAL	A total of 5,853 patients enrolled in trials in the SEAL database received rituximab as part of induction therapy	The survival of patients achieving PFS24 marginally lower but clinically indistinguishable from the age-, sex-, and country-matched background population	Maurer et al. 2018 [23]
Danish Lymphoma Registry Population-based study	Newly diagnosed with DLBCL in 2003 and 2011	Suggested that of pEFS24 could be a potential surrogate for OS, although excess mortality still due to late relapses	Jakobsen et al. 2017 [72]
Swedish Cancer Registry Population based study	Newly diagnosed 2001–2014	Patients achieving EFS24 aged <60 years had an OS that matched the standard population. In multivariate analysis, only age >60 years significantly affected OS after EFS24 compared with the standard population and concluded that follow-up beyond EFS24 should be considered for patients aged >60 years	Abu Sabaa et al. 2021 [73]
Wudhikarm 2020 Population based study	Newly diagnosed 2007–2014 (stage 1 DLBCL)	EFS12 is an independent predictor for OS	Wudhikarm 2020 [74]

An internal review of registry data identified a number of studies that looked at survival in parallel to other endpoints. The first reported population-based study was that by the Danish Lymphoma Registry study, which included patients with newly diagnosed DLBCL between 2003 and 2011. The study did not support complete normalisation of survival in the overall population of patients with DLBCL achieving pEFS24, but in the age-stratified analyses, the survival of patients <50 years of age was normalised to the general population after achieving pEFS24. The study, however, concluded that as the overall residual loss of lifetime was low, the pEFS24 remains an appealing and relevant milestone for

patient counselling, and could be a surrogate endpoint in clinical trials. The study also identified that excess mortality diminished when analysing death from lymphoma as a competing event to death from other causes, suggesting that early and late relapse is responsible for increased mortality in patients with DLBCL [72].

A very recent population-based study using data from the Swedish Cancer registry evaluated the subsequent mortality of patients who had achieved EFS24, and included Swedish DLBCL patients diagnosed between 2001–2014 who were receiving R-CHOP or R-CHOP-like therapy [73]. The study found that patients aged <60 years had an OS that matched the standard population. In the multivariate analyses, only the age >60 years covariate significantly affected OS after EFS24 when compared with the standard population. The study concluded that follow-up beyond EFS24 should be considered for patients aged >60 years. The authors of the Swedish study also referred to the British Columbia (n=2,046) study, one of the largest on the subject, where EFS24 was calculated from diagnosis. In this study, the 5-year risk of relapse decreased after achieving EFS24 (from 33 to 11%), but OS for EFS24 patients remained worse than that of the age- and sex-matched local population regardless of age, IPI score and disease stage. However, a pathological subtype analysis showed that patients achieving EFS24 who had either germinal centre B-cell-like or primary mediastinal B-cell lymphoma did have an OS comparable to the standard population [75].

Additional registry studies that drew similar conclusions to the aforementioned studies include the HemoBase registry, conducted in the Netherlands between 2005 and 2018 [76], and the nationwide Thai registry conducted between 2007 and 2014 [74].

It appears that the overall conclusion from these studies is that a minimal and often clinically negligible excess mortality has been observed following achievement of EFS24 and PFS24. All studies emphasise the relevance of these 24-month outcomes, as most of the lymphoma-related outcomes occur before this milestone. The Danish population study was the only population-based study that directly related the excess mortality to deaths following late relapses.

Results per study

Table 43: Efficacy results of POLARIX (NCT03274492) - IPI score 2-5 and IPI score 3-5 populations

				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**		

PFS, median IPI 2-5	Pola+R-CHP	440	33 (33-NE)	NA	NA	NA	HR: 0.73	0.57-0.95	0.0177	The Kaplan-Meier method was used to estimate PFS in each treatment group. HRs and corresponding 95% CIs were estimated with the use of a stratified Cox proportional hazards analysis. The stratification factors were geographical region, IPI score and bulky disease defined as one lesion ≥7.5 cm. The stratified HR is presented here.	CCOD: June 28, 2021 [1,30,32]
	R-CHOP	439	NE								
PFS, 1-yr rate IPI 2-5	Pola+R-CHP	440	83.91% (80.43-87.39)	4.14%	-1.05; 9.32	NA	NA	NA	NA	12-month milestone PFS rate was estimated by Kaplan-Meier methodology, and the corresponding 95% CI was calculated based on the normal approximation with standard errors via the Greenwood method, and between-group difference was informally tested using the z-test, with standard errors computed via the Greenwood method.	CCOD: June 28, 2021 [1,32]
	R-CHOP	439	79.77% (75.92-83.61)								
PFS, 2-yr rate IPI 2-5	Pola+R-CHP	440	76.7% (72.7-80.8)	6.50%	0.52-12.49	NA	NA	NA	NA	Same methodology as applied for the 1-year PFS rate.	CCOD: June 28, 2021 [1,30,32]
	R-CHOP	439	70.2% (65.8–74.6)								

PFS, median IPI 3-5	Pola+R-CHP	273	NE	NA	NA	NA	HR: 0.65	0.47-0.88	0.0053	Same methodology as applied for IPI score 2-5 population. The stratified HR is presented here.	CCOD: June 28, 2021 [34]
	R-CHOP	272	NE								
PFS, 1-yr rate IPI 3-5	Pola+R-CHP	273	81.52% (76.85–86.20)	5.37%	-1.61; 12.35	NA	NA	NA	NA	Same methodology as applied for IPI score 2-5 population.	CCOD: June 28, 2021 [34]
	R-CHOP	272	76.15% (70.97–81.34)								
PFS, 2-yr rate IPI 3-5	Pola+R-CHP	273	75.16% (69.91–80.42)	10.05%	2.20-17.89	NA	NA	NA	NA	Same methodology as applied for IPI score 2-5 population.	CCOD: June 28, 2021 [1,32]
	R-CHOP	272	65.12% (59.29–70.94)								
EFS, median IPI 2-5	Pola+R-CHP	440	NE	NA	NA	NA	0.75	0.58-0.96	0.0244	Treatment comparisons were performed using the stratified log-rank test. Kaplan–Meier methodology was used to estimate the EFS distribution for each treatment arm and curves were constructed for the visual description of the difference between the	CCOD: June 28, 2021 [1,30,32]

