Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende glofitamab til behandling af diffust storcellet B-celle lymfom (DLBCL)

Vers. 1.0

Bilagsoversigt

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

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Til Medicinrådet

Vi mener generelt, at Medicinrådet kommer med inkonsistente argumenter i forhold til hvornår man kan sammenligne data fra NP30179 med retrospektive observationelle studier. Dette fører til modstridende konklusioner fra Medicinrådets side. Det uddyber vi i de følgende sektioner.

Medicinrådets vurderede usikkerhed ved den indirekte sammenligning af NP30179 med SCHOLAR-1
Som Medicinrådet selv nævner, findes ingen standardbehandling i 3L DLBCL, og af den grund er der mangel på robuste kliniske studier som kan bruges til grundlag for sammenligning af nye behandlinger i 3L DLBCL. Derfor er SCHOLAR-1 studiet brugt og anerkendt af flere HTA bodies (Cadth, NICE, NoMA og Medicinrådet selv), i vurderingen af nye behandlinger i 3L DLBCL (Yescarta og glofitamab bla). Dansk lymfomgruppe's kliniske retningslinjer refererer også til SCHOLAR-1. Desuden er SCHOLAR-1 et af de største observationelle studier med samlet data på patientniveau indenfor refraktær/relapse DLBCL, og af disse grunde er Roche af den overbevisning, at SCHOLAR-1 er det bedst egnede studie. Al-Mashadi et al. 2023 beskriver i øvrigt SCHOLAR-01 således "In our cohort, outcomes were very poor and similar to the SCHOLAR-1 study, despite fundamental differences in study design".

Medicinrådet skriver, at der er stor usikkerhed ved Roche's uforankrede indirekte sammenligning af et enarmet fase 1/2-studie med et retrospektivt observationelt studie. Vi mener dog, at usikkerheden er minimeret, da der er blevet justeret for otte vigtige prognostiske faktorer. Desuden vil mange af de forskelle der er mellem patientpopulationerne i SCHOLAR-1 og NP30179, være til SCHOLAR-1s fordel, som Medicinrådet også selv nævner: "*I NP30179 har patienterne gennemsnitligt modtaget flere behandlinger"; "I NP30179 er der ca. en tredjedel der tidligere har modtaget CAR-T behandling, mens ingen er behandlet med CAR-T i SCHOLAR-1".* Medicinrådet kritiserer også, at den justerede population i NP30179 som ender på 33 patienter, er en meget lille effective sample size (ESS). Dog mener Medicinrådet i deres naive sammenligning med det danske registerstudie, at en sample size på 24 patienter er robust nok til en sammenligning.

Overførbarhed af data fra NP30179 (justeret og ujusteret) til danske patienter
Medicinrådet mener, at der er stor indirekthed ift. overførbarhed til danske patienter da den vægtede studiepopulation i NP30179 er yngre, har mindre komorbiditet, og er højt selekteret ift. danske patienter. Dog er det her værd at nævne, at Danmark var et af de bedst rekrutterende lande til NP30179 studiet: 41 danske patienter var en del af NP30179 studiet, og ud af ITT populationen på 155, var 11 danske. Vi mener derfor ikke, at patienter er "højt" selekteret, da der er en fin dansk repræsentation. Medicinrådet foreslår, at de fremhævede forskelle ift. overførbarhed må være til NP30179s fordel. Men hvad Medicinrådet fravælger at nævne er, at andre forskelle er til danske patienters fordel. I NP30179 studiet, var 89.7% af ITT refractory (negativ prognostisk faktor) sammenlignet med 76.3% i det danske registerstudie. Roche anerkender at der er bias i forhold til overførbarhed, men vi mener at den går begge veje, og er langt fra kun til glofitamabs fordel.

Brugen af det danske registerstudie (Al-Mashadi et al. 2023) i en indirekte sammenligning
Medicinrådet har efterspurgt Roche, om en indirekte sammenligning med det danske registerstudie (i øvrigt data der er gjort muligt, da Roche/Genentech har finansieret studiet). Til denne forespørgsel forklarede Roche, at en indirekte sammenligning ikke var mulig grundet manglen på prognostiske faktorer, der kunne justeres for. Af den grund bør man anvende SCHOLAR-01, hvor der netop kunne justeres for vigtige prognostiske faktorer. Såfremt en naiv ujusteret sammenligning foretages mellem det danske registerstudie og NP30179, som Medicinrådet vælger at gøre, må den være behæftet med endnu større usikkerhed end den MAIC analyse der blev foretaget fra Roche's side. Konklusioner vedr. effekten af glofitamab bør absolut

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ikke bero på denne slags naive sammenligninger, men derimod indirekte sammenligninger, hvor der justeres for prognostiske og effektmodificerende faktorer som der er gjort i den præsenterede MAIC-analyse.

I den narrative sammenligning af NP30179 med det danske registerstudie har Medicinrådet desuden valgt at tage udgangspunkt i subgrupper fra det danske registerstudie hvor den første gruppe (subgruppe 1) var defineret som egnet til klinisk studier (n=68), og den anden (subgruppe 2) var selekteret på baggrund af kemoterapi (DHAP/ICE/GDP) som intervention (n=24). Vi mener, at disse naive sammenligninger er behæftet med betydelige usikkerheder. I subgruppe 1 for eksempel, har 20+19 modtaget behandling i et klinisk studie eller "anden" behandling, hvor det antages at "anden" er glofitamab. Dvs at 58% af subgruppe 1 højst sandsynligt har modtaget glofitamab eller anden bispecifik behandling, hvilket man må antage har haft stor indflydelse på overlevelsen i den positive retning. I subgruppe 2 er medianalderen 66 år, almentilstanden er bedre og sygdomsbyrden er mindre end gennemsnittet (IPI 0-2 62.5% vs 46% i den populationen). Denne subgruppe har derfor meget bedre performance end den fulde population i registerstudiet som man må antage repræsenterer den danske population, og den er derfor ikke repræsentativ. Desuden, og endnu mere problematisk er, at 100% af patienterne er 3L, hvor 29% i NP30179 har modtaget 4 eller flere behandlingslinjer. Desuden argumenterer forfatterne i det danske registerstudie selv for, at de patienter der har indgået i glofitamab kliniske studier, højst sandsynligt er mindre kemo-sensitive end subgruppe 2 grundet deres højere antal tidligere behandlinger. Når Medicinrådet derfor skriver, at der er en risiko for at behandling med glofitamab ikke øger overlevelsen sammenlignet med SOC på baggrund af det danske registerstudie, mener vi, at det er en meget problematisk og udokumenteret påstand grundet de argumenter og usikkerheder nævnt ovenfor - og samtidig findes der ingen SOC i 3L. Desuden skriver Medicinrådet selv i sin konklusion af Roche's præsenterede sammenligning med SCHOLAR-1, at der er grundlæggende metodiske forskelle på data fra et klinisk studie og registerdata, som vanskeliggør sammenligningen. Denne påstand må nødvendigvis også gøre sig gældende for det danske registerstudie, og dette er endnu et eksempel på, hvordan Medicinrådets argumentation er inkonsistent.

STARGLO data - glofitamab i kombination med GemOx til behandling af relapse/refraktær DLBCL
Medicinrådet skriver, at EMA godkendelsen af gloftimab i 3L DLBCL baseret på NP30179 er betinget af indsendelse af fase III-studiet GO41944. Dette studie er netop blevet præsenteret ved det årlige møde i European Hematology Association i Madrid, og data er allerede indsendt til Medicinrådet, da de indeholder patienter i 3L som får behandling med glofitamab i kombination med gemcitabin og oxaliplatin (GemOx) (en relevant komparator jvf. Medicinrådets egen vurderingsrapport). Studiet har OS som primær endepunkt og viser en OS-fordel for glofitamab plus GemOx sammenlignet med kemoimmunterapi (25,5 måneder versus 12,9 måneder; HR=0,62; 95% CI 0,43-0,88). Dette er en væsentlig forbedring for disse patienter, der efter progression på flere linjer kemoterapi har udsigt til endnu en inferiør behandling med nuværende behandlingstilbud. Vi vil derfor på det kraftigste opfordre Medicinrådet til at tage disse data med i overvejelserne eller sætte anbefalingen i clock-stop indtil disse data er taget i betragtning.

Konklusion
Glofitamab har dokumenteret en betydelig overlevelsesgevinst for patienter med r/r DLBCL i to studier (både NP30179 og GO41944), hvor den mediane overlevelsesgevinst overstiger 12 måneder. Dette er betydeligt for en patientgruppe, som har gentagne tilbagefald i deres sygdom (3.linje behandling) har en virkelig dårlig prognose. I dag findes der ingen standardbehandling og da der ikke er effektive og tolerable behandlingstilbud, og patienterne tåler ofte ikke mere kemoterapi (jvf. samtale med klinikere). Hæmatologerne er med de nuværende behandlinger afhængige af at kunne tilbyde patienterne inklusion i kliniske studier. Det er ikke et behandlingstilbud man kan tilbyde alle patienter.

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24.06.2024
CAF/MGK

Forhandlingsnotat

Dato for behandling i Medicinrådet	28.08.2024
Leverandør	Roche
Lægemiddel	Columvi (glofitamab)
Ansøgt indikation	Til behandling af voksne patienter med recidiverende eller refraktært diffust storcellet B-celle lymfom efter to eller flere systemiske behandlinger.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har følgende pris på Columvi (glofitamab):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Columvi	2,5 mg	1 stk.	6.228,98	[redacted]	[redacted]
Columvi	10 mg	1 stk.	24.624,72	[redacted]	[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Der er på nuværende tidspunkt ingen konkurrence i 3. linje. Medicinrådet har modtaget en ansøgning på Tepkinly (epcoritamab), Zynlonta (loncastuximab), Kymriah (tisagenlecleucel) og Yescarta (axicabtagene ciloleucel) til behandling i 3. linje. Tabel 2 viser lægemiddeludgiften for et års behandling med Columvi.

[redacted]

Tabel 2: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. år (SAIP, DKK)
Columvi	10 mg	1 stk.	Cyklus 1: 2,5 mg IV dag 8 10 mg IV dag 15 Cyklus 2-12: 30 mg IV dag 1 *	[redacted]	[redacted]

*En cyklus er 21 dage

Status fra andre lande

Tabel 3: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of glofitamab (COLUMVI) for relapsed or refractory diffuse large B-cell lymphoma (DLBCL)

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Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[other]	[definition of color-code]

1. Basic information

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Overview of the pharmaceutical	
Proprietary name	COLUMVI
Generic name	Glofitamab
Marketing authorization holder in Denmark	Roche Registration GmbH, Emil-Barell-Strasse 1, 79639 Grenzach-Wyhlen,Tyskland
ATC code	L01FX28
Pharmacotherapeutic group	Bispecific antibody
Active substance(s)	Glofitamab
Pharmaceutical form(s)	Concentrate for solution for infusion
Mechanism of action	Glofitamab is a bispecific monoclonal antibody that binds bivalently to CD20 expressed on the surface of B cells and monovalently to CD3 in the T-cell receptor complex expressed on the surface of T cells. By simultaneous binding to CD20 on the B cell and CD3 on the T cell, glofitamab mediates the formation of a synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B cells.

Overview of the pharmaceutical	
Dosage regimen	Fixed dosing schedule. Dosing every 21 days (except cycle 1). 12 cycles in total

Treatment cycle, Day		Dose of glofitamab	Duration of infusion
Cycle 1 (pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab*	
	Day 8	2.5 mg	4 hours
	Day 15	10 mg	4 hours
Cycle 2	Day 1	30 mg	4 hours
Cycle 3 to 12	Day 1	30 mg	2 hours

*obinutuzumab is not part of this application, but has been listed in this table since all patients in study NP30179 received obinutuzumab as pre-treatment on Cycle 1 Day 1.

Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Glofitamab as monotherapy is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.
Other approved therapeutic indications	None
Will dispensing be restricted to hospitals?	Yes
Combination therapy and/or co-medication	All patients in study NP30179 received a single 1 000 mg dose of obinutuzumab as pre-treatment on Cycle 1 Day 1 (7 days prior to initiation of glofitamab treatment) to lower the circulating and lymphoid B cells. Obinutuzumab was administered as an intravenous infusion at 50 mg/h. The rate of infusion was escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h. Additionally, premedication to reduce the risk of cytokine release syndrome, must be administered (intravenous glucocorticoid, oral analgesic/anti-pyretic and anti-histamine). At least 1 dose of tocilizumab for use in the event of CRS must be available prior to glofitamab infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.
Packaging – types, sizes/number of units, and concentrations	Columvi 2.5 mg concentrate for solution for infusion Each vial of 2.5 mL contains 2.5 mg of glofitamab at a concentration of 1 mg/mL. Columvi 10 mg concentrate for solution for infusion Each vial of 10 mL contains 10 mg of glofitamab at a concentration of 1 mg/mL.

Overview of the pharmaceutical	
Orphan drug designation	Glofitamab was designated as an orphan medicine for the treatment of DLBCL in the European Union on 15 October 2021 (https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-21-2497).

2. Abbreviations

Abbreviation	
1L	First line
2L	Second line
3L	Third line
3L+	Third line and above
AE	Adverse events
AESI	Adverse events of special interest
AIC	Akaike Information Criterion
ASCT	Autologous Stem Cell Transplantation
AUC	Area under the free carboplatin plasma concentration vs. time curve
BIC	Bayesian information criterion
BSA	Body Surface Area
BSC	Best supportive care
CCOD	Clinical cut-off dates
CE-plane	Cost-effectiveness plane
CEAC	Cost-effectiveness acceptability curve
CEOP	Cyclophosphamide, Epirubicin, Oncovin/vincristine, Prednisone
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CM	Centimetres
CRS	Cytokine release syndrome
CT	Computerized tomography
CTC	Common Terminology Criteria
CVP	Cyclophosphamide, Vincristine, Prednisone
D8	Day eight
DHAP	Dexamethasone, High-dose Cytarabine, Cisplatin
D15	Day fifteen
DKK	Danish kroner
DMC	Danish Medicines Council

DMCG	Danish Multidisciplinary Cancer Group
DLBCL	Diffuse large B-cell lymphoma
DLG	Danish Lymphoma Group
DRG	Diagnosis related groups
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EQ-5D-3L	EuroQol- 5 dimensiond; 3 three-levels;
EQ-5D-5L	EuroQol- 5 Dimension; 5 three-levels;
ERG	Electroretinogram
FACT-Lym LymS	Functional Assessment of Cancer Therapy – Lymphoma plus the 15-item Lymphoma Subscale
FDA	US Food and Drug Administration
GDP	Gemcitabine, Dexamethasone, Cisplatin
GemOx	Gemcitabine, Oxaliplatin
HGBCL	High-grade B-cell lymphoma
HMRN	Haematological Malignancy Research Network
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health-state utility value
HTA	Health technology assessment
ICE	Ifosfamide, Caboplatin, Etopside
ICER	Incremental cost-effectiveness ratio
INV	Investigator
IPD	Individual Patient Data
IRC	Independent review committee
ITC	Indirect treatment comparison
ITT	Intention-to-treat
IV	Intravenous
JAR	Joint assessment report
KG	Kilogram
KM	Kaplan Meier
LDH	Lactate dehydrogenase
LYFO	The Danish Lymphoma Registry
M^2	Square meters
MAIC	Matching-Adjusted Indirect Comparison

Mg	Milligram
MRI	Magnetic resonance imaging
MUGA	Multigated acquisition
NA	Not applicable
NE	North east
NICE	The National Institute for Health and Care Excellence
NHL	Non-Hodgkin's-Lymphoma
NMB	Net monetary benefit
NOS	Not otherwise specified
NR	Not reported
OS	Overall survival
PET-CT	Positron Emissions Tomography – Computerized Tomography
PFS	Progression-free survival
PH	Proportional hazard
PMBCL	Primary mediastinal B-cell lymphoma
PO	Per Oral
PREBEen	Pixantrone, Rituximab, Etoposide, Bendamustine
PRO	Patient reported outcome
Pola+BR	Polatuzumab + bendamustine and rituximab
PP	Per-protocol
PPP	Pharmacy purchase prices
PPS	Post-progressed survival
PSA	Probabilistic sensitivity analysis
Q3W	Once every 3 weeks
QALY	Quality adjusted life years
QoL	Quality of life
RCT	Randomised controlled trial
R/R	Relapse or refractory
R-chemotherapy	Rituximab + DHAP/ICE
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
RWD	Real-world Data
SAE	Serious Adverse Event

SC	Subcutaneous
SCT	Stem cell therapy
SG	Standard gamble
SLR	Systematic literature review
SmPC	Summary of product characteristics
trFL	Transformed follicular lymphoma
TTO	Time trade-off
TTOT	Time to off treatment
Tx	Treatment
UK	The United Kingdom
VAS	Visual analogue scale
WTP	Willingness to pay

3. Tables and Figures

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4. Summary

This application, submitted to the Danish Medicines Council (DMC) on May 26 2023, provides the basis for the assessment of glofitamab for relapse or refractory (R/R) diffuse large B-cell lymphoma in comparison with Danish standard of care which in this case is chemotherapy (ifosfamide, caboplatin, etopside (ICE)/dexamethasone, high-dose cytarabine, cisplatin (DHAP)/gemcitabine, dexamethasone, cisplatin (GDP) +/- rituximab (R).

Glofitamab (COLUMVI) as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy. The positive opinion granted by EMA's Committee for Medicinal Products for Human Use (CHMP) on April 26th 2023, is based on results from the phase I/II NP30179 study which included patients with DLBCL not otherwise specified (NOS), high-grade B-cell lymphoma (HGBCL), transformed follicular lymphoma (trFL) or primary mediastinal B-cell lymphoma (PMBCL) with an Eastern Cooperative Oncology Group (ECOG) performance-status (PS) score of 0 or 1, and who had relapsed or was refractory to, at least two previous lines of therapy. Glofitamab given as a fixed course treatment in the NP30179 study, showed early and long-lasting complete responses in people with heavily pre-treated or refractory DLBCL (1, 2).

Glofitamab (RO7082859) is a novel T-cell–engaging, bispecific, full-length monoclonal antibody that has a novel 2:1 configuration which enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells. The simultaneous binding to CD20 on the B cell and CD3 on the T cell, mediates the formation of a synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B cells (1, 3).

DLBCL is characterised by rapidly growing tumors in the lymph nodes, spleen, liver, bone marrow or other organs (4). Despite DLBCL being an aggressive lymphoma, it often responds well to treatment. First-line standard of care, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) aims to be curative, however, about 3 to 4 out of 10 patients relapse or are refractory to treatment (5-7). The R/R group of patients have dismal outcome, and is therefore a major cause of morbidity and mortality for patients with DLBCL (8). In Denmark, the median OS in DLBCL patients who have received a minimum of two prior therapies, is 6 months (95% CI 5-9), and the 2-year OS and PFS is 26% (95% CI 19-33) and 13% (95% CI 7-18), respectively (9).

In Denmark, approximately 500 new DLBCL patients are diagnosed per year (7), and of these, it is estimated that 6-10% reach third line (3L) therapy. However, only approximately 2 out of 3 of these patients receive treatment due to their refractory and fitness status (based on clinical expert opinions and data from the Danish Lymphoma Database (LYFO)). According to the Danish clinical guidelines for DLBCL, updated in 2021 (10), there is no standard of care for 3L DLBCL patients. Treatment will rarely be curative, and often patients will suffer from co-morbidities. If 3L patients are sensitive to chemotherapy, different chemotherapy regimens +/- R will be administered. The poor outcomes of the R/R DLBCL patient group, nevertheless, reflects the need for better treatment options beyond chemotherapy.

Clinical assessment

In the clinical assessment of glofitamab for the treatment of R/R DLBCL, the efficacy and safety was evaluated from the single-arm NP30179 phase I/II study. Due to the nature of the study, no direct evidence comparing glofitamab to chemotherapy +/- R was available. Consequently, a systematic literature review (SLR) was conducted to identify relevant studies for comparison. Electronic searches were carried out in MEDLINE (via PubMed) and in CENTRAL (via Cochrane Library) on March 12, 2023. Of the 184 references (including one hand-searched) that were identified, 8 references were eligible for inclusion in a matching-adjusted indirect comparison (MAIC) feasibility assessment.

Based on the feasibility assessment, only the retrospective multicohort study SCHOLAR-1 (6) qualified as a comparator study. SCHOLAR-1 represents one of the largest patient-level pooled analyses based on 4 individual studies: Lymphoma Academic Research Organization (LYSARC) Collaborative Trial in Relapsed Aggressive Lymphoma (CORAL) (11, 12), Canadian Cancer Trials Group (LY.12) (13), MD Anderson Cancer Center (MDACC) (14) and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence [IA/MC]) (15, 16).

Methods

For the purpose of this application, efficacy outcomes from NP30179 have been reported in the intent-to-treat (ITT) population at the clinical cut-off date (CCOD) of June 15, 2022 (*data on file, (17)*). The ITT consists of R/R DLBCL patients who were enrolled to receive glofitamab monotherapy after pre-treatment with obinutuzumab. Outcomes were assessed by both an independent review committee (IRC) and by investigator (INV), however, only INV-assessed outcomes were used in the MAIC to ensure outcome comparability with SCHOLAR-1.