	R-CHOP	439	NE							treatment arms. HRs and corresponding 95% CIs were estimated with the use of a stratified Cox proportional hazards analysis using the same stratification factors as in the primary analysis of PFS. The stratified HR is presented here.	
EFS, 1-yr rate IPI 2-5	Pola+R-CHP	440	82.5% (78.9-86.1)	3.9%	-1.5; 9.2	NA	NA	NA	NA	Same methodology as applied for the PFS rates.	CCOD: June 28, 2021 [32]
	R-CHOP	439	78.7% (74.8-82.6)								
EFS, 2-yr rate IPI 2-5	Pola+R-CHP	440	75.6% (71.5-79.7)	6.2%	0.1-12.2	NA	NA	NA	NA	Same methodology as applied for the 1-year EFS rate.	CCOD: June 28, 2021 [1,32]
	R-CHOP	439	69.4% (65.0-73.8)								
EFS, median IPI 3-5	Pola+R-CHP	273	NE	NA	NA	NA	0.65	0.48-0.88	0.0056	Same methodology as applied for IPI score 2-5 population. The stratified HR is presented here.	CCOD: June 28, 2021 [34]
	R-CHOP	272	NE								
EFS, 1-yr rate	Pola+R-CHP	273	80.4% (75.7-85.2)	6.1%	-1.04; 13.23	NA	NA	NA	NA	Same methodology as applied for IPI score 2-5 population.	CCOD: June 28, 2021

IPI 3-5	R-CHOP	272	74.3% (69.0-79.6)								[34]
EFS, 2-yr rate IPI 3-5	Pola+R-CHP	273	74.1% (68.8-79.4)	9.97%	2.06-17.87	NA	NA	NA	NA	Same methodology as applied for IPI score 2-5 population.	CCOD: June 28, 2021 [34]
	R-CHOP	272	64.1% (58.3-70.0)								
BICR-assessed CR rate IPI 2-5	Pola+R-CHP	440	78.0% (73.8-81.7)	3.9%	-1.9; 9.7	0.16	NA	NA	NA	BICR-assessed CR rate at end of treatment (EOT). An estimate of CR rate and its 95% CI was calculated using the Clopper–Pearson method for each treatment arm. The 95% CIs for the difference in CR rate between the two treatment arms were computed using the Wilson method. The CR rate was compared between the two arms using the CMH test stratified by the same factors used in the PFS primary analysis.	CCOD: June 28, 2021 [1,32]
	R-CHOP	439	74.0% (69.7-78.1)								
BICR-assessed CR rate IPI 3-5	Pola+R-CHP	273	75.1% (69.5-80.1)	5.61%	-2.17; 13.29	0.1446	NA	NA	NA	Same methodology as applied for IPI score 2-5 population.	CCOD: June 28, 2021 [34]
	R-CHOP	272	69.5% (63.6-74.9)								

OS, median IPI 2-5	Pola+R-CHP	440	NE	NA	NA	NA	HR: 0.94	0.67-1.33	0.7326	Treatment comparisons were performed using the stratified log-rank test. Kaplan–Meier methodology was used to estimate the OS distribution for each treatment arm and curves were constructed for visual description of the difference between the treatment arms. HRs and corresponding 95% CIs were estimated with the use of a stratified Cox proportional hazards analysis using the same stratification factors as in the primary analysis of PFS. The stratified HR is presented here.	CCOD: June 15, 2022 [34]
	R-CHOP	439	NE								
OS, 1-yr rate IPI 2-5	Pola+R-CHP	440	92.2% (89.7-94.7)	-2.5%	-5.8; 0.9	NA	NA	NA	NA	Same methodology as previously described for OS.	CCOD: June 15, 2022 [34]
	R-CHOP	439	94.6% (92.5-96.8)								
OS, 2-yr rate IPI 2-5	Pola+R-CHP	440	88.7% (85.7-91.7)	-0.01%	-4.3; 4.2	NA	NA	NA	NA	Same methodology as previously described for OS.	CCOD: June 15, 2022 [34]
	R-CHOP	439	88.7% (85.7-91.7								
	Pola+R-CHP	273	NR (NR-NR)	NA	NA	NA	0.90	0.61-1.34	0.61		

OS, median IPI 3-5	R-CHOP	272	NR (NR-NR)							Same methodology as previously described for OS. The stratified HR is presented here.	CCOD: June 15, 2022 [34]
OS, 1-yr rate IPI 3-5	Pola+R-CHP	273	90.4% (86.9-93.9)	-3.2%	-7.8; 1.4	NA	NA	NA	NA	Same methodology as previously described for OS.	CCOD: June 15, 2022 [34]
	R-CHOP	272	93.6% (90.6-96.5)								
OS, 2-yr rate IPI 3-5	Pola+R-CHP	273	86.7% (82.6-90.7)	1.2%	-4.7; 7.0	NA	NA	NA	NA	Same methodology as previously described for OS.	CCOD: June 15, 2022 [34]
	R-CHOP	272	85.5% (81.2-89.8)								
PFS, median IPI 3-5	Pola+R-CHP	273	NR (NR-NR)	NR	NA	NA	HR: 0,70	0.52-0.94	0.0209	Same methodology as previously described for PFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	NR (NR-NR)								
PFS, 1-yr rate IPI 3-5	Pola+R-CHP	273	81.6% (77.1-86.4)	5.7 %	-1.25; 12.70	0.1583	NA	NA	NA	Same methodology as previously described for PFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	75.9% (70.8-81.2)								
PFS, 2-yr rate IPI 3-5	Pola+R-CHP	273	75.4% (70.2-80.6)	10.1 %	2.31;17.88	0.0373	NA	NA	NA	Same methodology as previously described for PFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	65.3% (59.5-71.1)								

EFS, median IPI 3-5	Pola+R-CHP	273	NR (NR-NR)	NR	NA	NA	HR: 0,71	0.53-0.95	0.0274	Same methodology as previously described for EFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	NR (NR-NR)								
EFS, 1-yr rate IPI 3-5	Pola+R-CHP	273	80.1% (75.3-84.9)	6.1	-1.08; 13.23	0.0921	NA	NA	NA	Same methodology as previously described for PFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	74.1% (68.7-79.4)								
EFS, 2-yr rate IPI 3-5	Pola+R-CHP	273	74.0% (68.7-79.39	9.7 %	1.78; 17.51	0.0148	NA	NA	NA	Same methodology as previously described for PFS	CCOD: June 15, 2022 [34]
	R-CHOP	273	64.3% (58.5-70.2)								
[redacted]											

Table 44: Safety results of POLARIX (NCT03274492) - Safety evaluable-population and IPI score 3-5 population

				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**		
Grade 3-4 AEs Safety population	Pola+R-CHP	435	251 (57.7%)	0.2%	NA	NA	NA	NA	NA	Safety was analysed in the safety population, including all patients who received ≥ 1 dose of study treatment.	CCOD: June 28, 2021 [32]
	R-CHOP	438	252 (57.5%)								
Grade 3-4 AEs IPI 3-5	Pola+R-CHP	271	168 (62.5%)	1.6%	NA	NA	NA	NA	NA	Safety was analysed in the IPI score 3-5 population, including all patients with IPI score 3-5 who received ≥ 1 dose of study treatment.	CCOD: June 28, 2021 [34]
	R-CHOP	269	165 (60.9%)								
Grade 3-4 TRAEs Safety population	Pola+R-CHP	435	235 (54.0)	3.5%	NA	NA	NA	NA	NA	Safety was analysed in the safety population.	CCOD: June 28, 2021 [34]
	R-CHOP	438	221 (50.5)								
[redacted]											
SAEs	Pola+R-CHP	271	94 (34.9%)	-1.3%	NA	NA	NA	NA	NA		

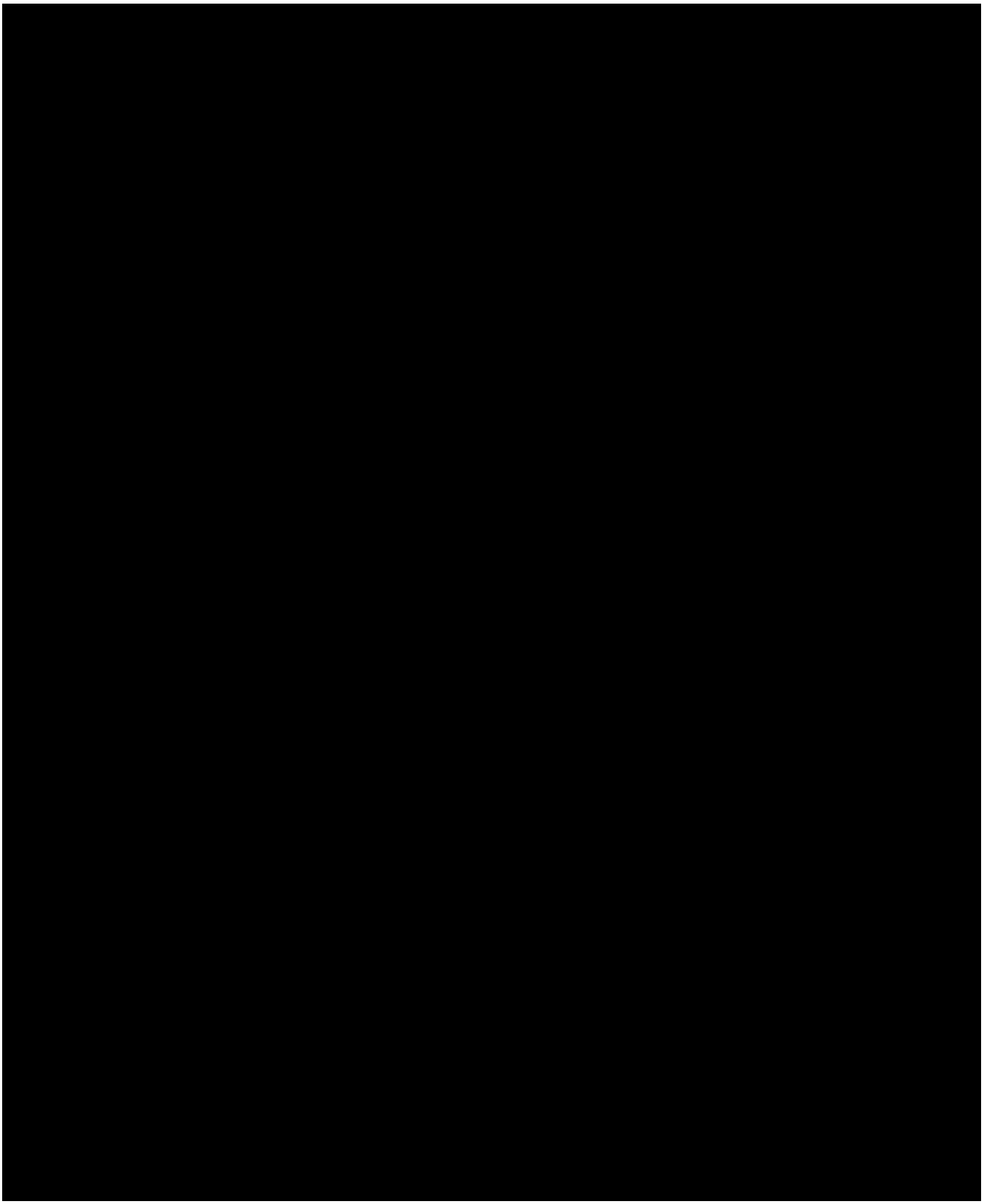
Appendix E Safety data for intervention and comparator