In order to compare the efficacy of glofitamab to that of chemotherapy +/- R, a MAIC was conducted for complete response (CR) rate, overall response rate (ORR), and overall survival (OS) based on available data for glofitamab and the chemotherapy regimens represented in SCHOLAR-1. The MAIC method essentially adjusts for between-trial differences in baseline characteristics and SCHOLAR-1 reported sufficient baseline characteristics for such an adjustment to be made. Data on progression-free survival (PFS), health related quality of life (HRQoL) and safety was not available in SCHOLAR-1, and therefore, narrative comparisons were performed for these endpoints using data from NP30179 and each of the individual studies in SCHOLAR-1 when available.

Results and conclusion

In the MAIC, the odds ratios (OR) identified, demonstrated superiority of glofitamab over chemotherapy +/- R. The CR rates were [redacted] and 7% (95% CI: 3-15) in NP30179 and SCHOLAR-1, respectively. In the unadjusted base-case model, the OR was [redacted] and in the adjusted model OR was [redacted]. The ORR was [redacted] and 26% (95% CI: 21-31) in NP30179 and SHCOLAR-1, respectively. The unadjusted base-case model found an OR of [redacted] and in the adjusted model the OR was [redacted] Likewise for OS, the hazard ratio (HR) was in favour of glofitamab. In NP30179, the median time to death was [redacted] while in SCHOLAR-1 the median OS was 6.3 months (95% CI: 5.9-7.9). The unadjusted base-case model found a HR of [redacted] and in the adjusted model it was [redacted] The results generated from the MAIC were therefore consistently in favor of glofitamab. It is, however, important to interpret these results in the context of the limitations associated with the analyses.

An important endpoint in NP30179 is duration of complete response (DOCR). However, DOCR was not estimable in the ITT population at the June 2022 CCOD, but was reported from a supporting cohort in which patients were enrolled into the study at an earlier stage than the ITT. From this cohort, the DOCR event-free rate after 24 months was [redacted]). Knowing that lasting remissions for at least two years has shown to be a good indicator for favorable long term prognosis (18), these results are very significant.

As mentioned, narrative comparisons were performed for PFS, HRQoL of safety. In NP30179 the median INV-assessed PFS was [redacted] This was compared to the PFS reported in MDACC where the median PFS was lower, 2.8 months (95% CI: 2.4-3.3). In CORAL, only the three-year PFS was reported which was 37% (95% CI: 31%-42%). Regarding HRQoL, the reported scores in NP30179 were compared to LY.12. Whereas HRQoL was stable in NP30179, patients in LY.12 reported more fluctuations over time. Furthermore, while most median scores were very close to the baseline assessment throughout the assessment in NP30179, mean scores in LY.12 were all below the baseline assessment. However, the tool used for HRQoL assessment differed between the studies which makes it difficult to properly compare the data. To address the safety of glofitamab, the safety data was

compared to the safety data reported in the CORAL study and in the LY.12 study. The proportion of patients experiencing grade 3-4 AEs was comparable across the safety populations in NP30179 and LY.12. In CORAL, the total proportion of patients experiencing grade 3-4 AEs was not reported. The most commonly reported grade 3-4 AE in the NP30179 study were neutropenia, anaemia, thrombocytopenia and hypophosphatemia and were therefore mainly related to the immune system and the blood and lymphatic system. On the other hand, serious infections seemed to be the most commonly reported grade 3-4 AE in the CORAL study, and also the most commonly reported SAE in the LY.12 study. CRS was the most commonly reported AE of any grade in NP30179, however, only [redacted] of the safety-evaluable population experienced CRS grade 3-4. Most CRS were reported during the first glofitamab treatment cycle, and of the grade ≥2 CRS, these were resolve in most cases. The CRS AEs were therefore manageable and predictable. The differences in baseline characteristics between study populations, which have not been adjusted for in the narrative comparison, may impact the data. These limitations should be considered when interpreting the conclusions.

Conclusively, the MAIC results were consistently in favour of glofitamab, which combined with the high event-free rate at 24 months, highlights the durability of glofitamab. The safety profile of glofitamab is also well tolerated, and with few CRS grade 3-4. Therefore, based on the clinical efficacy and safety, glofitamab seems to be offering a superior treatment option for 3L DLBCL patients.

The health economic analysis

Methods

A cost-effectiveness model was developed in Microsoft Excel® to assess the cost-effectiveness of glofitamab vs. R-chemotherapy R-DHAP and R-ICE for patients with R/R DLBCL as a 3L treatment option. A partitioned survival model approach was used and informed by data from the most recent CCOD of June 2022 of the NP30179 trial and by the indirect treatment comparison of glofitamab vs. chemotherapy +/- R presented in section 7.3.

As per the 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 when relevant.

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. Scenario analyses were also conducted.

Results and conclusion

In the base case analysis, glofitamab resulted in QALYs gained in comparison to R-chemotherapy. Costs associated with glofitamab were higher compared to R-chemotherapy for the health state PFS. This was explained by the higher proportion of patients remaining in the PFS health state in the glofitamab arm vs. the R-chemotherapy arm, underlining the new intervention's effectiveness compared to current standard treatment in Denmark. Additionally, glofitamab is likewise associated with higher cost in the PPD state due to the longer survival compared to R-chemotherapy .

At the AIP level, the base-case analysis showed an incremental cost of 430,986 DKK and a gain of 2.92 QALYs, resulting in an incremental cost-effectiveness ratio (ICER) of 147,511 DKK per QALY gained. Based on a projected uptake of 100% of patients in 3L DLBCL the annual budget impact, in case of a positive recommendation of glofitamab, the first five years is estimated to be: *Year 1)* [redacted], *Year 2)* [redacted], *Year 3)* [redacted], *Year 4)* [redacted], and *Year 5)* [redacted].

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

5.1 The medical condition and patient population

5.1.1 Overview of the disease condition

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid malignancy in adults. It belongs to the Non-Hodgkin's lymphoma (NHL) group of disease, where the annual incidence of NHL in Europe and in the US is 15-20 cases/100.000. DLBCL accounts for approximately 35% of NHL cases, equivalent to 500 new cases per year in Denmark (7). The incidence increases with age with the median age at diagnosis being 67 years (10). DLBCL can also occur in younger patients, including young adults and children (19), however, elderly patients have poorer prognosis and inferior outcomes compared to younger patients (20). DLBCL is a heterogeneous malignancy with an aggressive phenotype, but potentially curable. Without treatment, DLBCL patients have an estimated life expectancy of less than one year (8). With treatment, 60-65% of patients are cured, however, patients who fail frontline therapy, have poor outcomes (5, 7).

DLBCLs are defined as a heterogeneous group of malignancies composed of large cells with nuclei at least twice the size of a small lymphocyte. They more often occur de novo but can also represent the progression or transformation of a less aggressive B-cell neoplasm, such as follicular lymphoma. Morphologically, DLBCLs usually consist of a neoplasm of large B-lymphoid that grow diffusely, partly or completely effacing the normal structure of the involved organ (8). Based on morphological, immuno-phenotypical and genetic features, DLBCL comprises distinct subtypes according to previous WHO Classification of lymphoid neoplasm (21).

5.1.1.1 Clinical signs and symptoms

DLBCL is marked by rapidly growing tumors in the lymph nodes, spleen, liver, bone marrow or other organs. As such, patients with DLBCL typically present with rapidly enlarging masses at nodal or extranodal sites; this results in damage to the involved and surrounding tissues and organs and requires immediate treatment. The swollen nodes can form large lumps, known as bulky disease (4). The majority of cases (60%) originate in the lymph nodes, with the remaining (40%) presenting at extranodal sites (22). The most common extranodal sites are the gastrointestinal tract, head and neck, and skin and soft tissue. Bone marrow is involved in 10–30% of cases (23).

Primary disease symptoms include enlarged lymph nodes, night sweats, unusual weight loss, loss of appetite, extreme tiredness or fatigue, fever and extreme itchiness (8, 10) which can often lead to impairment in aspects of health-related quality of life (HRQoL), including physical functioning and fatigue (24).

Relapsed DLBCL is characterized by the appearance of any new lesion after a complete response to treatment along with the return of symptoms (enlarged lymph nodes, night sweats, unexplained fever and unintentional weight loss), while refractory DLBCL is characterized by progressive disease or no response from the start of previous treatment (25).

5.1.1.2 Burden of disease

DLBCL tends to be a fast-growing (aggressive) lymphoma, but it often responds well to front-line therapy. First-line (1L) standard of care, rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone (R-CHOP) aims to be curative, however, about 3 to 4 out of 10 patients relapse or are refractory to treatment (5-7). The relapse/refractory (R/R)- group of patients have dismal outcome, and is therefore a major cause of morbidity and mortality for patients with DLBCL (8). Most relapses occur within the first 12-18 months, and second line treatment including platinum-based chemotherapy and autologous stem-cell transplantations, results in long-term survival in only a minority of patients (15, 26). In the SCHOLAR-1 study, a multicohort retrospective study of outcomes in patients with

refractory DLBCL patients, the median OS for the full population (measured from the start of salvage therapy), was 6.3 months (95% CI 5.9-7.0), and 6.1 months (95% CI 5.2-7.0) for patients who were refractory to second-line or later line therapy (6). Similarly, OS is poor in Danish R/R DLBCL patients who have received two or more prior lines of therapy. In a Danish real-world study, the median OS was reported to be 6 months (95% CI 5-9) (9). Thus, the clinical efficacy of platinum-based chemotherapy offered to R/R DLBCL patients, remains limited.

The clinical course of DLBCL can be debilitating due to constitutional symptoms, local symptoms of lymphadenopathy and bone marrow failure that may lead to infections, anemia, thrombocytopenia, organ failure, and death. Patients with disease progression also experience increased risk of side effects of treatments (27). As a consequence, salvage therapy for R/R DLBCL is limited by a patient's ability to tolerate the therapy. Patients treated with a greater number of cycles of chemotherapy reported increased symptoms (pain, neuropathy and dyspnoea) compared with patients treated with a lower number of cycles (28). All together, the disease symptoms, along with the treatment-related side effects, often lead to impairments in aspects of HRQoL (29, 30). Taking the poor outcome, both in terms of clinical efficacy and side effects, of R/R DLBCL patients into account, there is a need for new and improved treatment options.

5.1.2 Diagnosis and staging

DLBCL is diagnosed through surgical biopsy, usually of an involved lymph node or extranodal site. Histological evaluation is performed in accordance with the WHO classification of lymphoid neoplasms, which categorizes lymphomas on the basis of cytology, immunophenotype, and genetic and clinical features (21). A morphological diagnosis of DLBCL should be confirmed by immunohistochemistry or flow cytometry. If there is a low level of confidence in the diagnosis, for example owing to a small biopsy specimen or if the putatively neoplastic population has a normal phenotype by immunohistochemistry, demonstration of B-cell monoclonality by polymerase chain reaction-based methods should be considered (23) . For patients presenting with DLBCL, the extent of the disease is evaluated by staging, which is crucial to determine the best front line 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. At the time of diagnosis, 70% of patients present with advanced-stage disease (Ann Arbor Stage III or IV) (5). The gold standard for staging DLBCL patients is a PET-CT scan (8, 23). The stages and definition are shown in Table 1.

In patients who are considered to have relapsed based on imaging studies, the diagnosis should be confirmed by biopsy before proceeding to second-line therapy. In these circumstances, a needle-core biopsy is used. Additionally, relapsed patients should have the same examinations as at first diagnosis (23).

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 DLBCL 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 (8, 23):

- 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 (low to high risk groups). 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). The aaIPI is used in the Danish clinical guideline in combination with staging, maximum bulk of disease, age and comorbidity to determine treatment regime (31). In R/R DLBCL patients, IPI is also determined, however, it does not impact choice of treatment. Nevertheless, it is still a valid form of prognosis. Similar to front line DLBCL patients, R/R DLBCL patients with lower IPI, have much better outcome. As reported in SCHOLAR, median OS in low risk IPI groups (0-1 points) was 9.6 months (95% CI, 7.4-16.6) as compared to 3.8 months (95% CI, 2.9-5.0) for the high-intermediate to high-risk IPI groups (≥3 points) (6).

In addition to IPI, DLBCL has a range of molecular prognostic and risk factors. Based on gene expression profiling, two distinct molecular subtypes of DLBCL, the germinal center B-cell–like (GCB) subtype and the activated B-cell–like (ABC) subtype, are believed to arise from different stages of lymphoid differentiation (cell of origin) with the ABC subtype having an inferior outcome (3-year PFS, approximately 40 to 50% vs 75% with the GCB subtype) (5). Individual biomarkers assessed by immunohistochemistry or gene expression profiling have also been identified as having prognostic significance, such as TP53 mutations, *MYC* rearrangement and *BCL2* and *BCL6*. Double-hit lymphomas, with dual translocations involving both *MYC* and *BCL2* or *BCL6* genes, have a particularly aggressive clinical course and poor response to standard chemotherapy (32). The molecular profiling of DLBCL patients has not been standardized in the clinical practice, and does therefore not on a routine basis influence treatment choices. Despite the risks, the molecular variants confer in the course of the disease (33), IPI scores remain an important indicator of disease severity and prognosis.

5.1.4 Patient populations relevant for this application

Glofitamab as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy. The positive opinion granted by EMA's Committee for Medicinal Products for Human Use (CHMP), is based on results from the phase I/II NP30179 study which included patients with DLBCL not otherwise specified (NOS), HGBCL, transformed FL or PMBCL with an ECOG performance-status score of 0 or 1, and who had relapsed or was refractory to at least two previous lines of therapy (34).

5.1.4.1 Characteristics and Prognosis

The characteristics of the candidate patient population, has been extracted from a Danish real-world study that analyzed the outcome of 190 R/R DLBCL patients following third-line treatment from 2012 to 2019 in a population-based setting[1] (9, 35), see Appendix C for detailed patient characteristics. The median age of the 190 patients was

[1] The preliminary data was presented at ASH 2022, but the main results are still on file (manuscript in preparation).

71 years (range 20-90) at the time of third or higher line (3L+) therapy (96.3% of patients were 3L). Median time since last treatment was 5.8 months (range 0.5-61) and 76.3% patients were classified as refractory. Most patients had advanced stage disease (64.7%), extranodal involvement (60.5%) and/or elevated LDH (56.8%). 28.9% had ECOG score ≥2, 21.6% had an IPI score ≥4 and 16.8% of patients had CNS involvement. All patients were previously treated with rituximab and anthracycline based therapy (CHOP/CHOEP) in either first or second line. As second line treatment, approximately 70 % had received different combinations of chemotherapy, and of all second line patients, approximately 17% had received autologous stem cell transplantation (ASCT). When patients are considered for third line treatment in the clinic today, they are therefore heavily pretreated with chemotherapy.

The third line treatment that all patients had received in the population-based setting, naturally resembled the Danish clinical practice where no current specific standard treatment exists. Overall, the treatment regimens were in line with Danish clinical guidelines (10), and were: best supportive care; different salvage chemo combination; radiotherapy or treatment in clinical study protocols. The salvage chemo combinations will be described in more detail in section 5.2. The median OS in all 3L+ patients from the study was 6 months (95% CI 5-9), and the 2-year OS and PFS were 26% (95% CI 19-33) and 13% (95% CI 7-18) respectively (9). These poor outcomes of the 3L+ patient group reflect the need for better treatment options.

5.1.4.2 Incidence and prevalence

In the annual national report from the Danish Lymphoma Group (DLG) and the Danish Lymphoma Database (LYFO) from 2021, an average of 500 DLBCL patients are reported to be diagnosed every year in Denmark (7). Based on thorough discussions with clinical experts (36) and their knowledge of the data in the LYFO database, it is estimated that 6-10% of DLBCL patients reach third line. However, only approximately 2 out of 3 of these patients receive treatment due to their refractory and fitness status, Figure 1.

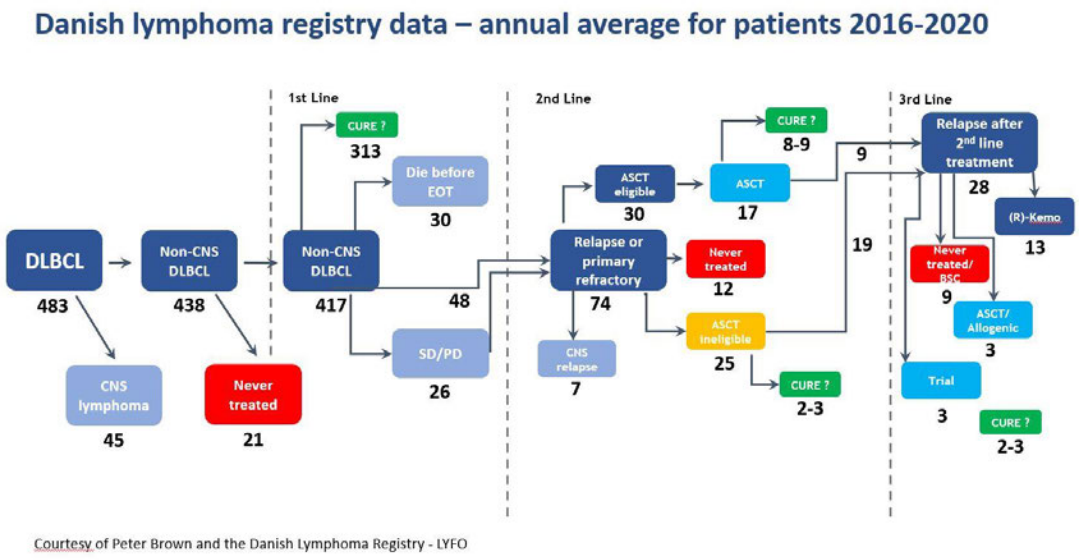


Figure 1: DLBCL patient flow. Patient numbers and type of treatment has been extracted from the Danish Lymphoma Registry (LYFO). The illustration is courtesy of Peter Brown, clinical expert.

The yearly increase in incidence for lymphomas has been approximately 2-3% during the last couple of decades, and this increase has primarily been driven by DLBCL. Though the exact cause is unknown, it is notifiable, however, that the median age of patients diagnosed with malignant lymphomas has increased over the last four years from 69 to 72, suggesting that the increased life expectancy in the population in general, contributes to the increase in incidence (7). The incidence and prevalence in the past 5 years is presented in Table 2.

Table 2: Incidence and prevalence in the past 5 years

Year	2017	2018	2019	2020	2021
Incidence in Denmark 1L[1]	425	460	501	473	516
Incidence in Denmark 3L[2]	26	28	31	28	31
Prevalence in Denmark 1L	-	-	-	4068[3]	-

[1]Incidence in 2017 has been extracted from the 2020 national LYFO report (37), and incidence in 2018-2021 is from the 2021 national LYFO report (7). [2]According to clinical experts (36), 6-10% of DLBCL patients reach third line therapy. Incidence is here reported as the 6% of the yearly incidence in 1L. [3]Data for 2020 is extracted by a clinical expert from the LYFO database. The prevalence is unknown for 2016-2019.

5.1.4.3 Number of patients

The 3L+ DLBCL population is a very heterogeneous group of patients who have received a range of different prior therapies (9), and Figure 2. There is not a distinct subgroup among the 3L+ patients who will be candidates for glofitamab, rather it will always be an evaluation of the individual patient, reviewing parameters such as time since last treatment line, performance status, and refractoriness to chemotherapy. Consequently, based on expert opinions and data from the LYFO database (36), approximately 20 patients per year will be candidates to glofitamab, Figure 1. A subset of all 3L+ patients will continue to go into clinical trials, receive chemo combinations, or best supportive care. The estimated number of patients eligible for treatment with glofitamab from 2023 to 2027 is outlined in Table 3. The yearly increase in incidence has been incorporated into the numbers.

Table 3: Estimated number of patients eligible for glofitamab treatment

Year	[2023]	[2024]	[2025]	[2026]	[2027]
Number of patients in Denmark who are expected to use the pharmaceutical in the coming years	20	21	21	22	22

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

According to the Danish clinical guidelines for DLBCL, updated 2021 (10), there is no evidence to support one superior treatment for 3L+ R/R DLBCL patients. Treatment will rarely be curative, and choice of treatment should balance effect and side effects. The majority of patients will suffer from comorbidities and for these patients, intensive chemo regimens should be excluded. In addition, most 3L+ patients will be refractory to prior lines of therapy, which in the majority of cases have been a chemo regimen, suggesting that patients will most likely not respond to additional chemo therapy (9). If the patients are still chemo-sensitive, allogenic stem cell transplantations (SCT) can be considered. The guidelines recommend to enroll patients in clinical trials if such are available. If the patients are not candidates for allogenic stem cell treatment nor clinical trial protocols, the following treatments can be considered: R + chemo (GDP (gemcitabine, dexamethasone, cisplatin); CEOP (cyclophosphamide, epirubicin, Oncovin/vincristine, prednisone); CVP (cyclophosphamide, vincristine, prednisone) or GemOx (gemcitabine, oxaliplatin)); monotherapy with gemcitabin, pixantrone, bendamustin; or CCVP with or without rituximab.