Safety data for the intervention and comparator in accordance with section 4.2 of the guideline is provided in Section 7.1.2 and Appendix D.

Appendix F Comparative analysis of efficacy and safety

POLARIX provides a direct comparison between polatuzumab vedotin plus R-CHP and R-CHOP and the results can be used to address the clinical question. The comparative results are presented in Section 7.1.2 and Appendix D.

Appendix G Extrapolation



[redacted]

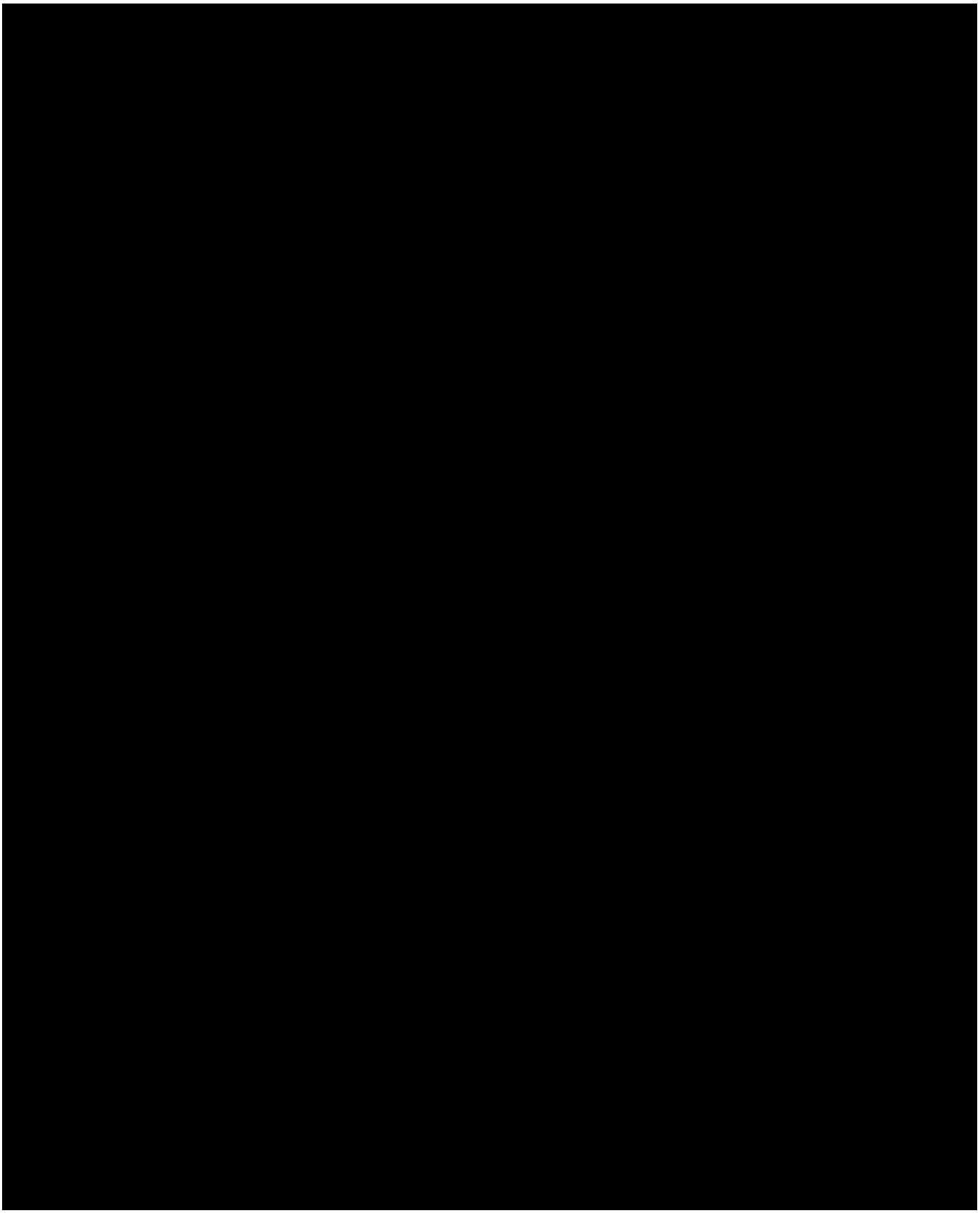
Appendix H – Literature search for HRQoL data

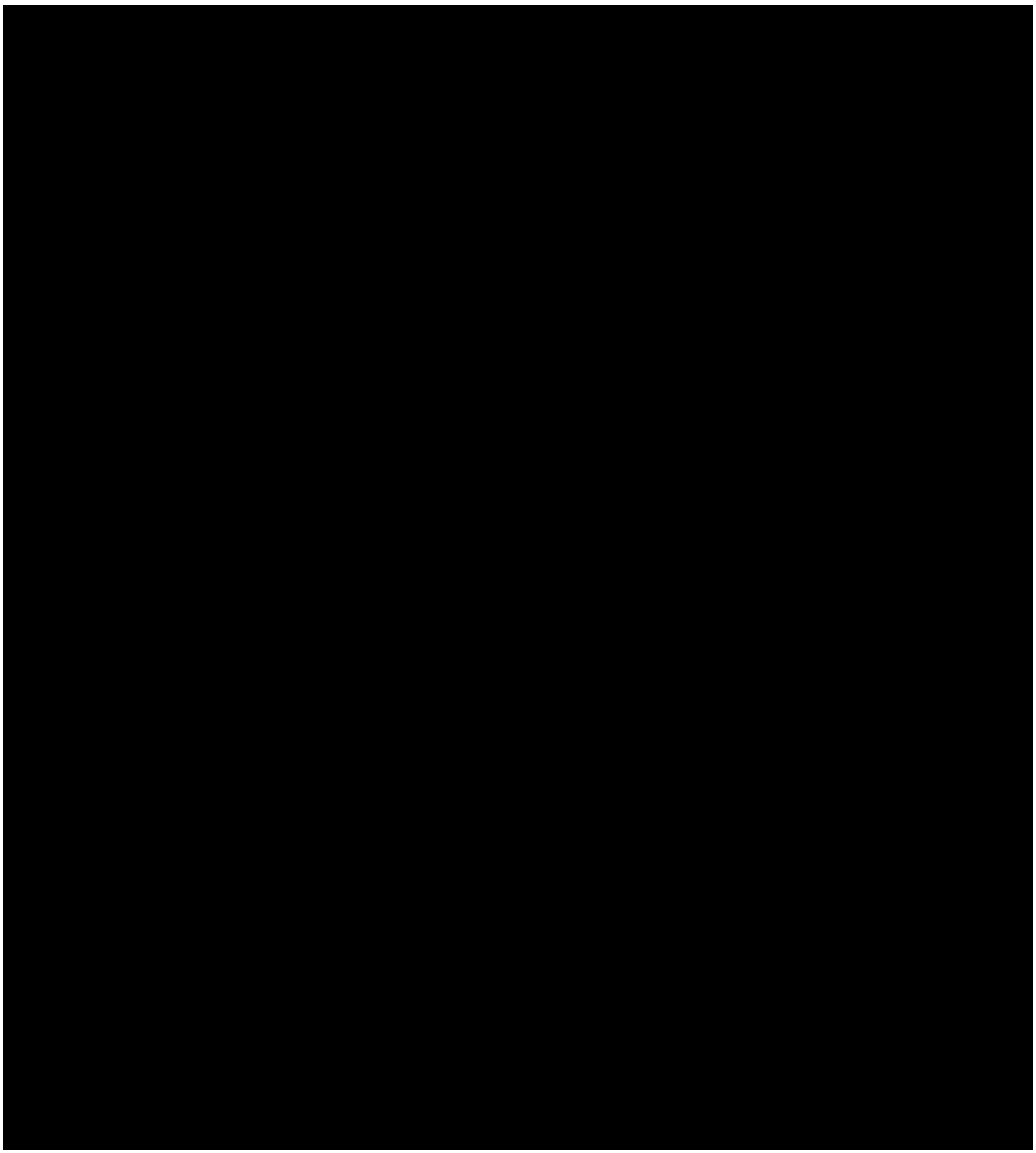
NA

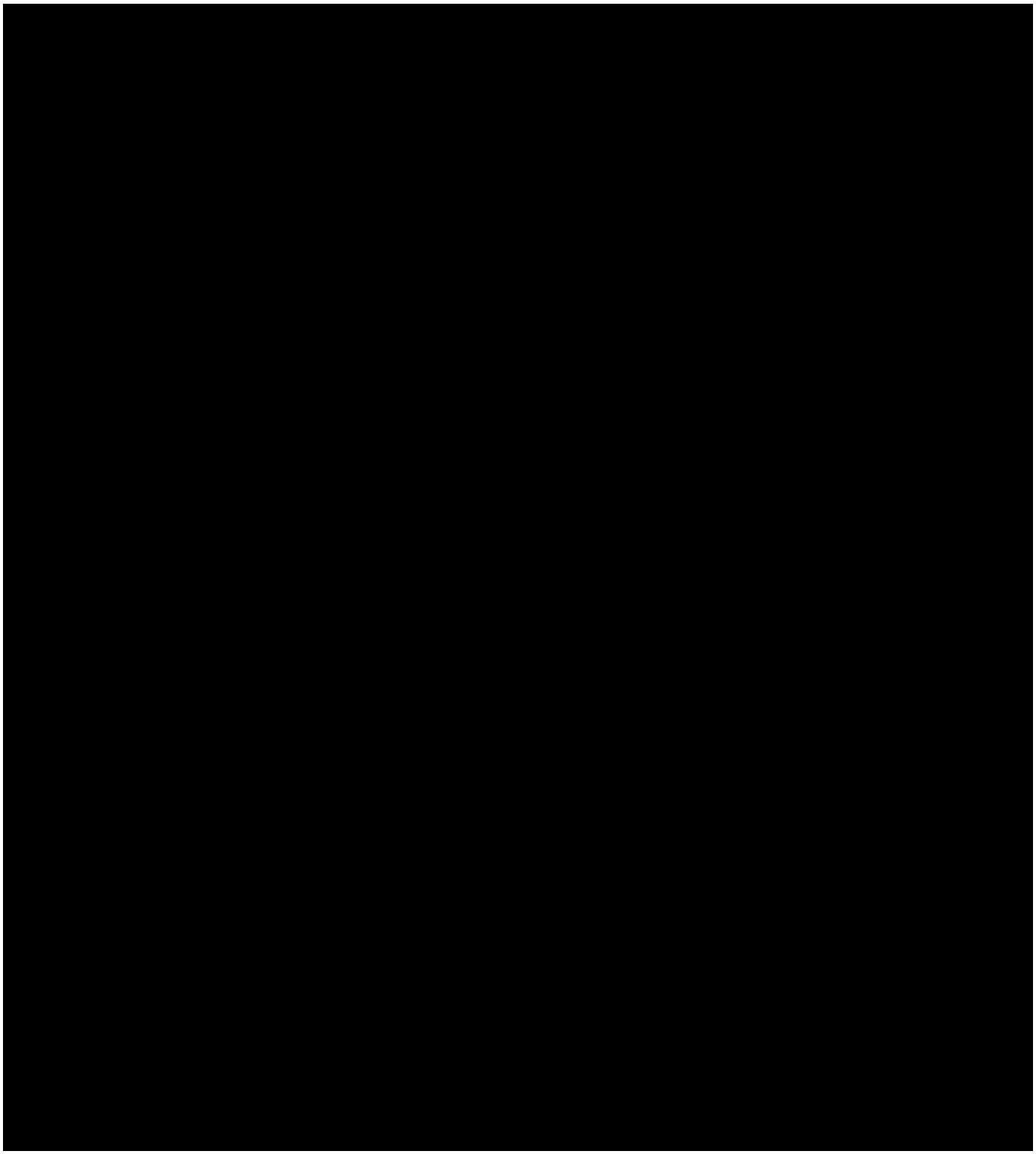
Appendix I Mapping of HRQoL data