According to the Danish real-world study previously described, the most prevalent regimens in 3L+ were best supportive care (BSC) (19.5%) and platinum-based salvage chemotherapy (ICE/DHAP/GDP, for descriptions see section 5.2.3) (13.7%). From the registry study, 22% received other types of chemotherapy (GemOX, CCVP, PREBEen

(pixantrone, rituximab, etoposide, bendamustine), bendamustine etc.), 13.2% received treatment in clinical trials and 31.6% were categorized as "other". The "other" category included ibrutinib or lendalidomide alone or in combination with chemotherapy, CNS directed chemotherapy and rituximab monotherapy. Of all treatments given in 3L+ in the registry study, 42% were in combination with rituximab, 3.7% was consolidated with allogenic SCT and 4.7% with ASCT (9). Thus, the data from the real world setting reflects, as suggested by the Danish clinical guidelines, that there is no single superior treatment for 3L+ R/R DLBCL patients. Treatment choice will, as mentioned in section 5.1.4.3, always be an evaluation of the individual patient where parameters such as performance status, comorbidities and refractoriness to chemotherapy are determining factors, and often BSC will be the only option, Figure 1.

Figure 2: Sankey p .

5.2.2 Choice of comparator(s)

As described in paragraph 5.2.1, there is no standard treatment for R/R DLBCL patients who have received two or more prior lines of therapy. Therefore, the combination therapies suggested in the Danish clinical guidelines (10) and the previous assessment of Axicabtagene Ciloleucel (Yescarta) in R/R DLBCL by the DMC (38) have been consolidated with the Danish real-world study (9). On the basis of that, it was found that ICE/DHAP/GDP +/- R were the most relevant comparators.

5.2.3 Description of the comparator(s)

The chemo regimens ICE, DHAP and GDP are most often given in combination with rituximab. In this section, rituximab will be described separately followed by a description of the chemo regimens.

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 CD20 antigen on B-lymphocytes has also been demonstrated to induce cell death via apoptosis (39).

Rituximab is a solution for intravenous (IV) 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 IV 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. Rituximab is supplied at 100 mg or 500 mg concentrates for solution for infusion (40).

5.2.3.2 ICE

The ICE combination treatment is administered over three days every three weeks at a maximum of 3-4 treatment cycles. ICE consists of Ifosfamide (I), Carboplatin (C) and Etopside (E).

Ifosfamide (L01AA06)
Ifosfamide is an alkylating agent of the nitrogen mustard type. Ifosfamide induces cell death by inhibiting the cell cycle. The activate metabolites of ifosfamide, phosphoramide mustard derivatives and acrolein, cause cell damage by cross-linking to strands of DNA which leads to apoptosis, and they upregulate reactive oxygen species (ROS) which causes DNA damage and ultimately inhibition of protein synthesis (41).

Ifosfamide is administered IV on day 2 over a course of 22 hours at a total concentration of 5000 mg/m^2 of body surface area (see Appendix K).

Carboplatin (L01XA02)
Carboplatin is a platinum complex and alkylating agent similar to cisplatin. It interferes with DNA and thereby it affects the cell cycle which ultimately leads to cell death (41).

Carboplatin is a concentrate for infusion, and is administered IV. on day 2 over a course of 1 hour infusion. The recommended dosage is 5 x (GFR+25) mg where GFR is calculated from the Cockcroft-Gault formula which takes age, sex, weight and creatinine levels into account. The dose cannot exceed a total of 600mg (see Appendix K).

Etoposide (L01CB01)
Etopside belongs to the class of chemotherapy drugs called plant alkaloids. Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA. This complex induces breaks in double stranded DNA and prevents repair by topoisomerase II binding. This ultimately leads to cell death (41).

Etopside is a concentrate for infusion, and it is administered IV at 100mg/m^2 of body surface area per day on day1 through day3 over a course of 1 hour (see Appendix K).

5.2.3.3 DHAP

The DHAP combination treatment consists of Dexamethasone (D), high dosis Arabin/Cytarabin (HA) and Cisplatin (P). It is administered over four days every three weeks, at a maximum of 3-4 treatment cycles.

Dexamethasone (H02AB02)
Dexamethasone is a corticosteroid that halts cancer cell growth (42).
It is administered orally at 40 mg per day on day1 through day4 (see Appendix K).

Cytarabine (Ara-C) (L01BC01)
Cytarabine is a pyrimidine nucleoside analog that incorporates into DNA and thereby inhibits the synthesis of DNA. This ultimately leads to cell death. The mechanism of action is similar to that of gemcitabine (41).

Cytarabine is administered IV at day2 and day3 over a course of three hours. The total concentration combining the two doses is 4000mg/m^2 of body surface area (see Appendix K).

Cisplatin (L01XA01)
Cisplatin is a platinum-based chemotherapy. It is an alkylating agent that cross-links to DNA, which causes DNA damage and ultimately cell death (41).

Cisplatin is administered IV on day 1 over a course of 24 hours. The total concentration is 100mg/m^2 of body surface area (see Appendix K).

5.2.3.4 GDP

GDP is a combination treatment consisting of Gemcitabine (G), Dexamethasone (D), Cisplatin/Platinol (P). The GDP combination treatment is given over eight days every three weeks, at a maximum of six treatment cycles.

For dexamethasone and cisplatin mode of action descriptions, please refer to the DHAP combination treatment above.

Gemcitabine (L01BC05)
Gemcitabine is a nucleoside (cytidine) analog that incorporates into DNA and thereby inhibits the synthesis of DNA. This ultimately leads to cell death. The mechanism of action is similar to that of cytarabine (41).

Gemcitabine is administered IV at 1000mg/m^2 of body surface area per day on day1 and day8 over a course of 30 minutes (see Appendix K).

Dexamethasone (H02AB02)
Dexamethasone is administered orally at 40mg on day1-4 (see Appendix K).

Cisplatin (L01XA01)
Cisplatin is administered IV on day1 at 75mg/m^2 of body surface area (see Appendix K).

5.3 The intervention (glofitamab)

Glofitamab (RO7082859) is a novel T-cell–engaging, bispecific, full-length monoclonal antibody that has a novel 2:1 configuration which enables bivalent binding to CD20 on B cells and monovalent binding to CD3 on T cells. The simultaneous binding to CD20 on the B cell and CD3 on the T cell, mediates the formation of a synapse with subsequent T-cell activation and proliferation, secretion of cytokines and release of cytolytic proteins that results in the lysis of CD20-expressing B cells (1, 3). Glofitamab has been studied in the phase I/II NP30179 study, where glofitamab given as a fixed course showed early and long-lasting complete responses in people with heavily pre-treated or refractory DLBCL. This led to the recent positive opinion granted by EMA's CHMP.

Testing of CD20 expression levels is not required before treatment with glofitamab. This was, however, a concern raised by EMA. Specifically they were questioning whether previous anti-CD20 treatment would negatively impact the efficacy of glofitamab, and whether levels of CD20 expression correlates with efficacy of glofitamab. These concerns have been addressed thoroughly by Roche in the Rapporteurs Day 195 Joint Assessment Report (JAR) (*data on*

file). The overall conclusions were that CD20 is expressed in most patients with R/R DLBCL (2 out of 69 patients (2.9%) were negative for CD20 expression), and in the additional data provided in the JAR, there was no linear correlation between CD20 expression and response to glofitamab. As a result of the additional data provided by Roche, the EMA indication is not biomarker-restricted.

5.3.1 Posology

In the following section, administration of glofitamab is described based on information from the summary of product characteristics (SmPC) which is currently confidential and on file.

Pre-treatment with obinutuzumab:
All patients in study NP30179 received a single dose of 1000 mg obinutuzumab as pre-treatment on Cycle 1 Day 1 (7 days prior to initiation of glofitamab treatment) to lower the circulating lymphoid B cells (see Table 4). Obinutuzumab was administered as an IV infusion at 50 mg/h. The rate of infusion was escalated in 50 mg/h increments every 30 minutes to a maximum of 400 mg/h.

Glofitamab is given as an IV infusion in 12 cycles. Glofitamab dosing begins with a step-up dosing schedule which is designed to decrease the risk of cytokine release syndrome (CRS). Glofitamab must be administered as an IV infusion according to the dose step-up schedule leading to the recommended dose of 30 mg as shown in Table 4. In the first cycle of treatment, 2.5 mg of glofitamab is administered on Day 8, and 15 mg on Day 15. In the remaining cycles, glofitamab is given at 30 mg on Day 1 of cycle two to 12. Each cycle is 21 days. Treatment with glofitamab is recommended for a maximum of 12 cycles or until disease progression or unmanageable toxicity.

At least 1 dose of tocilizumab for use in the event of CRS must be available prior to Columvi infusion at Cycles 1 and 2. Access to an additional dose of tocilizumab within 8 hours of use of the previous tocilizumab dose must be ensured.

Table 4: Glofitamab monotherapy dose step-up schedule for patients with R/R DLBCL.

Treatment cycle, Day		Dose of glofitamab	Duration of infusion
Cycle 1 (Pre-treatment and step-up dose)	Day 1	Pre-treatment with obinutuzumab	
	Day 8	2.5 mg	4 hours[1]
	Day 15	10 mg	
Cycle 2	Day 1	30 mg	
Cycle 3 to 12	Day 1	30 mg	2 hours

[1] For patients who experience CRS with their previous dose of glofitamab, the duration of infusion may be extended up to 8 hours.

5.3.2 Premedication and prophylaxis

Glofitamab should be administered to well-hydrated patients. Recommended premedication for CRS is outlined in Table 5.

Table 5: Premedication before glofitamab infusion.

Treatment cycle (Day)	Patients requiring premedication	Premedication	Administration
Cycle 1 (Day 8, Day 15); **Cycle 2 (Day 1);** **Cycle 3 (Day 1)**	All patients	Intravenous glucocorticoid[1]	Completed at least 1 hour prior to Columvi infusion

		Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
All subsequent infusions	All patients	Oral analgesic / anti-pyretic[2]	At least 30 minutes before Columvi infusion
		Anti-histamine[3]	
	Patients who experienced CRS with the previous dose	Intravenous glucocorticoid[1, 4]	Completed at least 1 hour prior to Columvi infusion

[1]20 mg dexamethasone or 100 mg prednisone/prednisolone or 80 mg methylprednisolone. [2]For example, 1000 mg paracetamol. [3]For example, 50 mg diphenhydramine. [4]To be administered in addition to the premedication required for all patients.

5.3.3 Patient monitoring

All patients must be monitored for signs and symptoms of potential CRS during infusion and for at least 10 hours after completion of the infusion of the first glofitamab dose (2.5 mg on Cycle 1 Day 8). Patients who experienced Grade ≥ 2 CRS with their previous infusion should be monitored after completion of the infusion.

6. Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

In order to assess the clinical evidence available for treatment of adult patients with R/R DLBCL after two or more lines of systemic therapy, and assess the feasibility of conducting indirect treatment comparisons (ITCs) of glofitamab with relevant treatment regimens used in Danish clinical practice - a systematic literature review (SLR) was conducted.

The Medicines Council methods guide for assessing new pharmaceuticals, version 1.2, has provided guidance for the literature search. The search for peer-reviewed published full-text articles has been set up using the search strings provided in Appendix A. Since it was suspected that limited evidence would be available for the comparator of interest (chemotherapy +/- R), there was a need to broaden the scope of the review so that the population included DLBCL as a whole. Also, no restrictions were applied in terms of treatment line. In addition, no strict restrictions were applied to the study design, which included interventional and observational studies (see search strategy, Appendix A). Electronic searches were carried out in MEDLINE (via PubMed) and in CENTRAL (via Cochrane Library) on March 12, 2023. The searches contain terms descriptive of the area as outlined in the search strings. The Search Builder for each search is available in Appendix A.

In total 113 and 69 references were identified in MEDLINE and CENTRAL, respectively. Two reviewers independently screened the references by title and abstract and full-text according to the defined in- and exclusion criteria (Appendix A) using a reference management tool. Of the 182 references, 29 were included for full-text review. Following full-text review, 7 references were deemed relevant for the ITC feasibility assessment. For an overview of the selection of studies, please refer to the Prisma diagram in Appendix A. A list of the 22 studies that were excluded after full-text review, as well as the reason for exclusion, is also shown in Appendix A. A well-known publication previously accepted as a comparator study (SCHOLAR-01) in assessments of new medicines for indications similar to the EMA-approved indication for glofitamab (refer to section 7.1.2) was missing from the electronic searches. Therefore, the electronic searches were supplemented by this publication, which was then included in the feasibility assessment:

- Crump, M., et al., Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood, 2017. **130**(16): p. 1800-1808.

The SCHOLAR-1 international, multicohort, retrospective research study SCHOLAR-1, has been identified previously by international HTA assessments for the same indication (43-46). Please refer to section 7.1.2 for more details.

6.2 List of relevant studies

A total of 8 references from 8 studies were found to be eligible for inclusion – 7 references following full text review and 1 hand-searched reference (see Appendix A).

These 8 studies were assessed to identify those most appropriate for inclusion in an ITC, in this case a matching-adjusted indirect comparison (MAIC) has been used (refer to section 7.3.1 for definition of MAIC). The feasibility assessment was performed based on a list of criteria that was defined from internal medical and clinical scientific feedback, to limit the risk of introducing bias in the comparisons. The list of criteria can be found in Appendix A.

Following the feasibility assessment of the 8 studies for a MAIC, (Appendix A), only one reference was found relevant for comparison to NP30179; the SCHOLAR-1 study performed by Crump et al., Table 6. SCHOLAR-1 represents one of the largest patient-level pooled analyses to characterize outcomes for a population of patients with refractory DLBCL after chemotherapy treatment (for more details of the study, refer to section 7.1.2). SCHOLAR-1 met the listed criteria referred to above, and was chosen as the comparator study. A total of 8 baseline characteristics of interest were reported for the pooled population (n=636), with a follow-up of what appeared to be 180 months based on the OS Kaplan-Meier (KM) curve. Therefore, a MAIC could be performed using the SCHOLAR-1 study.

For the NP30179 study, the publications identified will not be used, since data from a more recent data cut was available in an internal interim clinical study report (17), which therefore forms the basis of this application.

An overview of the included studies in SCHOLAR-1, is presented in Appendix A, and more detailed information about the study characteristics of the included clinical studies can be found in Appendix B.

Table 6: Overview of the included references in assessment of glofitamab

Reference	Study NCT	Patient population	Intervention and comparator (sample size (n))	Primary and secondary outcome and follow-up period
Study NP30179, A Multicenter, Open-Label, Phase I/II Study to Evaluate the Safety, Efficacy, Tolerability and Pharmacokinetics of Escalating Doses of Glofitamab in Patients with Relapsed/ Refractory B-Cell Non-Hodgkin's Lymphoma (17, 34) Additional references from previous CCOD (1-3):	NP30179 NCT03075696	Adult patients with R/R DLBCL, after two or more lines of systemic therapy	Glofitamab N=155	Primary: - CR (IRC assessed) Key Secondary: - INV-assessed CR - IRC-assessed and INV-assessed ORR - DOCR - PFS - OS - HRQoL - Safety

Crump, M., et al., Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood, 2017. **130**(16): p. 1800-1808 (6)	SCHOLAR-1 (multicohort retrospective)	Adult patients with refractory DLBCL (including the subtypes PMBCL and trFL)	Chemotherapy N=636	- CR - PR - ORR - OS

Abbreviations: clinical cut-off dates – CCOD; complete response - CR; diffuse large B-cell lymphoma – DLBCL; duration of complete response – DOCR; Health Related Quality of Life – HRQoL; investigator – INV; independent review committee - IRC; overall response rate – ORR; overall survival - OS; partial response – PR; progression-free survival – PFS; relapse/refractory – R/R; transformed follicular lymphoma - trFL

Please note that the Danish real-world study (9) referred to in section 5, did not come up in the SLR since it is a manuscript in preparation. However, a MAIC feasibility assessment was still conducted, but due to missing baseline characteristics, it did not qualify for a MAIC. The reasons were as follows: patient number was too low for the group with the relevant comparator (DHAP/ICE/GDP); missing values for ECOG-PS and histologic subtype and no information on refractoriness to first line treatment.

One of the CORAL extension studies (47) came up in the SLR, and was included in the MAIC feasibility assessment. Due to the prior usage of both the CORAL extension studies (47, 48) in the assessment of Yescarta by the Medicine Council (38), both of the studies were assessed for their MAIC feasibility. Again, these studies were discarded due to a lack of relevant baseline characteristics.

7. Efficacy and safety of glofitamab compared to chemotherapy for treatment of patients with R/R DLBCL, who have received a minimum of two prior lines of therapy

7.1 Relevant studies

In the following section, a brief description of each study included in this application is provided together with any relevant differences between the studies in terms of study and patient characteristics. 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 NP30179

NP30179 is a phase I/II, multicenter, open-label study evaluating the safety, efficacy, tolerability and pharmacokinetics of escalating doses of glofitamab as a single agent after a fixed, single-dose pre-treatment of obinutuzumab in patients with R/R NHL.

The primary endpoint of NP30179 is complete response (CR) rate as assessed by an independent review committee (IRC). Key secondary endpoints include investigator (INV)-assessed CR, IRC-assessed and INV-assessed overall response rate (ORR), duration of CR (DOCR), progression-free survival (PFS), overall survival (OS), patient reported outcome (PRO), that is HRQoL and safety.

NP30179 is divided into three parts: single and multiple-patient dose escalation cohorts (parts I and II, respectively) and dose expansion cohorts (part III) (Figure 3).

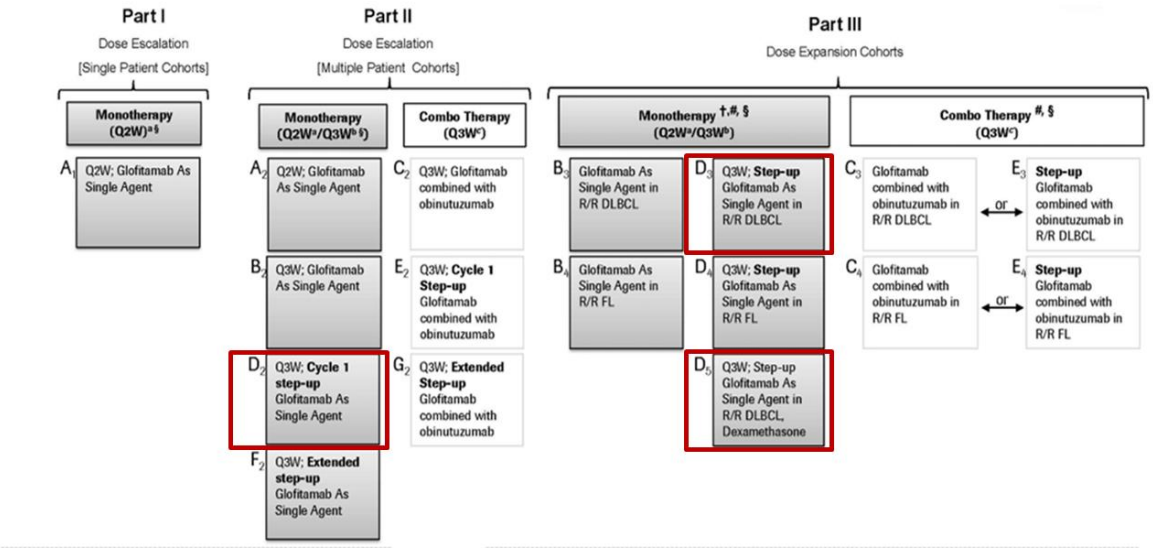


Figure 3: NP30179 Study Design with relevant cohorts marked in red.
Abbreviations: DLBCL - diffuse large B-cell lymphoma; FL - follicular lymphoma; IMC - internal monitoring committee; R/R, relapsed or refractory.

†Patients in part III dose-expansion monotherapy cohorts may receive glofitamab on a every 2 weeks dosing schedule with fixed dosing or every 3 weeks with step-up dosing (cycle 1 step-up or extended step-up), if supported by emerging data and/or recommended by the internal monitoring committee. #Based on determined maximum tolerated dose/optimal biological dose, both or one expansion cohort may be selected for monotherapy B_3 and/or D_3, B_4 and/or D_4, while C_3 or E_3 and C_4 or E_4 may be selected. §Mandatory paired fresh baseline (7 days in advance of the first dose of glofitamab) and on-treatment tumor biopsies (day 9 of cycle 1) are collected in a subset of patients.

This application only reports data on R/R DLBCL patients (DLBCL not otherwise specified (NOS), high-grade B-cell lymphoma (HGBCL), primary mediastinal B-cell lymphoma (PMBCL), and transformed follicular lymphoma (trFL)) with a minimum of two prior lines of systemic therapy (cohort $D_2(sub_2)$, D_3 and D_5 marked in red in Figure 3). To be enrolled in the R/R DLBCL cohorts in NP30179, patients must have relapsed after or failed to respond to at least two prior systemic treatment regimens including at least one prior regimen containing anthracycline, and at least one containing an anti CD20-directed therapy. All patients with current or past history of central nervous system lymphoma were excluded.

The intent to treat (ITT) population includes a total of 155 R/R DLBCL and consists of: 7 patients treated at the recommended phase II dose in the dose-escalation part of the study (cohort $D_2(sub_2)$ marked in red in Figure 3); 108 patients from the pivotal dose-expansion cohort (cohort D_3 marked in red in Figure 3); and 40 patients from the dose-expansion part who were pretreated with mandatory dexamethasone (cohort D_5 marked in red in Figure 3) as compared to investigator's choice of pretreatment with either methylprednisolone, prednisone, or dexamethasone. All 155 patients in the ITT population were enrolled to receive glofitamab monotherapy at the recommended phase II dose (step-up doses 2.5 mg on day 8 of cycle 1 and 10 mg on day 15 of cycle 1, followed by 30 mg on day 1 of cycle 2 through 12 cycles with one cycle lasting 21 days) after pre-treatment of 1000 mg obinutuzumab (Figure 4) and had minimum of 6 months follow up for response.