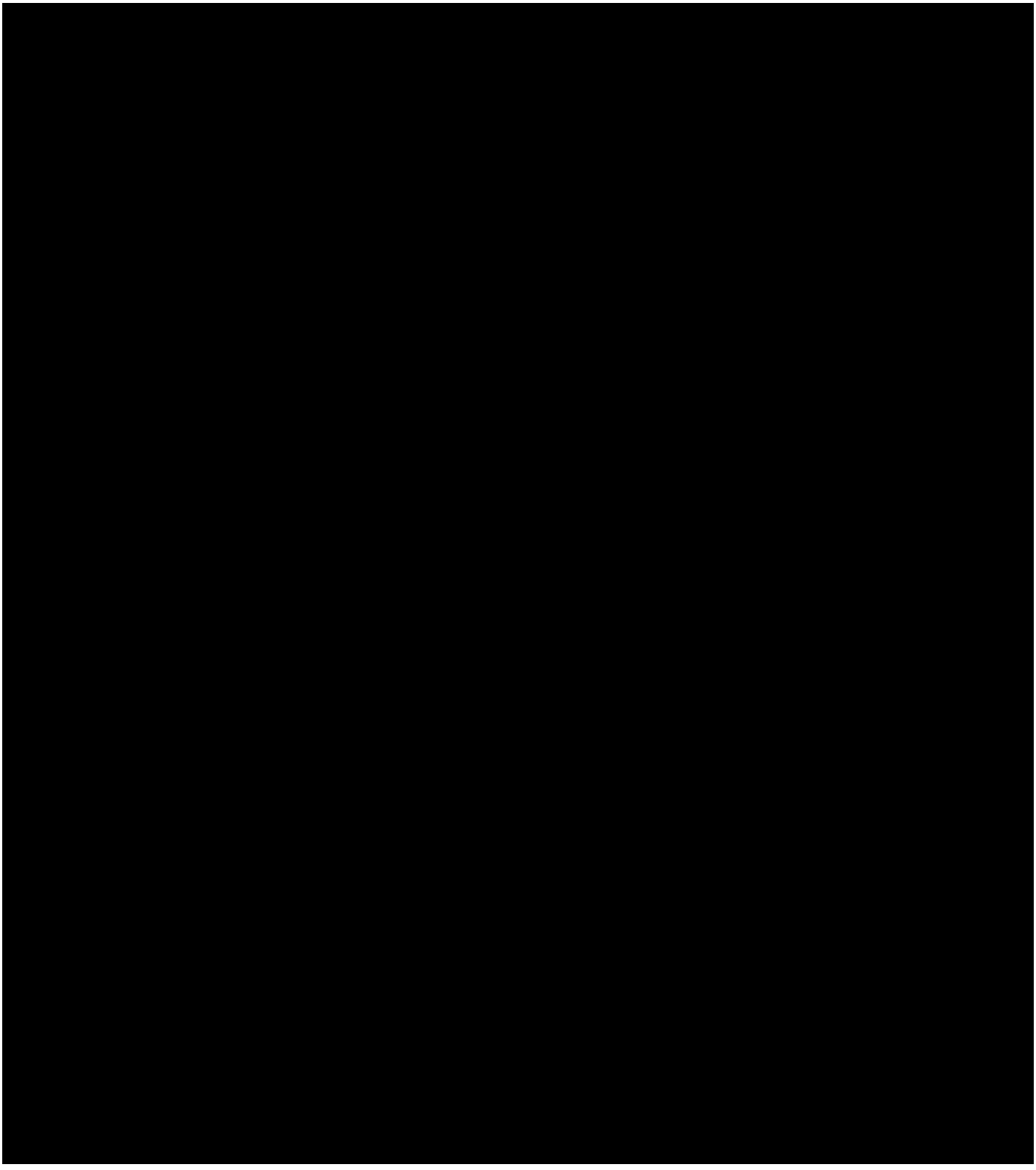
No mapping has been used for the base case in the health economic analysis.

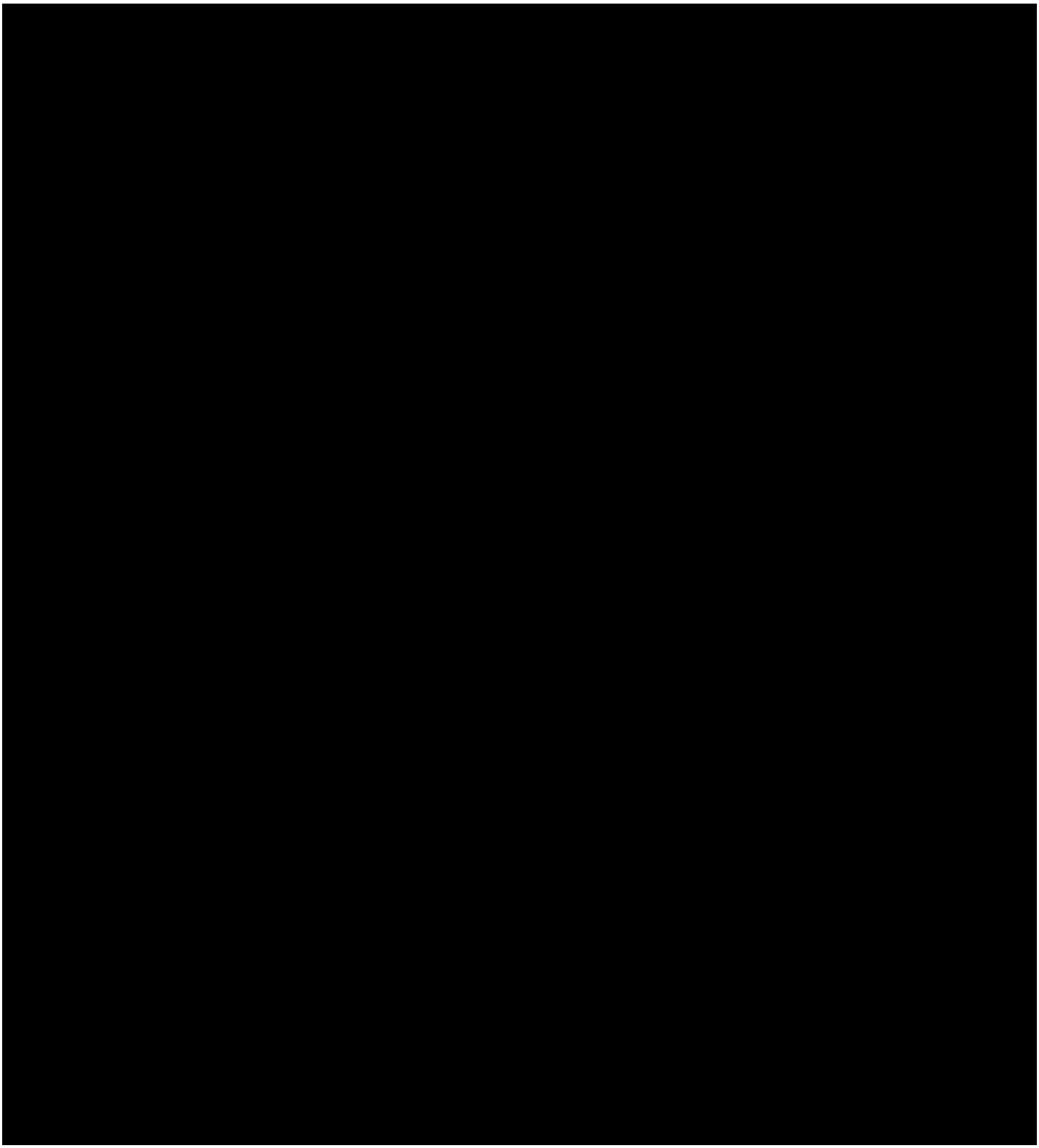
[redacted]