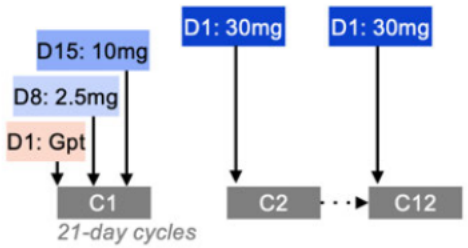


Figure 4: Dosing Schedule for the fixed-duration treatment (maximum of 12 cycles) of IV administration of glofitamab in the ITT population in NP30179.
Abbreviations: Gtp – obinutuzumab pretreatment.

One patient in the pivotal dose-expansion cohort was enrolled in error and did not receive study treatment. As a consequence, the safety-evaluable population includes a total of 154 patients who all received at least one dose of any study treatment (obinutuzumab or glofitamab).

In addition, to explore long-term outcomes and provide additional evidence on the durability of CR after glofitamab treatment a supporting cohort was evaluated from the CCOD of June 15, 2022. The supporting cohort consists of a total of 101 patients who were enrolled into the study earlier than patients in the ITT population. These patients met the same inclusion and exclusion criteria as the patients in the ITT population but received glofitamab in doses of 10 mg or higher but lower than the recommended phase II dose (Figure 4). Consequently, patients in the supporting cohort may have received fixed doses of glofitamab at 10 mg, 16 mg, or 25 mg; a single step of 10 mg followed by 16 mg; or two steps of 2.5 mg and 10 mg followed by 16 mg. The treatment duration was 8 to 12 cycles in the supporting cohort.

PRO analyses were performed in patients from the part III dose-expansion cohorts (pivotal cohort and mandatory dexamethasone cohort) who had a baseline assessment and at least one post-baseline assessment before the date of progression.

Patients in the ITT population were enrolled from January 2020 through September 2021 and data for each outcome has been evaluated at three clinical cut-off dates (CCOD) as outlined in Table 7. However, the main focus of this assessment is on outcomes reported in the ITT population and the safety-evaluable population reported from the latest CCOD of June 15, 2022. These data are currently not publicly available, but are confidential from the Roche internal NP30179 clinical study report and the EMA assessment report (17, 34).

Table 7: A summary of CCODs and the reported populations

Clinical cut-off date (CCOD)	References	Efficacy analysis	Safety analysis	Included in this application
September 14, 2021	*Data on file*	Pivotal cohort (n=108*)	Pivotal cohort (n=107)	Yes
March 14, 2022	ASH, 2022, (2) Dickinson, 2022, (1)	Pivotal cohort (n=108*) ITT population (n=155*) Supporting cohort (n=101)	Pivotal cohort (n=107) Safety-evaluable population (n=154)	No**
June 15, 2022	(17, 34)	Pivotal cohort (n=108*) ITT population (n=155*) Supporting cohort (n=101)	Pivotal cohort (n=107) Safety-evaluable population (n=154)	Yes

Abbreviations: CCOD – clinical cut-off dates; ITT – Intent-to-treat; ASH – American Society of Haematology ; EMA – European Medicines Agency.
*One patient in the pivotal cohort was enrolled in error and did not receive study treatment (obinutuzumab or glofitamab). ** The publication presents data from an earlier CCOD (Marts 14, 2022), than the most recent CCOD of June 15, 2022, and thus, data from Dickinson et al. is not presented in this assessment.

7.1.2 SCHOLAR-1

SCHOLAR-1 represents one of the largest patient-level pooled analyses to characterize outcomes for a population of patients with refractory DLBCL (including PMBCL and trFL) (6). The study has previously been accepted as a comparator study in assessments of new medicines for indications similar to the EMA-approved indication for glofitamab. EMA used SCHOLAR-1 in their assessment leading to the approval of Yescarta (31) and Tisagenlecleucel-T (Kymriah) (49), and additionally, The National Institute for Health and Care Excellence (NICE) (United Kingdom) and Canada's Drug and Health Technology Agency (CADTH) used SCHOLAR-1 as comparator study in their local assessment of Yescarta (46, 43) and (Kymriah) (44), respectively. A similar approach was accepted by the Health Technology Assessment (HTA) institute in Norway when assessing Kymriah (45). SCHOLAR-1 is therefore a widely accepted study by several HTA bodies highlighting its validity as a comparator study when evaluating glofitamab against chemotherapy +/- R regimens.

SCHOLAR-1 is an international, multicohort, retrospective research study evaluating response and survival outcomes in patients with refractory DLBCL after chemotherapy treatment (6). In SCHOLAR-1 patient-level data was collected from four sources: 2 large phase 3 clinical trials (Lymphoma Academic Research Organization [LYSARC] Collaborative Trial in Relapsed Aggressive Lymphoma [CORAL] (11, 12) and Canadian Cancer Trials Group [LY.12]) (13), and 2 observational cohorts (MD Anderson Cancer Center [MDACC] (14) and University of Iowa/Mayo Clinic Lymphoma Specialized Program of Research Excellence [IA/MC]) (15, 16). The four sources will be described briefly below.

CORAL (11, 12), is a worldwide phase III multicenter randomized trial evaluating responses, survival and safety in patients with DLBCL who were in their first relapse or who were refractory after first line therapy. Patients were randomly assigned to receive either R-DHAP or R-ICE with a goal of consolidative ASCT. A total of 477 patients were enrolled in CORAL including an additional cohort enrolled at a later time point than the study start. Data presented in this application is based on a population consisting of 396 patients in the relevant study arm of CORAL.

LY.12 (13) is a randomized controlled multicenter trial which assigned 619 patients with aggressive non-Hodgkin's lymphoma whose disease was refractory or had relapsed after first line therapy. Patients were assigned to receive either R-GDP or R-DHAP as second line (2L) therapy before ASCT to evaluate responses, survival, quality of life and safety.

MDACC (14) is a retrospective observational study evaluating response and survival in 191 patients with R/R DLBCL and trFL who had relapsed or were refractory to initial R-CHOP/CHOP-like therapy, had failed salvage platinum-containing chemotherapy, and had received a second salvage therapy.

The IA/MC (15, 16) is a Midwest US observational cohort that enrolled unselected, newly diagnosed DLBCL patients treated with R- and anthracycline-based chemotherapy lymphoma to prospectively document primary and subsequent treatment and outcomes. Of the 552 patients from the MER cohort who entered into post-treatment observation, 112 (93 with DLBCL) suffered a relapse.

To be included in SCHOLAR-1, patients from each of the four studies must have had refractory DLBCL (including the subtypes PMBCL and trFL) and must have received an anti-CD20 monoclonal antibody and an anthracycline as one of their qualifying regimens. In SCHOLAR-1, refractory DLBCL was defined as progressive disease (received >4 cycles of 1L therapy), or stable disease (2 cycles of later-line therapy) as best response at any point during chemotherapy or relapse ≤12 months after ASCT. Patients in CORAL, LY.12, and IA/MC were included when meeting the refractory criteria at its first occurrence, whereas patients in MDACC were included only when meeting the refractory criteria from 2L therapy and onwards. All patients with primary central nervous system lymphoma were excluded from SCHOLAR-1. A total of 861 patient records were initially extracted from the 4 studies. However, on the basis of the refractory criteria, 636 patients (CORAL, n=170; LY.12, n=219; MDACC, n=165, and IA/MC, n=82.) were found eligible to be included in the analysis.

In SCHOLAR-1, data was reported on the endpoints CR, PR, ORR and OS in patient subgroups from each of the four studies, and in the overall population across the four studies. However, in this application only pooled outcomes in the overall population are presented. In cases where SCHOLAR-1 does not report data on relevant outcomes, data will be presented from the individual studies when available. However, it should be noted that the full populations in the original studies included patients, who did not meet the refractory criteria applied in SCHOLAR-1, and the individual populations are therefore larger than the subsets included in the SCHOLAR-1 analysis.

7.1.3 Comparability between NP30179 and SCHOLAR-1

As described in section 6.2, SCHOLAR-1 was found to be the most appropriate study for comparison for the assessment of glofitamab. There are, however, differences between SCHOLAR-1 and NP30179 including variations in inclusion/exclusion criteria as well as differences across some baseline characteristics (for a detailed overview of the baseline characteristics, refer to Appendix C).

Firstly, the population in NP30179 includes both relapse and refractory patients while SCHOLAR-1 only includes refractory patients. Therefore, SCHOLAR-1 does not consider patients who were never refractory to treatment, but whom would be relevant in the comparison to NP30179. Patients who relapsed and were non-refractory were, however, a minority in the NP30179 study (10.3%). Refractory status was also defined differently in the two studies. Patients in NP30179 did not have refractory disease according to the SCHOLAR-1 criteria (see section 7.1.2). Further, patients in NP30179 were enrolled if they had relapsed or refractory DLBCL NOS, trFL, PMBCL and HGBCL, while patients in SCHOLAR-1 were included if they had refractory DLBCL including the subtypes trFL and PMBCL. It should be noted that the disease subtype was not available for 96 patients in the CORAL study, but as per the study inclusion criteria, patients were categorized to have DLBCL. NP30179 only enrolled 3L and above patients whereas SCHOLAR-1 also enrolled patients in 2L (28%) besides 3L and above (49%). Additionally, in NP30179 there was a higher proportion of 5L and above patients (29%) compared to SCHOLAR-1 (<1%). The majority of patients in both NP30179 and SCHOLAR-1 had an ECOG PS of 0-1, 98.7% vs. 73%, respectively, though the fraction was higher in NP30179 since only a single patient with an ECOG PS of 2 was included. Disease stage were comparable with 22.6% and 27% of patients in stage I-II and 74.8% and 72% in stage III-IV in NP30179 and SCHOLAR-1, respectively. The median age was higher in NP30179 with 66 years compared to SCHOLAR-1 in which it was 55 years. The sex distribution was very similar in the two studies with 64.5% being male in NP30179 compared to 64% in SCHOLAR-1. Lastly, in terms of endpoint definitions, response endpoints were assessed according to the Lugano classification (50) in NP30179 vs. the 1999 International Working Group response criteria (51) in SCHOLAR-1.

Despite differences in the two study populations, it is, however, possible to adjust for this in the unanchored MAIC for CR, ORR and OS, in order to make the populations comparable. The above mentioned differences and limitations should, however, be taken into account when interpreting the results. The limitations will be discussed in more detail in section 7.3.2 when presenting the MAIC analysis.

As mentioned previously, in cases where there is no reported data in SCHOLAR-1 on relevant outcomes, specifically PFS, quality of life and safety, data will be presented for the individual studies when available, and applied in a narrative comparison. Therefore, the comparability between NP30179 and CORAL, LY.12 and MDACC will be outlined in brief in the following paragraphs (for a more detailed overview of baseline characteristics, refer to Appendix C). The IA/MC study has been excluded in the following, as it does not report data on relevant outcomes in regards to a narrative comparison.

In CORAL (11, 12), enrolled patients were relapsing or were refractory after only one prior line of therapy, whereas in NP30179, enrolled patients had received two or more prior lines of therapy. In CORAL, other lymphoma types different from DLBCL were also included (FL, T-cell lymphoma, and Hodgkin's lymphoma). However, only 13 patients out of the 396 were of these types. As mentioned previously, 96 patients in CORAL were categorized as DLBCL due

to lack of further information on their subtypes, and therefore their subtype specification is not known. ECOG PS was similar between the two studies, all but one patient treated with glofitamab in NP30179 had an ECOG PS of 0-1, and all patients enrolled in CORAL had an ECOG PS of 0-1 since this was an inclusion criteria in both studies. In CORAL, the patients in general had more progressive disease, since a lower proportion of patients were in stage I-II of their disease in NP30179 compared to CORAL. The median age was higher in NP30179, but sex distribution was similar between NP30179 and CORAL.

In LY.12 (13), patients were refractory or had relapsed after only one prior treatment line, compared to NP30179 where the mean number of prior treatment lines was 3.08. The histologies also differed since lymphoma types different from DLBCL (anaplastic large cell lymphoma and peripheral T-cell lymphoma) were included in the LY.12 study, where this was not the case in NP30179. The majority of patients across the two studies had an ECOG PS of 0-1. However, only a single patient with ECOG PS of 2 was enrolled in NP30179, whereas LY.12 included more than 10% with an ECOG PS of 2 or higher. The median age was higher in NP30179, but patients across NP30179 and LY.12 matched regarding disease stage and distribution of sex. In terms of endpoint definitions, quality of life was assessed using the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS) in NP30179 compared to the Functional Assessment of Cancer Therapy – General in LY.12.

In MDACC (14), patients had a lower median age as compared to patients in NP30179. No other baseline characteristics were available for patients in MDACC.

In spite of the above mentioned differences between the populations in NP30179 and CORAL, LY.12 and MDACC, the populations will be used in a narrative comparison. The above mentioned differences should, however, be taken into account when interpreting the narrative comparisons in section 7.3. Refer to appendix C for more details on the comparability between studies.

7.2 Efficacy and safety – results per study

In the following section, a summary of the key efficacy and safety findings for each included study is provided.
Data on the following outcomes have been extracted when available:

- Complete response rate
- Overall response rate
- Duration of complete response
- Overall survival
- Progression-free survival
- Patient reported outcome - Health Related Quality of Life as assessed by:
  - European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) v3.0 questionnaire
  - 15-item Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS)
- Safety
  - Incidence of adverse events (AE) by severity, serious adverse events (SAE) and discontinuation due to AEs
  - Qualitative description of the safety profile

The main analysis of this application is based on efficacy and safety results for glofitamab from the most recent CCOD of June 15, 2022 of NP30179 (17, 34). Efficacy outcomes are presented for the ITT population (n=155) and

safety outcomes are presented for the safety-evaluable population (n=154), unless otherwise specified. To support the main analysis, the primary endpoint of CR rate is presented for the pivotal cohort (n=108) (CCOD: September 14, 2021) and for the supporting cohort (n=101) (CCOD: June 15, 2022). Additionally, DOCR is presented for the supporting cohort (n=101) (CCOD: June 15, 2022).

For SCHOLAR-1, the pooled estimates of CR rate, ORR and OS across the four studies is presented. Data on PFS, quality of life and safety is presented for the individual studies in SCHOLAR-1 when available.

In SCHOLAR-1 (6), only INV-assessed endpoints are reported, whereas in NP30179 both IRC and INV-assessed endpoints are reported. As IRC-assessment may be considered more objective as compared to an INV-assessments (52, 53), both IRC and INV-assessed endpoints are presented for NP30179 in this application. However, only the INV-assessed endpoints will be used in the comparative analysis for comparability between NP30179 and SCHOLAR-1.

For detailed efficacy and safety results, please refer to appendices D and E.

7.2.1 Complete response rate

NP30179

NP30179 reports data on CR rate defined as the proportion of patients whose best overall response (BOR) was a CR based on either IRC- or INV-assessment of positron emission tomography-computerized tomography (PET-CT) scans using the Lugano criteria (50).

A comparison of CR between the pivotal cohort and historical controls was conducted using an exact binomial test with two-sided α level of 5% based on data from the initial CCOD of September 14, 2021. The historical CR rate for patients in the R/R DLBCL cohort was assumed to be 20% and the 95% CIs for the CR rate was calculated based on the Clopper-Pearson method.

The primary endpoint, namely IRC-assessed CR rate, for glofitamab was already met in the first interim analysis at the CCOD of September 14, 2021 in the pivotal cohort where 38/108 were in complete remission. At this CCOD the ICR-assessed CR rate was [redacted] which was statistically significantly greater (p<0.0001) than the historical control CR rate of 20%. The primary efficacy outcome result was comparable with the CR rate determined by the investigator which was [redacted]. Concordance between the IRC and the investigator on whether each patient achieved a CR was high, namely [redacted], with [redacted] complete responders and [redacted] non-complete responders identified by both IRC and INV.

The IRC-assessed CR in the ITT population at the CCOD of June 15, 2022 was [redacted]), meaning that [redacted] patients were in complete remission. This was comparable to the INV-assessed CR rate of [redacted] where [redacted] patients were assessed by investigator to be in complete remission. Concordance between the IRC- and INV-assessment on whether a patient achieved a CR was also high at this CCOD. Overall, concordance was [redacted] with [redacted] complete responders and [redacted] non-complete responders identified by both IRC and INV.

At the latest CCOD of June 15, 2022, [redacted] patients were in complete remission when assessed by IRC in the supporting cohort (in which patients were enrolled into the study earlier than the ITT population and who received lower doses of glofitamab (≥10 mg)). Consequently, the CR rate was [redacted]. When assessed by investigator, [redacted] patients were evaluated to have complete response, the CR rate was [redacted]. Concordance between the IRC- and INV-assessment on whether a patient achieved a CR in the supporting cohort was [redacted] with [redacted] complete responders and [redacted] non-complete responders identified by both IRC and INV.

SCHOLAR-1

In SCHOLAR-1, response to therapy (CR and ORR) for refractory disease were determined by the 1999 International Working Group response criteria per local review for randomized studies (51). In the observational cohorts, IA/MC and MDACC, response to therapy was assessed by investigator also using the International Working Group response criteria.

For the randomized studies CORAL and LY.12, responses were prospectively assessed as per the study schedule of assessments, while responses for the observational cohorts MDACC and IA/MC were determined at the time of patient treatment or management as per institution standard procedures. Responses were obtained from an electronic medical record or patient medical record. Higgin's Q statistic with a pre-specified value of $P > 0.1$ was used to evaluate the heterogeneity of response rates between the source databases (54). The *P* value was found to be non-significant ($P = 0.18$) suggesting that the heterogeneity between the four cohorts did not have a strong influence on the variability in the analysis. Consequently, data could be pooled for analysis. Patient-level data were submitted to a central database from which the pooled analysis was performed and response rates were estimated with a random effects model (55).

Of the 636 patients in the overall population, 523 patients were evaluated for response to chemotherapy after refractory disease. The pooled CR rate among these patients was 7% (95% CI: 3-15).

7.2.2 Overall response rate

NP30179

NP30179 reports data on ORR defined as the proportion of patients whose BOR was a CR or partial response (PR) based on either IRC- or INV-assessment of PET-CT scans by using the Lugano classification (50). In addition, 95% CIs were calculated with use of the Clopper-Pearson method for CR rate.

Of the 155 patients in the ITT population, [redacted] patients responded to glofitamab treatment as assessed by the IRC, while [redacted] patients responded as assessed by the investigator. Consequently, the IRC-assessed and INV-assessed ORR was [redacted] and [redacted], respectively, in the ITT population at the latest CCOD. Concordance between the IRC- and INV-assessed response in the ITT population on whether a patient achieved a OR was [redacted].

SCHOLAR-1

ORR was assessed and evaluated as described for CR in SCHOLAR-1 in 7.1.2.1 (see above). The pooled ORR was estimated to be 26% (95% CI: 21-31).

7.2.3 Duration of complete response

NP30179

One of the key secondary endpoints in NP30179, was DOCR as assessed by the IRC or investigator using the Lugano criteria (50). In NP30179, DOCR was defined as the time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurred first. The extent of follow-up for DOCR was estimated using the reverse Kaplan-Meier (KM) method, where censors and events were reversed from DOCR. The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOCR.

The median DOCR for the [redacted] patients who were in complete remission as assessed by the IRC in the ITT population was [redacted] at the latest CCOD of June 15, 2022 (Figure 5) since [redacted] remained in complete remission, and only [redacted] had disease progression [redacted] or had died (2 patients) by the time of the CCOD. Event-free rates at 6 and 12

months were [redacted] and [redacted], respectively and the 24 months even-free rate was [redacted] The median duration of follow-up for IRC-assessed DOCR was [redacted].

[redacted]

Likewise DOCR was [redacted] for the [redacted] patients with INV-assessed CR (Figure 6). [redacted] remained in complete remission and [redacted] had disease progression [redacted] or had died [redacted] by the time of the CCOD. The event-free rates were [redacted] and [redacted] at 6 and 12 months, respectively, and the 24 months even-free rate was [redacted] The median duration of follow-up for an INV-assessed DOCR was [redacted] The concordance between the IRC- and INV-assessed DOCR in ITT population was [redacted] overall.

[redacted]

In the supporting cohort, in which long-term outcomes were explored, the median IRC-assessed DOCR was [redacted] at the CCOD of June 15, 2022 (Figure 7). Of the [redacted] patients who achieved an IRC-assessed CR, [redacted] remained in complete remission, and [redacted] had disease progression or had died at the time of the CCOD. Event-free rates were [redacted] at both 6 and 12 months. Patients in this cohort were enrolled earlier into NP30179 compared to the ITT population, and thus, had longer follow-up, the 24-month. The DOCR after 24 months showed a durable response, as seen from the event-

free rate which was [redacted]). Hence, more than half of the patients in the supporting cohort achieved lasting remission for at least two years, which has shown to be a good indicator for favourable long term prognosis (15, 18, 56). The median duration of follow-up for IRC-assessed DOCR was [redacted].

[redacted]

The median INV-assessed DOCR was [redacted] (Figure 8). Of the [redacted] patients who achieved an INV-assessed CR, [redacted] remained in complete remission and [redacted] had disease progression by the CCOD. The event-free rates among complete responders at both 6 and 12 months were [redacted] and the event-free rate at 24 months was [redacted]. The median duration of follow-up for the INV-assessed DOCR was [redacted]. The concordance between the IRC- and INV-assessed DOCR in the supporting cohort was [redacted] overall.

[redacted]

Data on DOCR was not reported in SCHOLAR-1 nor in any of the individual studies included in SCHOLAR-1.

7.2.4 Overall survival

NP30179

NP30170 reports data on OS defined as the time from the first study treatment (obinutuzumab or glofitamab if obinutuzumab was not taken) to the date of death from any cause. The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. The KM-method was used to estimate 6-month and 12-month survival rates, along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.

[redacted] patients in the ITT population [redacted] had died with a median time to death of 1[redacted] (Figure 9) at the CCOD of June 15, 2022. The majority of deaths were in patients who never had a response to treatment. The survival rates at 6 and 12 months were [redacted] and [redacted], respectively, and the 24 months survival rate was [redacted]

[redacted]

SCHOLAR-1

SCHOLAR-1 reports data on OS, however OS was assessed differently in the individual studies included in SCHOLAR. In CORAL patients with refractory disease were assessed for survival approximately every 3 months for 1 year and then every 6 months for 3 years while patients in LY.12 were assessed at least once a year. In the observational studies IA/MC and MDACC, patients were followed up for survival per institution standard procedures. Patients who were alive at the time of data extraction were censored at the date of last contact. OS was analyzed using the KM method.

Of the 636 patients in the overall population in SCHOLAR-1, 603 patients were evaluated for survival. 84% of the patients had died with a median OS of 6.3 months (95% CI: 5.9-7.0) from the start of therapy (Figure 10). OS is referenced as described in the original SCHOLAR-01 publication and figure 10, showing event-free probability over time (extracted directly from the original publication) is, as done in the original publication referenced to as reflecting OS. The 12-months survival rate was 28% (95% CI: 25-32), and 24 months survival rate was 20% (95% CI: 16-23). Numbers at risk for each time point is not available in the original publication and therefore not presented in this application. The follow-up time is unclear, although the OS KM curve (Figure 10) might suggest up to 180 months follow-up.

[redacted]

7.2.5 Progression-free survival

NP30179

NP30179 reports data on PFS using the Lugano classification (50). PFS was defined as the time from the first study treatment (obinutuzumab or glofitamab if obinutuzumab was not taken) to the first occurrence of disease progression or death from any cause, whichever occurred first. The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS. The KM method was used to estimate 6-month PFS and 12-month PFS, along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.

In the ITT population, [redacted] had a PFS event as assessed by IRC at the CCOD of June 15, 2022. The earliest contributing event was disease progression in [redacted] and death in [redacted] while [redacted] had no event. The median IRC-assessed PFS was [redacted] (Figure 11) with 6- and 12-months PFS event-free rates of [redacted]) and [redacted]), respectively and the 24 months PFS even-free rate was [redacted] The median duration of follow-up for ICR-assessed PFS was [redacted]

[redacted]

When assessed by investigator, [redacted] had a PFS event. The earliest contributing event was disease progression in [redacted] and death in [redacted] with [redacted] without an event. The median INV-assessed PFS was [redacted] (Figure 12) with 6 and 12 month PFS event-free rates of [redacted] and [redacted], respectively, and the 24 months PFS even-free rate was [redacted]

SCHOLAR-1

Data on PFS is not presented in SCHOLAR-1, but data on PFS was reported in the observational study MDACC and in the clinical trial CORAL. In MDACC, the median INV-assessed PFS was 2.8 months (95%CI: 2.4-3.3), however, there is no information on how PFS is defined. In CORAL, PFS was defined as the time from study entry until disease progression or death, and was estimated by the KM method. Data on median PFS was not reported, but the three-year PFS was 37% (95% CI: 31%-42%) with no significant difference between the R-ICE and R-DHAP arms (31% and 42%, respectively; P=0.4) (Figure 13).

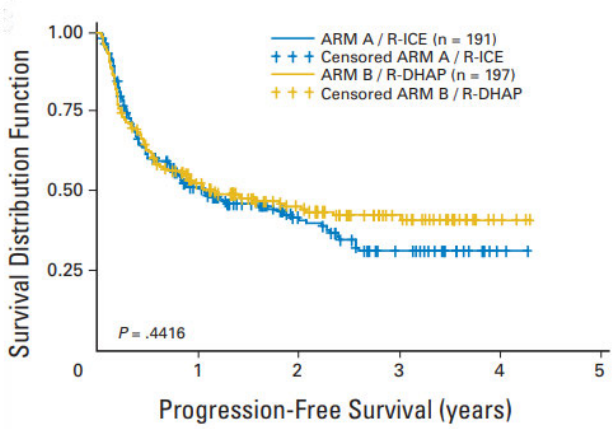


Figure 13: KM PFS in the two study arms of the CORAL study; R-ICE (blue) and R-DHAP (yellow).

7.2.6 Patient reported outcomes - Health related Quality of Life

NP30179

In NP30179, PRO were assessed in patients from the part III dose-expansion cohorts (pivotal cohort and mandatory dexamethasone cohort) who have had a baseline assessment and at least one post-baseline assessment before the date of progression.

PROs were assessed using two different instruments namely the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) v3.0 questionnaire (57) and the 15-item Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) Lymphoma Subscale (LymS) (58).

The EORTC QLQ-C30 questionnaire and FACT-Lym LymS were assessed at baseline; day 1, and 8 of cycle 1; day 1 of cycle 2, 3, 5, 7, 8, 9, and 12; at post-treatment follow-up visits until progression at 3, 6, 9, 12, 15, 21 and 24 months and at treatment completion.

EORTC QLQ-C30

The EORTC QLQ-C30 consists of 30 questions that assess five domains of patient functioning (physical, emotional, role, cognitive and social), three symptom scales (fatigue, nausea and vomiting, and pain), global health status/quality of life (GHS/QoL) and six single items (dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties). In this application, PRO based on the EORTC QLQ-C30 questionnaire are specifically reported for the physical functioning scale, GHS/QoL scale, and the fatigue symptom scale as these are deemed most relevant in understanding the HRQoL status of patients with R/R DLBCL (59).

Scores are transformed to a 0-100 scale, with higher scores on the five domains and GHS/QoL reflecting a good HRQoL and higher scores on the symptom scales and single items reflecting poor HRQoL. For the EORTC QLQ-C30 physical functioning and GHS/QoL subscales, a clinically meaningful change at any time was defined as a difference of at least 10-points (60).

A total number of 120 patients had an EORTC QLQ-C30 assessment at baseline and the number of patients assessed at each time of assessment during and post treatment is shown in Table 8. During treatment, a relatively high response rate is seen from baseline up until approximately d ay 1 of cycle 7.

Please note that only one patient was assessed during treatment at day 1 of cycle 1, and post treatment at the 21 months and 24 months follow up. For transparency, these three assessments have been included in the following plots, however, as they cannot be used statistically, they will not be considered in any other part of the data presentation.

Physical functioning

Generally, the scores for patients treated with glofitamab were high on the physical functioning scale reflecting a good HRQoL. The baseline mean (standard deviation [SD]) for physical functioning scores was [redacted]. Patients reported a stable score during treatment. The median (interquartile range [IQR]) ranged from [redacted]. At end of treatment, the median score was [redacted] A stable and slightly higher score level was found throughout the post treatment assessment where the median scores were all above baseline ranging [redacted] (Figure 26, appendix D).

A steady level of physical functioning in patients during treatment with glofitamab is also indicated by the median change from baseline (IQR) which ranged from [redacted]. Likewise at treatment completion, [redacted] and a similar trend was found post treatment where it ranged from [redacted] (Figure 27, appendix D).

The responder analysis in EORTC QLQ-C30 measure of physical functioning showed that the proportion of who experienced a clinically meaningful improvement during treatment ranged from [redacted] while a meaningful deterioration ranged from [redacted] At treatment completion, [redacted] and [redacted] had clinically meaningful improvement and deterioration, respectively. Post treatment it ranged from [redacted] experiencing a clinically meaningful improvement at [redacted]. The proportion of patients who experienced a clinically meaningful deterioration ranged from [redacted] (Figure 28 and Figure 29, appendix D).

GHS/QoL

The baseline mean (SD) for GHS/QoL scores was [redacted] During treatment, the median (IQR) ranged from [redacted] with a median baseline score of [redacted] At the end of treatment, patients reported a slightly higher score that is better HRQoL with a median score of [redacted] Likewise all median scores were [redacted] baseline post treatment where the median scores ranged from [redacted] (Figure 30, appendix D).

The median change from baseline (IQR) ranged from [redacted] during treatment. At treatment completion the median change [redacted] and post treatment with the median changes

ranging between [redacted] (Figure 31, appendix D).

The responder analysis in EORTC QLQ-C30 measure of GHS/QoL showed that the proportion of who experienced a meaningful improvement during treatment ranged from [redacted]. A meaningful deterioration ranged from [redacted]. At treatment completion [redacted] had clinically meaningful improvement and deterioration, respectively. Post treatment the proportion experiencing a clinically meaningful improvement ranged from [redacted]. The proportion of patients who experienced a clinically meaningful deterioration ranged from [redacted] (Figure 32 and Figure 33, appendix D).

Fatigue

Opposite to the scores for physical functioning and GHS/QoL, lower scores on the fatigue symptom scale reflect a good HRQoL. The baseline mean score (SD) for fatigue was [redacted] The median (IQR) during treatment ranged from [redacted] at [redacted] with a median baseline score of [redacted] Patients reported comparable median scores at the end of treatment that is [redacted] but post treatment the median scores were all below baseline. The median scores post treatment ranged from [redacted]s follow up (Figure 34, appendix D).

The median change from baseline during treatment ranged from [redacted] Patients reported [redacted] at the treatment completion assessment. The trend was very similar post treatment to that during treatment. The median change from baseline ranged [redacted] (Figure 35, appendix D).
[redacted]

The responder analysis in EORTC QLQ-C30 measure of fatigue showed that the proportion of who experienced a meaningful improvement during treatment ranged from [redacted]. A meaningful deterioration ranged from [redacted]. At treatment completion, [redacted])

had clinically meaningful improvement and deterioration, respectively. Post treatment it ranged, the proportion of patients experiencing a clinically meaningful improvement ranged from [redacted]. The proportion of patients who experienced a clinically meaningful deterioration ranged from [redacted] (Figure 36 and Figure 37, appendix D).

FACT-Lym LymS

The 15-item FACT-Lym LymS was developed to assess HRQoL in patients with NHL. The FACT-Lym LymS enables assessment of the changes from baseline with respect to B-symptoms and impact on HRQoL caused by symptom worsening or alleviation and treatment toxicity. Scores range from 0-60 with higher scores being reflective of better HRQoL (i.e., lower lymphoma-specific symptoms or concerns). A clinically meaningful change at any time was defined as a difference of at least 5 points (58).

Out of the 120 patients assessed with EORTC QLQ-C30, one patients was missing a baseline assessment on FACT-Lym LymS. The number of patients assessed for HRQoL data with the FACT-Lym LymS questionnaire at each visit in NP30179 is shown in Table 9.

[redacted]

The mean baseline (SD) lymphoma symptom scores was [redacted]. During treatment the median (IQR) ranged from [redacted] with a median baseline score of [redacted] At the end of treatment, the median score was [redacted]. It ranged from [redacted] 5.69-12.68) [redacted] respectively (Figure 38, appendix D).

The median change from baseline during treatment ranged from [redacted]. Hence, patients reported a stable level of HRQoL as assessed by FACT-Lym LymS during treatment. [redacted] However, post treatment patients reported a slight decrease that is the median change from baseline [redacted] (Figure 39, appendix D).

The proportion of patients reporting a clinically meaningful improvement ranged from [redacted](95% CI: 0.08 0.23)

[redacted], respectively. Patients who experienced a clinically meaningful deterioration ranged from 1[redacted] experienced a clinically meaningful improvement and deterioration, respectively. [redacted] had an improvement. The proportion of patients who experienced a clinically meaningful deterioration ranged from [redacted] (Figure 40 and Figure 41, appendix D).

LY.12

Information on HRQoL was not available in SCHOLAR-1. However, the clinical trial LY.12, which compared outcomes in R/R aggressive lymphoma patients treated with GDP vs DHAP, reports data on QoL. In LY.12, QoL is measured using the Functional Assessment of Cancer Therapy–General (FACT-G) tool (61), including the lymphoma-specific subscale and a subscale for neurologic toxicity (62). QoL was assessed at baseline, end of cycle 1, middle and end of cycle 2, and 1 month after stem-cell infusion. A clinically meaningful change was defined as a change in a QoL item rating of 10% or more when compared with the baseline value.

Using FACT-Total scores, more patients treated with GDP experienced improvement in QoL and fewer had deterioration in QoL compared to patients receiving DHAP when looking at the score change from baseline. Significant differences were seen at the end of the first cycle of treatment and at the midpoint of treatment cycle 2 (Figure 42, appendix D).

At the midpoint of cycle 2, 18% and 11% of patients treated with GDP and DHAP, respectively, experienced an improved clinically meaningful change score. A decline clinically meaningful change score that is 33% and 41% (p=0.04) was found in GDP and DHAP treated patients, respectively. 47% of patients receiving GDP required hospitalization compared to 99% of the DHAP treated patients (p<0.001). Platelet transfusions were required for 31% vs. 47% (p<0.001) in GDP and DHAP treated patients, respectively.

7.2.7 Safety

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 glofitamab and the comparators

Safety results from NP30179 will be presented for the safety-evaluable population which include all patients who received ≥ 1 dose of study treatment (n=154). At the CCOD of June 15, 2022, patients received a median of five treatment cycles of glofitamab. [redacted] of patients received less than [redacted] and the median treatment duration was [redacted]. The median number of treatment cycles was 1 and the median treatment duration was 1 day for both obinutuzumab and tocilizumab. The median total cumulative dose of glofitamab, obinutuzumab and tocilizumab was [redacted], respectively. The median dose intensity was [redacted] for all three treatments (Table 10).

Safety was not analysed in SCHOLAR-1, nor was safety information reported in the observational cohorts MDACC and IA/MC (Table 6). Therefore, the below information is based on safety outcomes reported in the safety populations of the two large phase 3 randomized controlled trials namely LY.12 (13) and CORAL (11, 12). However, no data was available on Study Drug Exposure in LY.12 or CORAL.

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

NP30179

The incidence, nature and severity of AEs were recorded by the investigator. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.0, and AEs were evaluated according to National Cancer Institute–Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (63). Investigators graded CRS by consensus criteria of Lee et al 2014 grading and Lee et al ASTCT 2019 grading (64, 65), and managed according to protocol guidance.

LY.12

In LY.12, AEs were graded according to CTCAE version 2.0 (66).

CORAL

In CORAL, AEs were graded according to CTCAE version 3.0 (67).

While safety data for the safety-evaluable population in NP30179 was comprehensive, only limited safety data could be extracted from both LY.12 and CORAL. Table 11 provides a combined overview of the incidences of different relevant safety outcomes reported in NP30179, LY.12 and CORAL.

Table 11: Incidence of safety outcomes in the safety-evaluable population in NP30179, LY.12 and CORAL

Safety parameter	NP30179	LY.12	CORAL

	[redacted]	R-GDP n=306	R-DHAP n=304	R-ICE n=202	R-DHAP n=194
Any AE, n (%)		-	-	-	-
Grade 3-4 AEs		143 (47)+	183 (61)+	-	-
Grade 5 AEs		-	-	-	-
Treatment-related AE, n (%)		-	-	-	-
Grade 3-4 treatment-related AEs		-	-	-	-
Grade 5 treatment-related AEs		2 (0.7) ++	6 (2.0) ++	1 (0.5) ++	3 (1.5)++
Any SAE, n (%)		-	-	58 (29)	68 (35)
Treatment-related SAEs		-	-	-	-
AE leading to treatment discontinuation, n (%)		-	-	-	-
Treatment-related AE leading to treatment discontinuation, n (%)		-	-	-	-
AE leading to dose interruption/modification, n (%)		-	-	-	-
Treatment-related AE leading to dose interruption/modification, n (%)		-	-	-	-

[redacted]

7.2.7.2 Qualitative description of the safety profile

NP30179

At the CCOD of June 15, 2022, AEs of any grade occurred in [redacted] in the safety-evaluable population in NP30179. Most AEs occurred during [redacted]. The median time to first AE from the first glofitamab dose was [redacted]. The most common AE was CRS which was reported in [redacted] (Lee et al 2014 grading) or [redacted] (ASTCT grading Lee et al 2019). CRS will be described in more detail in the section about adverse events of special interest (AESI) below. In terms of frequency, CRS was followed by neutropenia or neutrophil count reduction (37.7%), anaemia (30.5%) and thrombocytopenia/platelet count decreased (24.7%).

AEs grade 3-4 were reported in [redacted] with the most commonly reported grade 3-4 AEs (≥5% of patients) being neutropenia/neutrophil count decreased [redacted], anaemia ([redacted]), hypophosphatemia ([redacted]), and thrombocytopenia/platelet count decreased ([redacted] There was a low rate of discontinuation due to AEs that is [redacted] of the patients discontinuing treatment due to glofitamab-related AEs. Of these [redacted] discontinued due to neutropenia, [redacted] due to gastrointestinal haemorrhage, [redacted] due to myelitis and [redacted] due discontinued due to CRS.

SAEs of any grade were reported in [redacted] of which [redacted] reported an SAE related to glofitamab treatment. SAEs which occurred in ≥1% of patients in the safety-evaluable population are summarized in Table 12. The most frequently reported SAEs were CRS; in [redacted] and [redacted] as assessed according to the ASTCT 2019 grading criteria and the Lee et al. 2014 grading criteria, respectively. Other SAEs reported in three or more patients included sepsis ([redacted]), COVID-19 ([redacted]), COVID-19 pneumonia ([redacted] and tumour flare ([redacted]

Table 12: Incidence of SAEs by preferred term occurring in ≥1% of patients in the primary safety-evaluable population in NP30179.

Serious Adverse Events during the treatment period	[redacted]
MedDRA PT, n (%)	
CRS	
Sepsis	
COVID-19	
COVID-19 pneumonia	
Tumor flare	
Anemia	
Febrile neutropenia	
Neutropenia	
Pleural effusion	
Back pain	
Delirium	
Gastrointestinal hemorrhage	
Infection	

Pneumonia		[redacted]
Pyrexia		
Vascular device infection		

Abbreviations: ASTCT - American Society for Transplantation and Cellular [redacted] MedDRA - Medical Dictionary for Regulatory Activities; PT - preferred term; SAE - serious adverse event.
[a]According to the ASTCT 2019 grading criteria (65).
[b]According to the Lee et al. 2014 grading criteria (64)

[redacted] in the safety-evaluable population had died at the time of the CCOD. Of these, [redacted] occurred more than 30 days from last dose and [redacted] occurred within 30 days of last dose. The most frequent cause of death irrespective of time point was progressive disease, which accounted for a total of 61 deaths (75.3%). Nine patients died due to AEs, including COVID-19 pneumonia ([redacted], COVID-19 [redacted]), sepsis [redacted]), and delirium [redacted]). However, no patients died due to treatment related events.

<u>AESIs:</u>
The key clinically significant AESIs related to glofitamab, which may have implications for prescribing decisions and patient management include grade ≥2 CRS, serious infections, grade ≥2 tumour flare and tumour lysis syndrome (TLS):

CRS
At the CCOD of June 15, 2022, CRS events of any grade were reported in [redacted] in the safety-evaluable population by ASTCT 2019 grading and in [redacted] by Lee 2014 grading. However, most of these were of grade 1 since only [redacted] events by ASTCT 2019 grading, and [redacted] events by Lee 2014 grading. Grade 3–4 CRS AEs were reported [redacted] by ASTCT 2019 grading and [redacted] by Lee 2014 grading. [redacted] grade 5 CRS AEs were reported. As of the CCOD, grade ≥2 CRS events were resolved in [redacted] by ASTCT 2019 grading and [redacted] by Lee 2014 grading.

The most frequently reported signs and symptoms associated with CRS that is ≥5% of the 99 patients who experienced CRS of any grade by ASTCT 2019 grading were pyrexia [redacted], tachycardia [redacted] hypotension [redacted] chills [redacted] hypoxia [redacted]), headache [redacted], and nausea [redacted]). The frequently reported signs and symptoms of pyrexia, chills, and tachycardia were predominantly reported as NCI CTCAE grade 1 events, while those of hypotension and hypoxia were similarly distributed between grade 1 and grade 2 events. Grade 3 signs and symptoms were pyrexia, hypotension, pain, hypertension, tachycardia, hypoxia, CRP increased, dysarthria, back pain, and acidosis while grade 4 signs and symptoms were hypoxia, tachycardia and hypotension.

The majority of signs and symptoms associated with CRS were reported [redacted] reported CRS signs and symptoms during cycle 1, [redacted] patients reported CRS signs and symptoms during cycle 2, and [redacted] patients reported CRS signs and symptoms during cycle 3 and subsequent treatment cycles. During cycle 1 and prior to cycle 2, the most commonly reported (≥ 5%) CRS signs and symptoms (any NCI CTCAE grade) included the following: pyrexia, hypotension, tachycardia, chills, and hypoxia. During cycle 2 and prior to cycle 3, the only CRS signs and symptom (any NCI CTCAE grade) reported in ≥5% of patients was pyrexia. Only 3 patients experienced CRS signs and symptoms in cycle 3 and beyond.