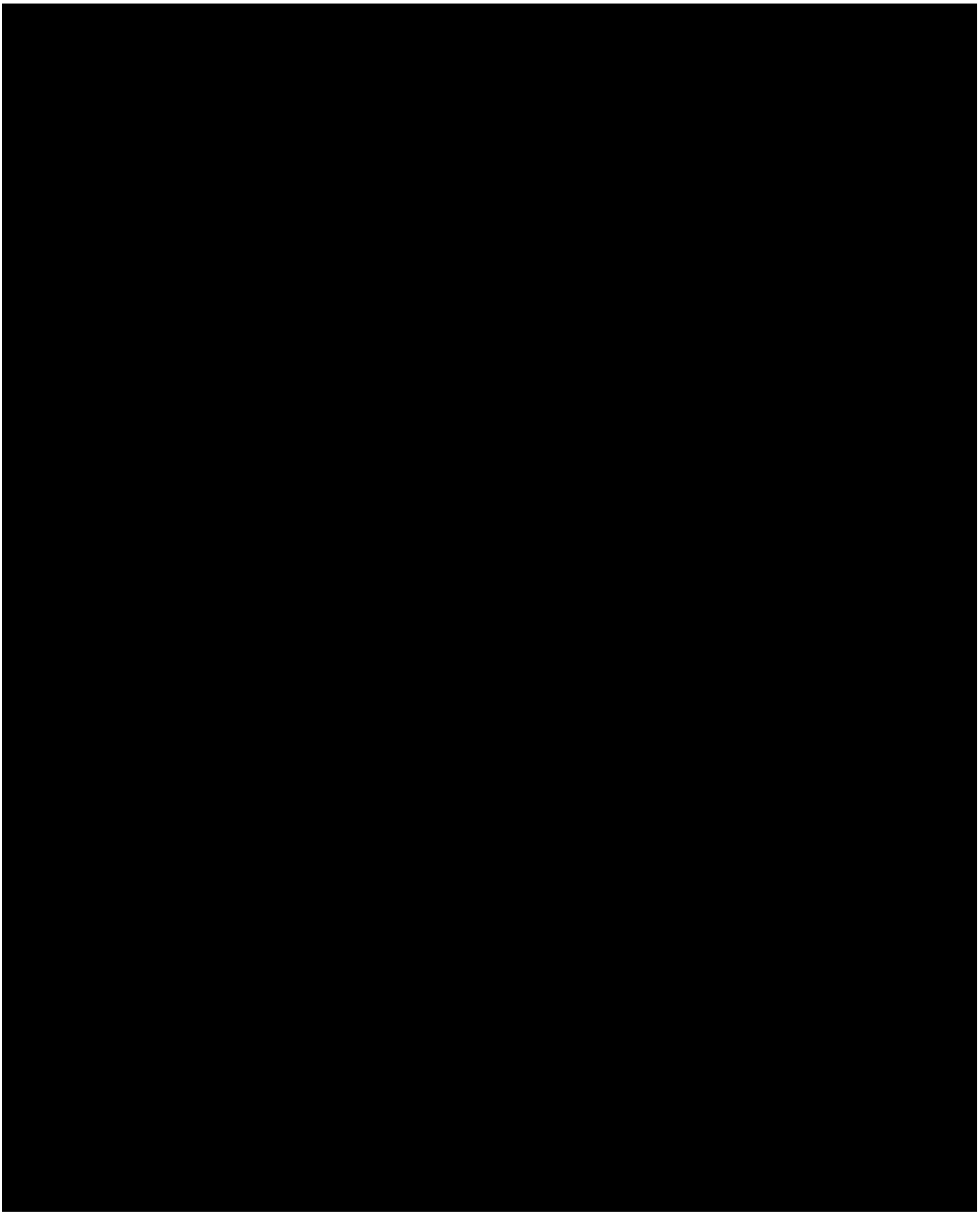


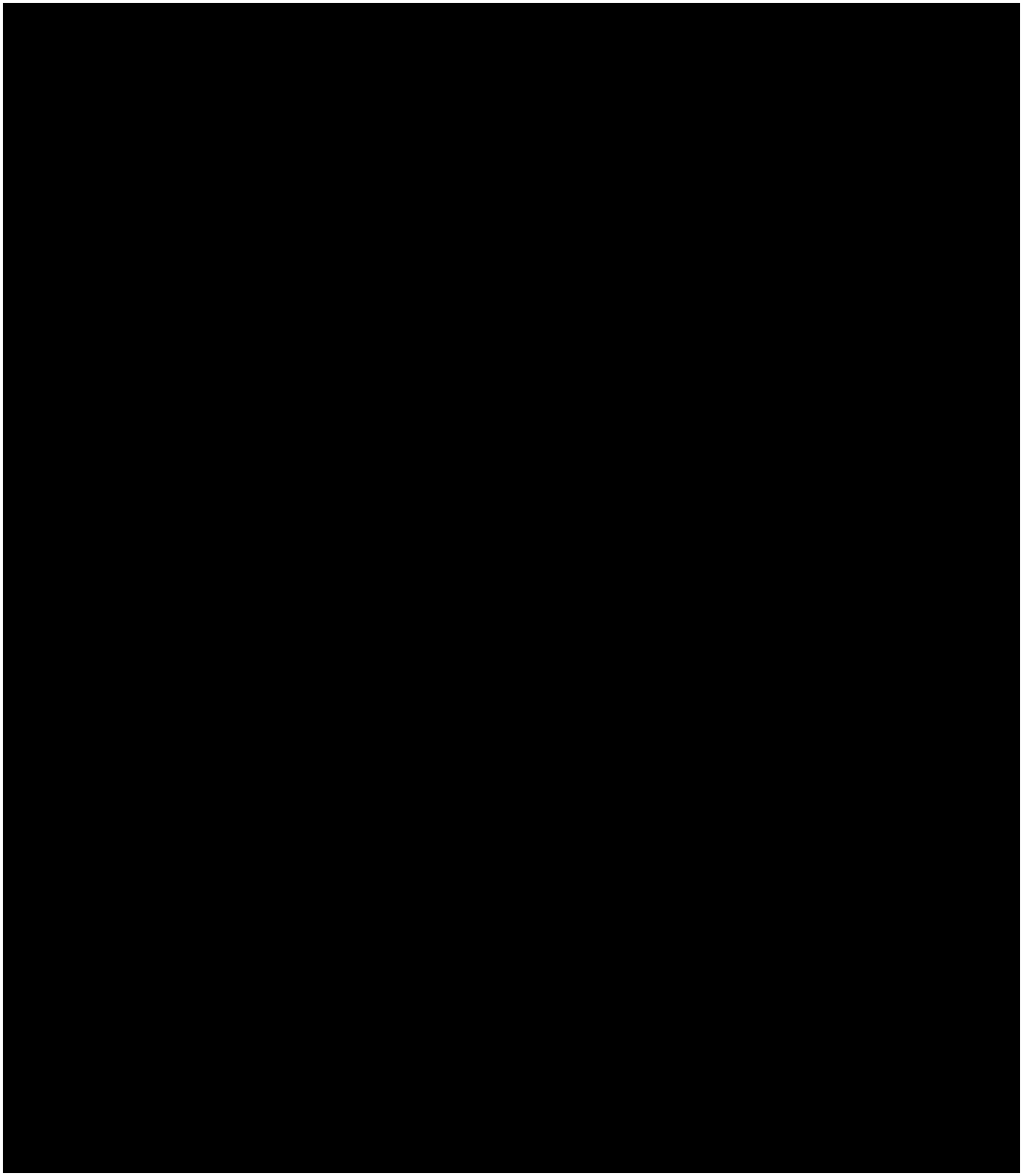












Appendix J Probabilistic sensitivity analyses