As seen from Table 12, a total of [redacted]erious CRS events were reported in [redacted] according to the ASTCT 2019 grading criteria. Of these, [redacted] serious CRS events required or prolonged hospitalization, one serious CRS event was life-threatening, and one serious CRS event resulted in persistent or significant disability/incapacity. ICU admission was required for [redacted] required tocilizumab, [redacted] used corticosteroids, and [redacted] used both tocilizumab and corticosteroids to treat CRS.

Serious infection

Serious infections were reported in [redacted] The most frequent serious infections reported in at least 2% of patients [redacted] COVID-19 pneumonia [redacted] and COVID-19 [redacted] Infection-related deaths were reported [redacted] (owing to sepsis, COVID-19 pneumonia and COVID-19). A serious infection was reported in [redacted] concurrent with grade 3-4 neutropenia. However[redacted] grade 5 AEs were considered related to glofitamab treatment.

Tumour flare

Tumour flare of any grade was reported in [redacted] Tumour flare occurred most frequently at cycle 1; no events were reported beyond cycle 2. Overall, [redacted] treated with glofitamab step-up dosing experienced a grade ≥2 tumour flare AE. Of the [redacted] reported a grade 2 event and 4 patients reported a grade 3 event. AEs in all patients were assessed as related to study treatment by the investigator and [redacted] received treatment for the AE. At the time of the CCOD, events were resolved in [redacted].

TLS

[redacted] experienced grade 3 TLS AE. In [redacted] the AE was considered related to glofitamab treatment by the investigator, and the patient received treatment for the AE. At the time of the CCOD, both events had resolved.

LY.12

In the LY.12 study, AEs of any grade was not reported, but grade 3-4 AEs were observed during the first two cycles of chemotherapy in 143 patients in the R-GDP arm (47%) and in 186 patients in the R-DHAP arm (61%). Infection with neutropenia was reported as a grade 3-4 AE, but it was unclear what the remaining grade 3-4 AEs were. Instead, the most frequently reported SAEs which occurred in more than 5% of the patients were reported (see Table 13). In the both the R-DHAP arm and the R-ICE arm, the most commonly observed SAEs were febrile neutropenia, infection (with and without neutropenia) and fatigue. In LY.12, 8 patients died as a result of protocol treatment–related complications: two during treatment with GDP (0.7%) and six after receiving DHAP (2.0%), see Table 11.

Table 13: Most frequently reported SAEs in the LY.12 study.

Serious Adverse Event during the treatment period		
	LY.12	
Adverse event, n (%)	**R-GDP n=306**	**R-DHAP n=304**
Thrombosis/embolism	18 (6)	18 (6)

Fatigue	30 (10)	28 (9)
Nausea	13 (4)	25 (8)
Vomiting	22 (7)	21 (7)
Infection • with grade 3 to 4 neutropenia • without neutropenia	 18 (6) 21 (7)	 28 (9) 22 (7)
Febrile neutropenia	28 (9)	70 (23)
Syncope	7 (2)	16 (5)

Abbreviations: DHAP – dexamethasone, cytarabine, cisplatin; GDP, gemcitabine, dexamethasone, cisplatin.
NOTE: Comparison of most frequently occurring serious adverse events, occurring in at least 5% of patients who received at least one dose of protocol therapy, at grade 3 or 4.

CORAL

In the CORAL study, neither total number AEs of any grade nor total number of grade 3-4 AEs were reported, only grade 3-4 infection (with and without neutropenia), and grade 3-4 renal toxicity grade 3-4. A total of 33 patients (17%) in the R-ICE arm and 31 patients (16%) in the R-DHAP arm experienced infection with grade 3-4 neutropenia, while 11 patients (6%) in the R-ICE arm and 15 patients (8%) in the R-DHAP arm experienced infection without neutropenia grade 3 or 4. Both grade 3-4 hematological and grade 3-4 non-hematological toxicities were more severe in R-DHAP than in the R-ICE arm. Non-hematological toxicities included grade 4 renal toxicity and occurred in 11 patients (6%) in the R-DHAP arm and in only 2 patients (1%) in the R-ICE arm. One toxic death occurred in the R-ICE arm and three toxic deaths in the R-DHAP arm. 58 patients in the R-ICE arm (29%), and 68 patients in the R-DHAP arm (35%) experienced at least one SAE. A total of 90 SAEs were reported in the R-ICE arm and 120 SAEs in the R-DHAP arm. In both the R-ICE and the R-DHAP arm, the most common SAEs were infections. The rate of serious infection concurrent with grade 3-4 neutropenia and without neutropenia were similar in both arms (Table 14).

Table 14: Main safety outcomes reported in the CORAL study.

Main safety outcomes reported during the treatment period		
Adverse event, n (%)	**CORAL**	
	R-ICE n=202	**R-DHAP n=194**
Infection • with neutropenia grade 3 or 4 • without neutropenia grade 3 or 4	 33 (17) 11 (6)	 31 (16) 15 (8)
Renal toxicity grade 3 or 4	2 (1)	11 (6)
Toxic death	1 (0.5)	3 (1.5)

Abbreviations: R-ICE - rituximab, ifosfamide, carboplatin, and etoposide; R-DHAP - rituximab, dexamethasone, cytarabine, and cisplatin.

7.3 Comparative analyses of efficacy and safety

This section presents the comparative analysis of glofitamab in R/R DLBCL vs. the retrospective study SCHOLAR-1, using the data presented in section 7.2. The analyses are based on the CCOD of June 15, 2022 from NP30179 of glofitamab and the original publication by Crump et al., 2017 (SCHOLAR-1) (6).

The comparative analysis is mainly based on a MAIC methodology, but for the outcomes PFS, HRQoL and safety that were not presented in SCHOLAR-1, a narrative comparison has been applied using the individual studies that formed the basis of the SCHOLAR-1 study.

An overview of the performed comparative analyses is presented in Table 15. The methods used are described in detail in section 7.3.1, and the results are presented in section 7.3.2.

Table 15: Overview of the performed comparative analyses

Outcome	Analyses	Study, population[1]
CR, ORR, OS	MAIC	SCHOLAR-1, refractory DLBCL (6)
PFS	Narrative comparison	MDACC (14), R/R DLBCL CORAL, R/R DLBCL (11, 12)
HRQoL	Narrative comparison	LY.12, R/R DLBCL (13)
Safety	Narrative comparison	LY.12, relapse/refractory DLBCL (13) CORAL, relapse/refractory DLBCL (11, 12)

[1]For detailed baseline characteristics of the study populations, refer to Appendix C.

7.3.1 Method of synthesis

7.3.1.1 Matching-adjusted indirect comparison

Due to the nature of the single-arm design of the NP30179 study, an indirect treatment analysis has to be performed to illustrate efficacy compared to the relevant comparator. For the purpose of this indirect treatment comparison an unanchored MAIC has been chosen to compare the efficacy of glofitamab vs. that shown in patients enrolled in SCHOLAR-1. The usual methods for conducting such "cross-study" comparisons and adjusting for differences in patient characteristics across studies, which, if not correctly adjusted for, will bias the results, are MAICs or simulated treatment comparisons (STC). Both methods rely on the same key assumptions, and usually have similar results. A MAIC approach has been selected for this analysis, as these tend to be more commonly used than STCs in health technology assessments. They are therefore more likely to be familiar to reviewers, and they can also generate adjusted KM curves, which can then be used in economic evaluations. MAIC analysis adjusts for imbalances in any effect modifiers or prognostic variables between the studies considered, which would in an unadjusted analysis have led to biases in the relative treatment effect. MAIC is a recently developed population adjustment method that uses individual patient-level data (IPD) from a subset of trials to form population-adjusted indirect comparisons between treatments in a specific target population (68, 69). MAIC essentially adjusts for between-trial differences in baseline characteristics.

The methodology of an unanchored MAIC is to assume that absolute treatment effects are constant regardless of the level of effect modifiers and prognostic variables (and all of these are required to be known; referred to as conditional constancy of absolute effects). These effect modifiers and prognostic factors must be reported in each

study included in the MAIC to enable population adjustment in the trial with IPD. In an unanchored MAIC, it is assumed that one has a treatment k_I (in this case, glofitamab) that has been studied in a population s_I for which one has IPD. One has a comparator of interest k_A (in this particular case, chemotherapy regimens +/- R) that has been studied in a population s_A for which one only has aggregate data.

The aim of the method is to re-weight the observed IPD results for k_I in population s_I to make it more similar to population s_A, thus enabling a comparison of k_I and k_A in a more comparable population.

The weights are calculated as follows (68, 69):

The IPD patient covariates X_{sI} are re-centred by subtracting the aggregate data mean covariate value $\underline{X_{aA}}$ to create $\underline{X_{sI}}$,
The weights are then the values $\hat{\alpha}$ that minimize the following equation:

$$\sum_{j=1}^{n_I} exp(\alpha^T X'_{jsI})$$

Analysis can then be performed on the reweighted data using standard models for binomial, rate, continuous or survival data, similar to in UAIC. Comparator patients are given a weight of 1.

Confidence intervals and p-values are calculated using bootstrapping to account for the fact that the weights are estimated rather than factual (70). Robust standard errors may also be used to estimate confidence intervals, for comparison. For outcomes such as time to event and binary where comparator pseudo-IPD are available, bootstrapping across both arms of the statistic of interest will be performed. For any outcomes where only the aggregate result is available for the comparator, bootstrapping of the glofitamab arm level statistic will be performed, and the bootstrap standard error for glofitamab will be estimated and used to compare to the aggregate arm level statistic.

Consideration will be given to also balancing the standard deviation for continuous covariates where this is reported, via the inclusion of squared covariate terms in the weight calculation (71), providing this does not substantially reduce the effective sample size (ESS).

A small number of patients in NP30179 may have missing data for at least one covariate. The missing covariates will be set to be equal to NP30179 level mean or mode for calculation of the weights, so that the patients are not dropped from the analysis. This will be done prior to any additional filtering to match a specific comparator study, so that the same replacement values are used in all comparisons. If the number of patients with missing covariate data is larger, alternative missing data handling mechanisms may be explored. For categorical covariates such as cell type of origin, where a larger number of missing data are expected due to design (cell type was only collected if available), missing will be treated as a separate category in its own right rather than excluded.

Following the calculation of weights, it is necessary to determine whether the optimization procedure has worked correctly and whether the weights derived are sensible. It is easier to examine the distribution of the weights by scaling them, so that the rescaled weights are relative to the original unit weights of each individual. In other words, a rescaled weight > 1 means that an individual carries more weight in the re-weighted population than the original data and a rescaled weight < 1 means that an individual carries less weight in the re-weighted population than the original data. The rescaled weight is calculated by multiplying by N_I and dividing by the sum of all weights. The weights utilized in the MAIC-analysis is provided in Appendix F.

7.3.1.1.1 Prognostic factors and effect modifiers

A MAIC should adjust for known prognostic variables and effect modifiers. Based on discussion with the Roche internal and external medical advisors, a list of potential prognostic factors and effect modifiers for R/R DLBCL to be considered in the MAIC was generated. These prognostic factors were further validated by the results of an SLR that was conducted to assess the prognostic factors of patients with R/R DLBCL. Prognostic factors and effect modifiers were classified as either high, medium or low priority according to clinical feedback as outlined in Appendix F.

A total of 8 baseline characteristics of interest are reported for the SCHOLAR-1 pooled population (n=636) at an unclear follow-up (although the OS KM curve would suggest up to 180 months' follow-up). Thus, there are up to 8 baseline factors that may be considered for adjustment in MAIC analyses. A summary of the baseline characteristics of the ITT population in NP30179 and the enrolled population in SCHOLAR-01, grouped according to the priorities of the effect modifiers, can be found in Appendix F.

Outcome data are reported for responses and OS in the response evaluable (n=523) and survival evaluable (n=603) populations, respectively. Furthermore, KM curves are reported for OS by response, refractory and post-refractory transplantation status, as well as by ECOG PS, disease stage and IPI score, and response data are reported by age, ECOG PS, disease stage and IPI score. However, baseline data are not reported for these subgroups, thus it is not appropriate to use these data in a MAIC. MAIC analyses were deemed feasible for CR, ORR and OS, though with some limitations that may impact the interpretation and generalizability of the results.

7.3.1.2 Narrative comparison

A narrative comparison has been performed for PFS, HRQoL and safety outcomes. Data on these outcomes were not available in SCHOLAR-1, and thus, data from the individual studies that formed the basis of SCHOLAR-1 has narratively been compared to the result found in NP30179. A narrative comparison has its limitations since there is no adjustments for baseline characteristics which means that differences can introduce a bias in the comparison. However, in cases where the baseline characteristics are similar between the study groups that are to be compared, a narrative comparison is appropriate and useful.

7.3.2 Results from the comparative analysis

In the following section, a summary of the results from the comparative analysis is provided. Data are presented for the following outcomes:

- Complete response rate
- Overall response rate
- Overall survival
- Progression-free survival
- Health Related Quality of Life
- Safety

In order to ensure the best possible comparability between NP30179 and SCHOLAR-1, INV-assessed CR, ORR and OS for glofitamab (NP30179) will be used in the MAIC analysis to align with the method of assessment used in the original studies used in SCHOLAR-1. A filtering procedure based on applying the SCHOLAR-1 eligibility criteria was adopted. Consequently, to align with the population enrolled in SCHOLAR-1, patients in the ITT-population in NP30179 who did not have refractory disease according to SCHOLAR-1 criteria, patients with HGBCL histology or patients with 4+ prior lines of therapy were excluded. This means that 74 out of 155 from the ITT-population in NP30179 were deemed relevant for inclusion in the MAIC analysis.

The base-case maximizes the bias/variance tradeoff whilst controlling for all priority prognostic factors that were feasible and controlling for age as a mean. In addition to the base-case analysis, two scenario analysis were conducted: 1) including all available factors and controlling for age as a median (i.e. value as reported and not converted to mean using (72); and 2) including patients who received up to 4 prior therapies (n=93) (patients with 4+ lines were reported to be <1% in SCHOLAR-1, but this was estimated by excluding patients who relapsed post-ASCT, leading to uncertainty) while controlling for all available factors and for age as a mean.

As mentioned in section 7.1.3 the population in SCHOLAR-1 included patients with only one prior line of therapy. It is not possible to adjust for in this analysis since such patients were not enrolled in the NP30179 ITT population. This is very likely to introduce a major bias in the results in favour of the chemotherapy regimens in SCHOLAR-1. Likewise, it is not possible to adjust for the ECOG PS 2+ patients included in SCHOLAR-1 as such patients were also not enrolled in the ITT population in NP30179. Therefore, ECOG was excluded from the analysis (as only the split between 0-1 and 2-4 was reported), resulting in a residual imbalance in ECOG PS 1+, which is likely to bias results in favour of glofitamab.
A summary of the baseline characteristics used in the MAIC base-case is provided in Table 16. No unambiguously outlier weights were found. Please refer to appendix F for the histograms of MAIC weights for diagnostic purposes. The results for the MAIC base-case (ESS corresponding to ~32.9 patients) analyses are presented in the following sections.

Table 16: Summary of baseline c

Variable	[redacted]	SCHOLAR-1 (n=636)
Age (mean)		52.50
Age (median)		55
ECOG PS >1 (%)		14
ECOG PS 0 (%)		-
ECOG PS 1 (%)		-
ECOG PS 2 (%)*		-
Ann Arbor Stage III–IV (%)		72.7
Ann Arbor Stage I (%)		-
Ann Arbor Stage II (%)		-
Ann Arbor Stage III (%)		-
Ann Arbor Stage IV (%)		-
IPI 3–5 (%)		40.23
IPI 0 (%)		-
IPI 1 (%)		-
IPI 2 (%)		24
IPI 3 (%)		-
IPI 4 (%)		-
IPI 5 (%)		-
PMBCL histology (%)		4.23
1 prior therapy (%)		28

Variable	[redacted]	SCHOLAR-1 (n=636)
2-3 prior therapies (%)		49
2 prior therapy (%)		-
3 prior therapy (%)		-
4 prior therapy (%)		-
Refractory to 1st line (%)		28.00
Refractory to last line (%)		50.00
Early relapse after SCT (%)		22.00

Abbreviations: ECOG PS - Easte[redacted]ample size; IPI - International Prognostic Index; NA - not applicable; PMBCL - primary mediastinal large B cell lymphoma; SCT - stem cell transplant.
*% of ECOG 2 is not 0 as it reflects ECOG at baseline. One patient scored 2 at baseline, however, no patient had ECOG 2 at screening as per trial eligibility criteria.

7.3.2.1 MAIC results for CR

The odd ratio (OR) for CR strongly favours glofitamab vs. the chemotherapy regimens +/- R in SCHOLAR-1 in both the unadjusted model [redacted] and the adjusted base-case model ([redacted], with the point estimate from the adjusted model being more favourable for glofitamab than that from the unadjusted model (Table 17). The CR result for both scenario 1 [redacted] and scenario 2 [redacted] also yield strongly favourable point estimates for glofitamab vs. SCHOLAR-1 and the 95% CIs exclude 1 and are therefore supportive of the conclusion of the base-case analysis.

Table 17: Summary of MAIC results for INV-assessed CR.

Method for estimating OR	OR (95% CI)		
	Base-case	Scenario 1	Scenario 2
Unadjusted logistic regression model	[redacted]		
Bootstrap median CR (95% CI) weighted logistic regression model			
Bootstrap median CR (95% BCa CI) weighted logistic regression model			

Abbreviations: BCa - Bias corrected accelerated; CI - confidence interval; CR - complete response; INV - investigator; MAIC - matching-adjusted indirect comparison; OR - odds ratio.
ORs presented for the comparison of glofitamab vs. SCHOLAR-1. ORs>1 favour glofitamab.

7.3.2.2 MAIC results for ORR

The OR for ORR strongly favours glofitamab vs. SCHOLAR-1 in both the unadjusted [redacted] and the adjusted base-case models [redacted] with the point estimate from the adjusted model being more favourable for glofitamab than that from the unadjusted model. The ORR results for both scenario 1

(and scenario 2 also yield strongly favourable point estimates for glofitamab vs. SCHOLAR-1 and the 95% CIs exclude 1 and are therefore supportive of the conclusion of the base-case analysis (Table 18).

Table 18: Summary of MAIC results for INV-assessed ORR.

Method for estimating OR	
Unadjusted logistic regression model	
Bootstrap median ORR (95% CI) weighted logistic regression model	
Bootstrap median ORR (95% BCa CI) weighted logistic regression model	

Abbreviations: BCa - Bias corrected accelerated; CI - confidence interval; CR - complete response; INV - investigator; MAIC - matching-adjusted indirect comparison; OR - odds ratio.
ORs presented for the comparison of glofitamab vs. SCHOLAR-1. ORs >1 favour glofitamab.

7.3.2.3 MAIC results for OS

The HR for OS strongly favours glofitamab vs. SCHOLAR-1 in both the unadjusted and adjusted ( ]) base-case models, with the point estimate from the adjusted model being more favourable for glofitamab than that from the unadjusted model Table 19. The OS results for both scenario 1 and scenario 2 also strongly favour glofitamab vs. SCHOLAR-1 and the 95% CIs exclude 1 and are therefore supportive of the conclusion of the base-case analysis, Table 19.

Table 19: Summary of MAIC results for INV-assessed OS.

Method for estimating HR	
Unadjusted Cox model	
Bootstrap median OS (95% percentile CI) weighted Cox model	
Bootstrap median OS (95% BCa CI) weighted Cox model	

Abbreviations: BCa - bias corrected comparison; OS - overall survival.
HRs presented for the comparison of glofitamab vs. SCHOLAR-1. HRs <1 favours glofitamab.

A summary of the KM curves are provided for the base-case in Figure 14. The KM curves scenario 1 and scenario 2 can be found in Figure 46 and Figure 47, respectively, in appendix F.

[redacted]

Conclusion of the MAIC

A series of MAIC analyses were conducted to compare the efficacy of glofitamab in NP30179 vs that of chemotherapy +/- R in patients included in the SCHOLAR-1 retrospective study. The MAIC results indicate that there is a relatively strong evidence in support of glofitamab being superior to chemotherapy +/- R regimens (+/- ASCT) administered in SCHOLAR-1 with respect to OS, ORR and CR. The conclusions from the MAIC results were consistent between the base case and the sensitivity analyses conducted. It is, however, important to interpret these results in the context of the limitations associated with the analyses. There were misalignments across NP30179 and SCHOLAR-1 in terms of inclusion/exclusion criteria. Although filtering procedures using common eligibility criteria related to the prognostic factors/effect modifiers of interest were applied (where possible) across cohorts to improve population overlap prior to conducting any MAIC, this was not always feasible. For example: SCHOLAR-1 enrolled patients with ECOG PS >1 (~14%) as well as 2L DLBCL patients (the proportion of 2L patients was ~28%) rather than 3L+ patients only. Second line patients were not enrolled in the NP30179 ITT population, and could not be excluded from the analysis, which may have biased the results (overall direction is unclear). A sizeable proportion of patients in SCHOLAR-1 (~30%) underwent stem-cell transplantation after determination of refractory status. This was higher than the proportion of patients who received stem-cell transplantation (~9%) or stem-cell transplantation/CAR-T cell therapies (~18%) as subsequent therapies in the ITT population in NP30179 initially considered for the analyses, and may have biased the results in favour of SCHOLAR-1. It was not possible to adjust for all known prognostic factors and effect modifiers, as they were not reported in SCHOLAR-1. In addition, there were misalignments across NP30179 and SCHOLAR-1 in terms of endpoint definitions. For example, ORR and CR results should be interpreted with caution, as tumour responses were assessed using the Lugano criteria in NP30179 vs. the 1999 IWG response criteria for SCHOLAR-1. Given the phase 2 single-arm study data currently available in support of glofitamab, and the lack of data for the relevant comparators specifically in 3L DLBCL, every effort has been made to derive the most robust possible indirect estimates of relative efficacy for this innovative therapy. These analyses indicate that glofitamab is a highly effective therapy that provides clinically meaningful improvements in survival outcomes compared with current chemotherapy regimens +/- R. Glofitamab therefore provides a much-needed targeted treatment option in 3L patients with DLBCL.

7.3.2.4 Narrative comparison of PFS

Data on PFS was not reported in SCHOLAR-1, but the median PFS was reported for the 191 patients included in the observational MDACC study, and the three-year PFS was reported for 396 patients in the clinical trial CORAL.

As outlined in section 7.2.5, the median PFS was 2.8 months (95% CI: 2.4-3.3 months) in MDACC, and the three-year PFS was 37% (95% CI: 31%-42%) in CORAL with no significantly difference between the R-ICE and R-DHAP arms (31% and 42%, respectively; P=0.4). In NP30179 evaluating glofitamab, the median IRC-assessed and INV-assessed PFS were [redacted], respectively. Both of the median PFS values for patients treated with glofitamab, are higher compared to the one reported in the MDACC study, especially the ICR-assessed PFS is considerably higher for glofitamab, [redacted] compared to 2.8 months in MDACC. Though there is a difference in favour of glofitamab when comparing PFS in the ITT population in NP30179 to the population in the MDACC study, the lack of baseline characteristics in MDACC (see Appendix C), raises uncertainties in the comparability of the patient populations, and this should be taken into account when comparing the PFS values. Median age is, however, lower in MDACC compared to NP30179, 56 years and 66 years, respectively, and the shorter PFS in MDACC, is therefore not driven by an older population.

The three-year PFS was not available in NP30179 as it had not been reached at the CCOD of June 15, 2022 and can therefore not be compared to the three-year PFS reported in CORAL.

7.3.2.5 Narrative comparison of HRQoL

In NP30179, HRQoL was assessed using the EORTC QLQ-C30 and the FACT-Lym LymS questionnaires whereas the FACT-G including the lymphoma specific and neurologic toxicity subscales was used to assess HRQoL in LY.12 (only reported a the total score).

Generally, HRQoL reported in NP30179 was stable during treatment, at treatment completion and post treatment whereas patients in LY.12 reported more fluctuation over time (refer to section 7.2.6). Further, while there was only small variations from baseline throughout the assessment in NP30179, mean scores in LY.12 were all below the baseline assessment. This may indicate that patients treated with chemotherapy, experience a lower HRQoL as compared to patients treated with glofitamab. For both studies, clinically meaningful improvements and deteriorations were found at most point of assessment; however, as the definition of when such were reached for FACT scores differed between studies, it is difficult to compare data.

A direct comparison of HRQoL across patients in NP30179 and LY.12 is difficult to perform due to the used of different assessment tools, and differences in the definitions of when a clinical meaningful change is seen. However, generally patients treated with glofitamab seem to have a more stable and slightly better HRQoL as compared to patients treated with chemotherapy.

7.3.2.6 Narrative comparison of safety data

AEs

When looking at the safety profile for glofitamab that was demonstrated in the safety-evaluable population in NP30179, the most common AEs (all grades) that occurred in more than 10% of the population, were CRS, neutropenia, anemia and thrombocytopenia. When tuning in specifically on grade 3-4, these were experienced by 57.8% of the population. The most commonly reported occurring in more than 5% of the population were neutropenia, anemia, thrombocytopenia, and hypophosphatemia. These were categorized as immune system disorders (CRS), blood and lymphatic system disorders (neutropenia, anemia, thrombocytopenia), and metabolism and nutrition disorders (hypophosphatemia).

AEs were not reported extensively in either LY.12 nor the CORAL study. In the LY.12 study, grade 3-4 AEs were seen in 47% and 61% of the patients in the R-GDP-arm and R-DHAP-arm, respectively. The proportion of patients in the safety-evaluable population in NP30179 with a grade 3-4 AE was therefore higher than the R-GDP arm, but lower than the R-ICE arm in the LY.12 study. In the CORAL study total numbers of grade 3-4 AEs were not reported. However, as part of SAE reporting, grade 3-4 AEs were reported for specific event terms such as serious infection with or without neutropenia and renal toxicity (Table 14). When adding those numbers together, 24% experienced grade 3-4 AEs in the R-ICE arm and 30% in the R-DHAP. Whereas serious infections seems to be the most commonly reported AE (grade 3-4) in the CORAL study, and also the most commonly reported SAE in the LY.12 study, the most commonly reported grade 3-4 AE in the NP30179 study was neutropenia/neutrophil count decreased. CRS was a commonly reported AE (any grade) in the NP30179, but only 3.9% had grade 3-4 CRS. Since serious infections were also reported in NP30179, these rates will be compared in more detail between the interventions in the below section when describing SAEs.

SAEs

SAEs occurred in [redacted] of the safety-evaluable population in NP30179. The most common SAEs which occurred in more than 3% of the population were CRS, sepsis, COVID-19, COVID19-pneumonia and tumour flare. Grouping infections, [redacted] were reported as serious infections.

In LY.12, the proportion of patients experiencing a SAE, was not reported. However, SAEs occurring in at least 5% of patients was reported. The most common SAEs in both arms were infections with and without neutropenia (13% in the R-GDP arm and 16% in the R-DHAP arm). Additionally, SAEs in the R-GDP arm which occurred in more than 3% of the population were thrombosis/embolism, fatigue, nausea, vomiting and febrile neutropenia. In the R-DHAP arm, they were the same, but also including syncope. Comparing the proportions of all serious infections in the R-GDP arm in the LY.12 study (6% + 7% = 13%) to the proportion of patients experiencing serious infections [redacted] in NP30179, the infection rates were slightly higher in the NP30179 study. Likewise, comparing the proportions of all serious infections in the R-DHAP arm (9% + 7% = 16%) to the proportion of patients experiencing serious infections [redacted] in NP30179, these were also slightly higher in the NP30179 study.

In the CORAL study, 29% of patients in the R-ICE arm and 35% of the patients in the R-DHAP arm experienced at least one SAE as compared to the total of 48.7% of the safety-evaluable population in NP30179. In both the R-ICE and the R-DHAP arm, the most common SAEs were infections. The rate of serious infection concurrent with grade 3-4 with and without neutropenia were 17% and 6%, respectively in the R-ICE arm and 16% and 8%, respectively, in the R-DHAP-arm. Where serious infection rates were slightly higher in the NP30179 study than in the LY.12 study (both arms), this was the opposite for the CORAL study. In the R-ICE arm they were 23 % (17% + 6%) and in the R-DHAP arm they 24 % (16% + 8%). Overall, glofitamab therefore seems to be causing more serious infections than R-GDP, but less than R-ICE, but when comparing to R-DHAP the results are inconclusive.

Conclusion

[redacted]

- AEs of any grade was reported in NP30179, but not in CORAL nor LY.12. In NP30179, the most common AEs (all grades) that occurred in more than 10% of the safety-evaluable population, were CRS, neutropenia, anemia and thrombocytopenia.
- CRS was the most commonly reported AE in NP30179, however, only [redacted] of the safety population experienced CRS grade 3-4. Most CRS were reported during the first glofitamab treatment cycle, and of the grade ≥2 CRS, these were resolve in [redacted] patients by ASTCT 2019 grading and [redacted] patients by Lee 2014 grading. The CRS AEs were therefore manageable and predictable.
- The proportion of patients experiencing grade 3-4 AEs was comparable across the safety populations in NP30179 and LY.12. In CORAL, the total proportion of patients experiencing grade 3-4 AEs was not reported.

- The most commonly reported grade 3-4 AE in the NP30179 study were neutropenia, anemia, thrombocytopenia and hypophosphatemia and therefore mainly related to the immune system and the blood and lymphatic system. Serious infections seemed to be the most commonly reported AE (grade 3-4) in the CORAL study, and also the most commonly reported SAE in the LY.12 study.
- In NP30179, SAEs occurred in [redacted] of the safety-evaluable population. In the LY.12 study, the total number of patients experiencing one or more SAEs was not provided, but in CORAL it was reported to be 29% in the R-ICE arm and 35% in the R-DHAP. SAEs therefore seemed to occur more frequently in NP30179 compared to the CORAL study.
- The most common SAEs which occurred in more than 3% of the safety-evaluable population in NP30179 were CRS, sepsis, COVID-19, COVID19-pneumonia and tumour flare.

The differences in baseline characteristics between study populations, which have not been adjusted for in the narrative comparison, may impact the experienced AEs. This, combined with the limited safety data available in the CORAL study and the LY.12 study, makes an overall conclusion of the safety profiles of glofitamab in comparison to R-DHAP, R-ICE and R-GDP subject to uncertainties.

8. Health economic analysis

8.1 Model

8.1.1 Model structure

A three-health state partitioned survival model is the structure used in the cost-effectiveness analysis to 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 submissions to the DMC (38, 73, 74).

The model structure and definition of health states is presented in Figure 15. Patients must be in one of the three mutually exclusive health states at the end of each seven-day model cycle. The three health states are: progression-free survival, post-progression survival (PPS), and death. All patients are progression-free at the start of the model. The use of a pre-progression, post-progression and death health states is the same as in the axicabtagene ciloleucel (Yescarta), polatuzumab + bendamustine and rituximab (Pola+BR), and tisagenlecleucel-T (Kymriah) assessments. The structure for these three assessments were deemed appropriate and considered acceptable by both AMGROS and the DMC (38, 73, 74).

Each health state is associated with costs and utility values. The percentage of patients in each health state at each model cycle is based on clinical data, extrapolated clinical data, enabling to accrued QALYs and costs over the model time horizon.

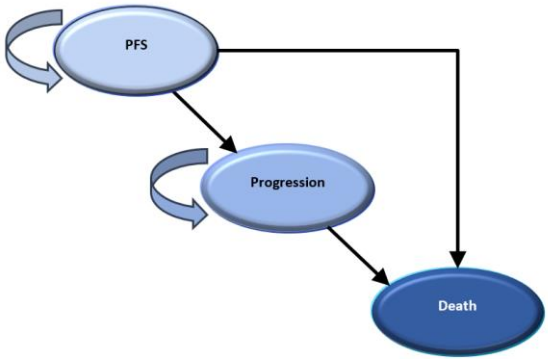


Figure 15: Model structure.

8.1.2 Health states

Progression free survival

PFS is the initial state in which all patients enter the model.

The proportion of patients in the PFS state over time is determined by the PFS curves modelled based on from the NP30179 study data for glofitamab, and relevant data for chemotherapy regimens +/- R (as detailed in Section 7).

Post-progression survival

The PPS state accommodates all patients who have experienced disease progression but have not died yet. The proportion of all patients in this state is calculated as the difference between the proportion of patients who are 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 15.

Death state

Death is as an absorbing state meaning that all patients eventually enter this state and cannot leave it. The proportion of patients alive at a given point in time is determined by the OS results for glofitamab and R-chemotherapy , from an indirect comparison of the NP30179 trial and the SCHOLAR-1 retrospective study using the MAIC methodology (as detailed in section 7.3).

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 (75). The model uses a lifetime horizon of 40 years, considered to represent a lifetime horizon for patients. Given the mean age of 63 years in the NP30179 trial and the fact that this treatment is for patients with R/R DLBCL after a minimum of two prior lines of systemic therapy, 40 years was considered a relevant approximation of a lifetime time horizon (75, 76).

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, supportive care, adverse events, patient time, and transportation. Indirect costs are not included, in line with the DMC's guidelines (75).

8.1.5 Cycle length, Discounting, and Half-cycle correction

Cycle length

A weekly cycle length is 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 estimations of the length of time patients remain in the health states and more flexibility and accuracy in relation to

costing. Furthermore, this cycle length was consistent with the cycle length used in the previous assessment of the Pola+BR for treatment of R/R DLBCL (73).

Discounting

A discount rate of 3.5% until year 35 and 2.5% from year 35-70 is applied to costs and efficacy, as defined by the Danish Ministry of Finance and in the DMC guidelines (75, 77).

Half-cycle correction

It is 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 is 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 is not expected to have a large impact on the results.

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

In the model, data from the NP30179 study (Sections 7) have been used to inform the clinical efficacy (OS and PFS), safety and time on treatment of glofitamab for the treatment of patients with R/R DLBLC who have received ≥2 prior systemic therapy lines. The NP30179 study is currently the only study available to provide clinical evidence for glofitamab in the intended population and can therefore be considered the best available evidence to inform the model.

While NP30179 is the source of glofitamab data for the cost-effectiveness analysis, it is a single-arm trial therefore no comparator data are available within the trial. Consequently, an ITC was required to provide comparative evidence vs. chemotherapy regimens +/- R for OS. The ITC employed a MAIC approach as described in Section 7.1.3. In SCHOLAR-01 multiple chemotherapy +/- R regimens was used, however to reduce the complexity of the health economic analysis, only R-ICE and R-DHAP is compared to glofitamab. R-ICE and R-DHAP will be referenced as R-chemotherapy throughout the health economics analysis unless otherwise stated.

As PFS data were not reported in SCHOLAR-1, a PFS curve for the R-chemotherapy was generated by applying a HR for PFS vs. OS to the extrapolated OS curve, with the implicit assumption that the cumulative hazard function for PFS would be proportional to cumulative hazard function for OS as done in the NICE submission, TA567, tisagenlecleucel for R/R DLBCL (78). Given the high correlation between PFS and OS in NHL, this assumption was considered to be reasonable (79). The ratio that was applied (0.65) was based on the mean cumulative HR from the CORAL study, which was one of the randomised controlled trials (RCT) included in the SCHOLAR-1 meta-analysis (11, 78).

Table 20 below presents some of the key parameters used in the health economic model (base case) and how these have been obtained.

Table 20: 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) Glofitamab	See section 7	Log-normal	PFS for glofitamab is based on the extrapolated PFS curve from the NP30179 trial ITT population (17)
Progression-free survival (PFS) R-chemotherapy	See section 8.2.1	HR: 0.65	PFS for R-chemotherapy is based on a ratio from OS to PFS (0.65) from tisagenlecleucel NICE submission applied to R-chemotherapy OS (78)
Overall survival (OS) Glofitamab	See section 7	Log-normal	OS for glofitamab is based on the extrapolated OS curve from MAIC (weighted curve from NP30179) (6, 17)
Overall survival (OS) R-chemotherapy	See section 7	HR: 0.42	HR from MAIC (0.42) applied to glofitamab OS curve (6, 17)
Time to off treatment (TTOT), Glofitamab	See section 8.3.3	KM curve (mean in months: 11.89)	TTOT for glofitamab is based on data from the NP30179 trial for the actual duration using the KM curve
Time to off treatment (TTOT), R-chemotherapy	No data available for the TTOT for R-chemotherapy . Instead, a Danish clinical expert was consulted and estimated a maximum of **4 treatments cycles** administered Q3W	Maximum of 4 treatment cycles (84 days).	TTOT data is not available. TTOT is set equal to the selected parametric distribution for PFS, capped at the treatment-specific maximum number of cycles estimated by a Danish clinical expert.
HSUV PFS (on treatment)	See section 8.4	0.73	Based on EORTC-QLQ-C30 from NP30179 trial mapped to EQ-5D-3L (Indirect) UK tariff (80).
HSUV PFS (off treatment)	See section 8.4	0.77	Based on EORTC-QLQ-C30 from NP30179 trial mapped to EQ-5D-3L (Indirect) UK tariff (80).
HSUV PPS	See section 8.4	0.63	Based on EORTC-QLQ-C30 from NP30179 trial mapped to EQ-5D-3L (Indirect) UK tariff (80).
Costs	See section 8.5		Medicinpriser.dk, interaktiv-drg.dk, labportalen.dk (81-83)

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 NP30179 trial and LY.12 study (13, 17) for patients in the Glofitamab arm and the R-chemotherapy arm respectively.

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

8.2.2.1 Patient population

Table 21 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 treated adult patients (at least 2 prior systemic treatments) with R/R DLBCL. This patient group is consistent with the EMA approved label for glofitamab in DLBCL.

The patient population characteristics are based on Individual Patient Data (IPD) from the safety population of the NP30179 trial, which include patients from the ITT population except one patient who did not receive at least one treatment, resulting in a total of 154 patients. The average age and proportion of females are used to characterise patients upon entering the model. In addition, using IPD data allows to derive distributions of patients' weight, applied to the dosing regimens of pharmaceuticals which administration depends on weight or body surface area (BSA). Similarly, the age distribution of patients is applied to Danish lifetables to derive the general population mortality. Using the average age and weight instead of distribution does not have an influential impact on the model results.

As stated in section 8.1.3, patients enter the model at an average age of 63 years, as informed by the NP30179 study for the R/R DLBCL population. 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 ECOG PS 0-1 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 NP30179 broadly reflects patients with R/R DLBCL in Danish clinical practice.

Table 21: Patient population.

Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Age mean	63	63	67 (median) (24)
Gender (% male)	64.9%	64.9%	More prevalent in men (84)
Weight (kg)	74.95	74.95	NA
Height (cm)	170.52	170.52	NA

Important baseline characteristics	Clinical documentation / indirect comparison etc.	Used in the model	Danish clinical practice
Body Surface Area (m^2)	1.86	1.86	NA
Patient population	Adults with R/R DLBCL who have received at least 2 prior lines of therapy (IPD data from the NP30179 trial - safety population)	Adults with R/R DLBCL who have received at least 2 prior lines of therapy (IPD data from the NP30179 trial - safety population)	Adults with R/R DLBCL who have received at least 2 prior lines of therapy

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice is described in section 5.3. Inputs regarding glofitamab in the model are informed by the clinical study NP30179 most recent CCOD June 15 2022.

Glofitamab was given the following label by EMA: "Glofitamab as monotherapy is indicated for the treatment of adult patients with R/R DLBCL, after two or more lines of systemic therapy".

The administration of glofitamab occurs through IV infusion, limited to a maximum of 12 treatment cycles every Q3W (21-day treatment cycle lengths). The initial treatment cycle involves a step-up dosing schedule with a 2.5 mg dosage on Day 8 (D8) and a 10 mg dosage on D15. Subsequently, treatment cycles 2 to 12 require a 30 mg dosage. The glofitamab step-up dosing schedule, along with pre-treatment involving a single dose of obinutuzumab (1000 mg) seven days before the first dose of glofitamab, serves to reduce the risk of CRS (1).

Table 22: Intervention.

Intervention	Clinical documentation (1)	Used in the model	Expected Danish clinical practice (1, 85)
Posology	Step-up schedule with 2.5mg in D8, 10mg in D15 and 30mg in treatment cycle 2-12 (every 3rd week)	Same as clinical documentation	Same as clinical documentation
Length of treatment (time on treatment) (mean/median)	79.0 days (Median) 5.0 Treatment cycles (Median)	Maximum 12 treatment cycles	Maximum 12 treatment cycles
Criteria for discontinuation	Consider end of treatment if unacceptable toxicity (86)	Consider end of treatment if unacceptable toxicity	Consider end of treatment if unacceptable toxicity
The pharmaceutical's position in Danish clinical practice	3L+	3L+	3L+

8.2.2.3 Comparators

According to the Danish clinical guidelines for DLBCL, there is no evidence to support one standard treatment for 3L+ R/R DLBCL patients (10). As described in section 5.2.1, it was found that R-DHAP, R-ICE and R-GDP were the most relevant comparators. In the following health economics analysis, only R-ICE and R-DHAP have been used to simplify

the model. These two therapies are referred to as R-chemotherapy in the model. The exclusion of R-GDP was validated by a Danish clinical expert within DLBCL (85). Consequently, patients in the health state of PFS receive R-DHAP or R-ICE.

The glofitamab data for the model originates from NP30179, a single-arm study without any comparator data, thus a MAIC was necessary to provide comparative evidence against R-chemotherapy. Section 7.1.3 outlines that the MAIC for chemotherapy regimens +/- R employs data from the SCHOLAR-1 study, which assumes that the efficacy of R-DHAP and R-ICE is equivalent. Thus, the only difference between the two treatments is the associated costs. As such, the model incorporates an input for the proportion of patients who will receive R-DHAP and R-ICE, respectively. For the base case, it is assumed that 50% of patients will receive R-DHAP and 50% will receive R-ICE. Nonetheless, two scenario analyses shall be undertaken to examine the effects of altering this proportion, while considering a proportion of 70/30% for every treatment regimen.

Table 23: Comparator.

Comparator	Clinical documentation (including source) (38, 85, 87, 88) (89-92)	Used in the model (number/value including source)	Expected Danish clinical practice (including source)(38, 85, 87, 88) (89-93)
Posology	**R-DHAP:** Rituximab: 375 mg/m^2, IV Dexamethasone: 160mg fixed, oral Cytarabine: 4000mg, mg/m^2, IV Cisplatin: 100mg mg/m^2, IV **R-ICE:** Rituximab: 375 mg/m^2, IV Ifosfamide: 5000 mg/m^2, IV Carboplatin: 450mg, AUC, IV Etoposide: 300mg mg/m^2, IV	Same as clinical documentation	Same as clinical documentation
Length of treatment (time on treatment) (mean/median)	4 cycles	4 cycles	4 cycles
The pharmaceutical's position in Danish clinical practice	Best available treatment	Same as clinical documentation	Same as clinical documentation

8.2.2.4 Relative efficacy outcomes

The relative efficacy outcomes are summarized in section 7. As data on PFS is not presented in SCHOLAR-1, PFS was generated applying the same approach as done for NICE TA567 as described in section 8.2.1 (78).

In the previous DMC assessment of Pola-BR for R/R DLBCL, the DMC prepared a protocol where PFS and OS were considered as important and critical efficacy outcomes, respectively. This is in line with the outcomes that are generally used within oncology.

Consequently, the included efficacy outcomes are considered highly relevant to determine the cost-effectiveness of glofitamab in 3L+ treatment of DLBCL, see Table 24 and Table 25.

Table 24: Clinical efficacy outcomes used in the model.

Clinical efficacy outcome	Clinical documentation	Used in the model (value)
Progression-free survival (PFS)	NP30179 trial and TA567	See Table 20
Overall Survival (OS)	NP30179 trial and SCHOLAR-1 (ITC)	See Table 20

Table 25: Relevance of clinical efficacy outcome for Danish clinical practice

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
Progression-free survival (PFS)	See section 7	Traditionally accepted in evaluations of drugs in oncology	Traditionally accepted in evaluations of drugs in oncology
Overall Survival (OS)	See section 7	Traditionally accepted in evaluations of drugs in oncology	Traditionally accepted in evaluations of drugs in oncology

8.2.2.5 Adverse reaction outcomes

Due to the sparsity of available data, an ITC for safety outcomes could not be conducted. Accordingly, the AE reaction outcomes and their corresponding frequencies for the glofitamab arm are derived from the safety-evaluable population of the NP30179 study, which consists of 154 patients. The selection of AE reaction outcomes for the R-chemotherapy arm is based on the DHAP arm in the LY.12, which involves 304 patients (94).

However, the model allows the selection between two sources: the safety population of the LY.12 study, or the study conducted by Witzig et al. in 2008, which comprises 57 patients in the safety population (94, 95). The impact on the results through a scenario analysis utilizing AEs from Witzig et al. 2008.

All AEs considered in the analysis have a grade ≥3, which is defined as a serious event requiring hospitalisation to potential life-threatening consequences (96). The number of occurrences and the number of patients experiencing the AE are included on the sheet "Adverse Events" for each treatment arm. The AEs included in the cost-effectiveness model are listed in Table 26.

Table 26: Adverse reaction outcomes.

AEs	Grade	Total numbers of AEs, Glofitamab, NP30179 (N=154)	Total numbers of AEs, R-chemotherapy , LY.12 (N=304)	Total numbers of AEs, R-chemotherapy , Witzig et al. 2008 (N=57)
Anaemia	≥ 3	[redacted]	0	13
Anorexia	≥ 3		0	3

Constipation	≥ 3	[redacted]	0	0
Diarrhoea	≥ 3		0	4
Fatigue	≥ 3		28	7
Febrile neutropenia	≥ 3		70	13
Hypokalaemia	≥ 3		0	13
Hypomagnesemia	≥ 3		0	2
Hypophosphatemia	≥ 3		0	0
Infection	≥ 3		22	4
Insomnia	≥ 3		0	0
Lymphopenia	≥ 3		0	0
Nausea	≥ 3		25	10
Neutropenia	≥ 3		28	45
Renal failure	≥ 3		0	2
Thrombocytopenia	≥ 3		0	52
Thrombosis/embo-lism	≥ 3		18	0
Tumor flare	≥ 3		0	0
Vomiting	≥ 3		21	7

8.3 Extrapolation of relative efficacy

Consistent with recommendations in the NICE DSU technical support document 14 (97), the selection of base case parametric functions for PFS and OS for glofitamab 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.

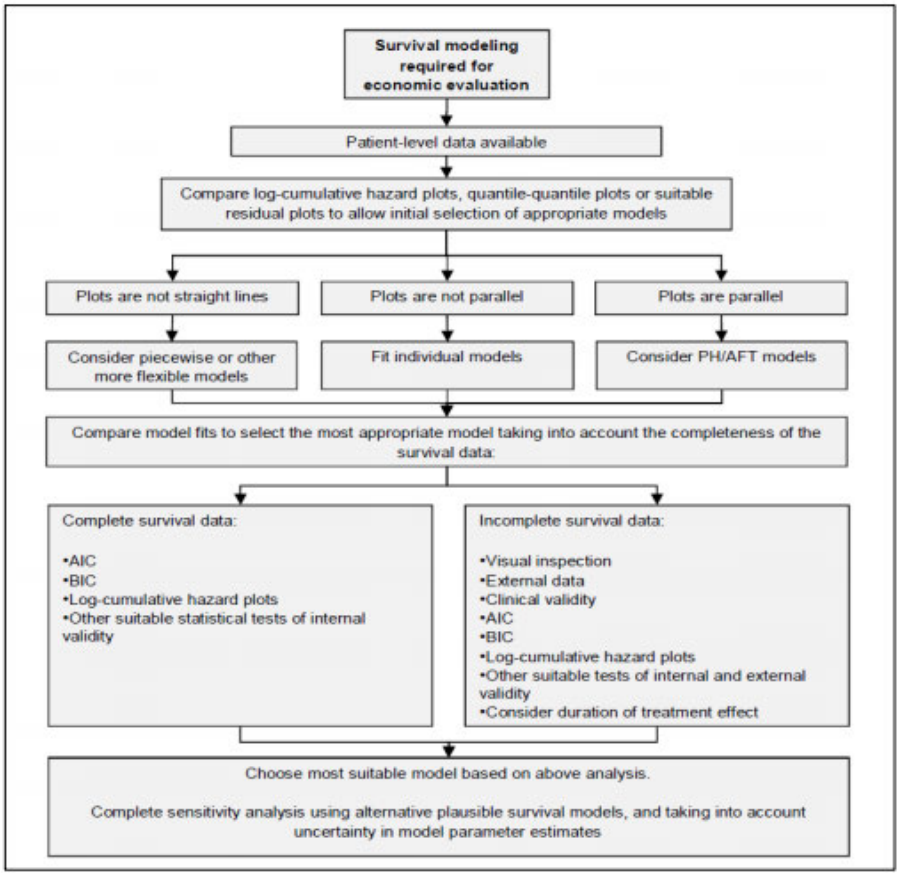


Figure 16: Survival Model Selection Process Algorithm by NICE DSU (98).

In order to extrapolate beyond the NP30179 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 NP30179 is applied for the glofitamab ITT population. Description on PFS for glofitamab from the NP30179 trial and graphs is presented in the clinical section 7.1.2.

In the absence of PFS data reported for the SCHOLAR-1 meta-analysis, the MAIC for chemotherapy +/- R lacked PFS data. Instead, the base case PFS for R-chemotherapy use the same approach as in the tisagenlecleucel (Kymriah) NICE submission (78). PFS for the chemotherapy +/- R was generated by applying a HR for PFS vs. OS to the extrapolated OS curve for chemotherapy +/- R, with the implicit assumption that the cumulative hazard function for PFS

would be proportional to hazard function for OS. Given the high correlation between PFS and OS in NHL, this assumption was considered to be reasonable (79). The HR of 0.65 was based on the mean cumulative HR from the CORAL study (11), which was one of the RCTs included in the SCHOLAR-1 meta-analysis.

8.3.1.1 Choice of parametric distribution

Table 27: Parametric distribution selected for PFS for glofitamab.

PH-Assumption	No PFS data for chemotherapy +/- R to test PH between glofitamab and chemotherapy +/- R.
Distribution selected – Glofitamab	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	No smoothed hazard plots available for PFS
Clinically plausibility	A Danish clinical expert has evaluated that a log-normal distribution would be clinically plausible for patients with R/R DLBCL, which is consistent with the log-normal parametric function previously chosen by the professional committee of the DMC for both PFS and OS in the Pola+BR submission who assessed the curves to be realistic (73, 85).
Comments	Choosing log-normal distribution for extrapolation generates a realistic and clinical plausible result. AIC and BIC values were very similar between the different 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.

Test of PH assumption

Due to the unavailability of PFS data for chemotherapy +/- R, testing the PH assumption is not feasible.

Goodness of fit

Fit statistics in form of AIC and BIC are presented for all curves in Table 28. 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 the most 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. Of the curves available, Log-normal gave a more likely estimate of a clinically plausible extrapolation and hence was chosen in the base case (Figure 17).

Table 28: AIC and BIC for PFS with ranks in brackets.

Parametric distribution	Glofitamab	
	AIC (rank)	BIC (rank)
Exponential	639.03 (7)	642.08 (7)
Weibull	631.38 (5)	637.47 (5)
Log-normal	612.35 (2)	618.44 (2)
Gen Gamma	608.08 (1)	617.21 (1)
Log-logistic	617.42 (4)	623.51 (4)
Gompertz	616.87 (3)	622.96 (3)
Gamma	635.19 (6)	641.28 (6)

Figure 17: PFS standard parametric extrapolation functions – glofitamab.

8.3.2 Overall survival

OS-data from the MAIC is applied using weighted curves and HR from the analysis. For glofitamab, the extrapolated OS curve for the weighted population is used. For R-chemotherapy, the HR from glofitamab to chemotherapy +/- R is used (0.42). Description of the MAIC for glofitamab and chemotherapy +/- R and graphs (Figure 14) presented in the clinical section 7.3.2, and in Appendix F (Figure 46 and Figure 47).

8.3.2.1 Choice of parametric distribution

Table 29: Parametric distribution selected for OS for glofitamab.

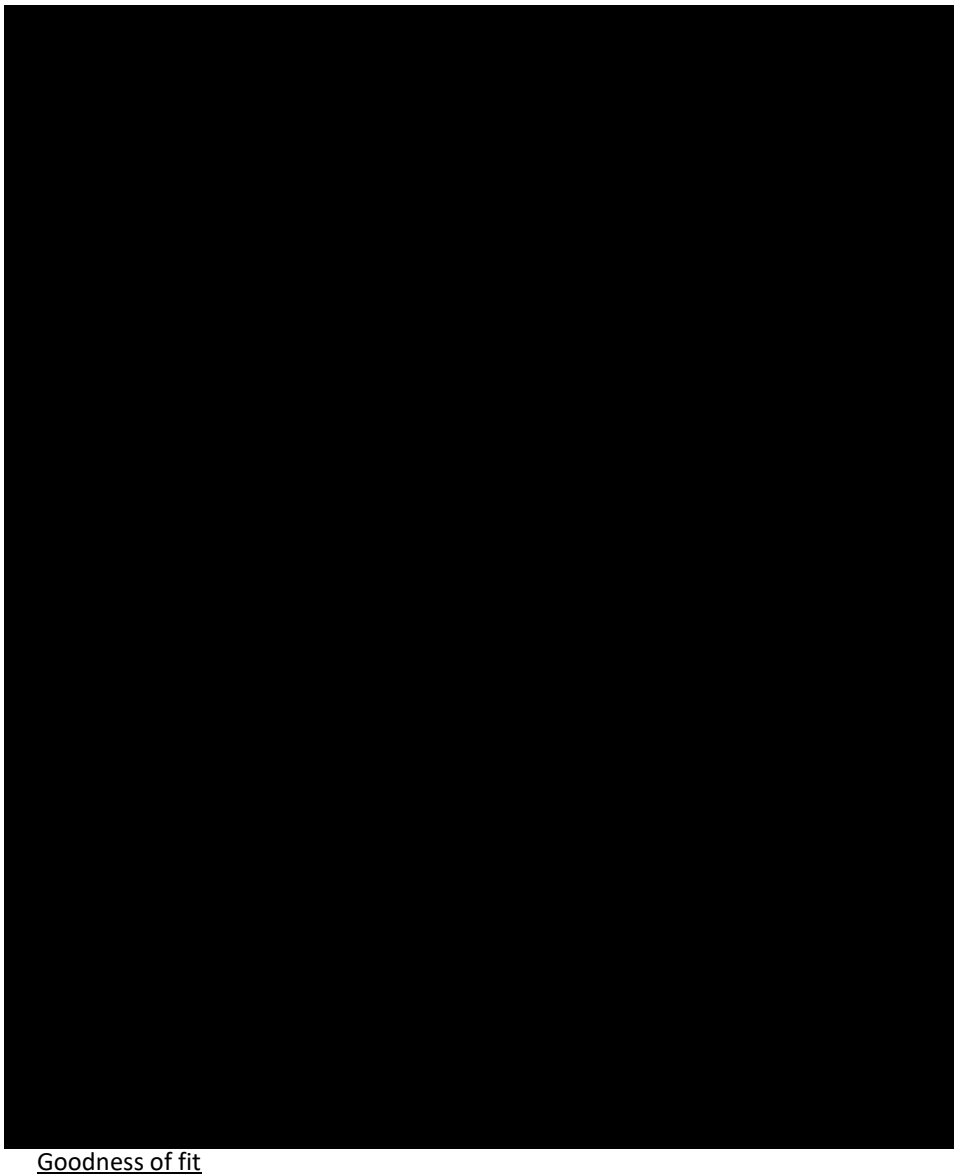
PH-Assumption	PH assumption is assumed, log-log (cumulative) hazard plots are relatively parallel and do not cross.
Distribution selected – Glofitamab	Log-normal
AIC-rank	3rd
BIC-rank	3rd

Visual Inspection	Good visual fit of the extrapolated curves to the observed KM data
Smooth Hazards plot	Despite immature data, Figure 18 demonstrates the behaviour of hazards that the clinical expert considers clinically plausible (The hazard rise due to the mortality of non-responders, but the composition of the patient group may also shift as long-term responders and survivors become a more significant portion of the cohort, resulting in a decrease in hazard), see Appendix G Extrapolation
Clinically plausibility	A Danish clinical expert assessed that, based on biology, the hazard function should have an initial increase followed by a decrease. This translates to a log-normal or log-logistic parametric function, however, the clinical experts assessed that a log-normal distribution would be most reasonable and clinical plausible for patients with R/R DLBCL (17). This is consistent with the log-normal parametric function previously chosen by the professional committee of the DMC for both PFS and OS in the Pola+BR submission as this was assessed clinical realistic (73, 85). Log-normal was likewise chosen for PFS and OS in the base case of the NICE assessment for tisagenlecleucel (Kymriah) (78).
Comments	Choosing log-normal for extrapolation generates a realistic and clinical plausible result, considering the expected hazard profile and statistical fit. This distribution has been used to long-term extrapolation in previous submission for Pola+BR, R/R DLBCL (73, 85).

[redacted]

Test of PH assumption

The log cumulative hazard plot and Schoenfeld residuals (Figure 19) showed that the plots for glofitamab and R-chemotherapy are relatively parallel and does not cross at any time. This indicates that the proportional hazard assumption is not violated, and thus is assumed.



Goodness of fit

Fit statistics in form of AIC and BIC are presented for all curves in Table 30. 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 considered 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. 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 (Figure 20). From the smoothed hazard plot and from the clinical expectation, the hazard of death is not constant, but instead will have at least one turning point. The functional form of a Log-normal will have a turning point. At the same time the log-normal, provides one of the best statistically fitting curve (Table 30) and hence was chosen in the base case.

Table 30: AIC and BIC for OS with ranks in brackets.

Parametric distribution	Glofitamab	
	AIC (rank)	BIC (rank)
Exponential	122.32 (1)	124.62 (1)
Weibull	124.01 (5)	128.70 (5)
Log-normal	122.87 (3)	127.48 (3)
Gen Gamma	124.86 (7)	131.78 (7)
Log-logistic	123.10 (4)	127.71 (4)
Gompertz	122.78 (2)	127.39 (2)
Gamma	124.21 (6)	128.82 (6)

Abbreviations: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion

[redacted]

8.3.3 Treatment duration

Extrapolation of Treatment duration

In the NP30179 trial glofitamab 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 for glofitamab in the cost-effectiveness model. The uncertainty around the treatment duration is explored in the probabilistic sensitivity analysis (PSA) using a multi normative function which accounts for the variance and covariance between parameters.

8.4 Documentation of HRQoL

8.4.1 Overview of health state utility values (HSUV) used in the health economic model

Within the cost-effectiveness model, there are two sets of utility values that can be applied, in addition to an option where utilities for proximity to death are applied, see Table 31. These proximity to death utilities were estimated only using the indirect mapping algorithm from Longworth et al, 2014 (80).

In the NP30179 study, the EORTC QLQ-C30 and the FACT-Lym LymS were the PRO scales used to assess the part III dose-expansion cohorts (pivotal cohort and mandatory dexamethasone cohort). All utilities were estimated through

a mixed regression model on post-baseline utilities only while controlling for centralized baseline utilities and using random intercepts for each patient. Therefore, the base case analysis uses utility values estimated through EORTC-QLQ-C30 mapped to EQ-5D-3L (direct and indirect mapping provided). Details of the approach used, and choice of mapping algorithm can be seen in Appendix I Mapping of HRQoL data. **Missing PRO-data is not imputeret, but treated as missing.**

The health state utility values utilized in the model were estimated through the EORTC-QLQ-C30 and mapped to EQ-5D-3L from the NP30179 study (Indirect mapping). As per the Danish guidelines, it is recommended to map health state utilities to Danish utility tariffs. However, due to the unavailability of a mapping algorithm from EORCT to EQ-5D-3L/5L Danish tariff as per the guidelines provided by the DMC, it was not possible to follow the recommended method for Danish utility values (75). Consequently, the model uses utilities with UK tariffs.

The age-adjusted methodology, as described in section 7.3 of the guideline by the DMC, was used to adjust the state utilities applied in the model (75, 99). Table 31 illustrates the HSUV used in the model.

Table 31: Set of utility value in the model.

Source	Treatment status	PFS	PPS
NP30179 Mapped Utility Values (Direct Mapping [UK tariff]), Proskorovsky et al 2014 **(100)**	On Tx	0.772	0.673
	Off Tx	0.836	
NP30179 **Mapped Utility Values (Indirect Mapping [UK tariff]), Longworth et al 2014 (80)**	**On Tx**	**0.729**	**0.629**
	Off Tx	**0.774**	
Scenario - Proximity to death utilities			
Proximity to death utilities (based on EORTC to EQ-5D 3L Indirect Mapping [UK tariff], Longworth et al 2014)	≤ 10 weeks before death (On Tx)	0.684	
	> 10 & ≤ 30 weeks before death (On Tx)	0.733	
	> 30 & ≤ 60 weeks before death (On Tx)	0.729	
	> 60 weeks before death (On Tx)	0.728	
	≤ 10 weeks before death (Off Tx)	0.565	
	> 10 & ≤ 30 weeks before death (Off Tx)	0.720	
	> 30 & ≤ 60 weeks before death (Off Tx)	0.724	
	> 60 weeks before death (Off Tx)	0.796	

8.5 Resource use and costs

Costs and resource use vary depending on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective described in the DMC guidelines (75).

The following section regarding cost and resource use is presented per health state, containing state-specific information regarding drug acquisition costs, administration costs, supportive care costs and AE costs. All costs reported are in Danish kroner (DKK) and were extracted from diagnosis-related groups (DRG) tariffs 2023, official unit cost catalogues, medicinpriser.dk, and labportalen.dk (81, 82, 101-103). All drug costs are reported as pharmacy purchase prices (PPP), where the lowest cost alternative was used in the health economic assessment. Patient and transportation costs were based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states (102).

8.5.1 Drug acquisition cost

PPP is used for all pharmaceuticals in the analysis. The drug acquisition costs are applied to patients in the health state of PFS and PPS in the cost-effectiveness model. Additionally, as described in the abovementioned sections, patients in the 3L treatment (PFS health state) are assumed to receive either glofitamab or R-chemotherapy (R-DHAP/R-ICE). The efficacy information for R-chemotherapy is derived from applying chemotherapies from SCHOLAR-1, while the costs are based on R-chemotherapy.

Treatment costs for subsequent lines of therapies (PPS health state) were also extracted. All drug costs are presented in Table 32. The model selects the cheapest per milligram package available.

Table 32: Drug acquisition cost.

Drug	Route	Small vial (mg)	Small vial (cost DKK)	Large vial (mg)	Large vial (cost DKK)	Source (81)
Glofitamab	IV	2.5	5,827.50	10	23,302.50	Glofitamab
Obinutuzumab*	IV	1,000	23,752.69	N/A	N/A	Obinutuzumab*
Rituximab	IV	100	3,115.99	500	7,789.98	Medcinpriser.dk (2023)
Dezamethasone	Oral	1	133.00	4	176.00	Medcinpriser.dk (2023)
Cytarabine	IV	1,000	100.00	2000	150.00	Medcinpriser.dk (2023)
Cisplatin	IV	50	100.00	100	200.00	Medcinpriser.dk (2023)
Polatuzumab vedotin	IV	30	14,814.26	**140**	**69,133.18**	Medcinpriser.dk (2023)
Bendamustine	IV	25	367.00	100	1,174.00	Medcinpriser.dk (2023)

Drug	Route	Small vial (mg)	Small vial (cost DKK)	Large vial (mg)	Large vial (cost DKK)	Source (81)
Fludarabine phosphate	IV	50	1310.15	N/A	N/A	Medcinpriser.dk (2023)
Ifosfamide	IV	40	380.00	N/A	N/A	Medcinpriser.dk (2023)
Carboplatin	IV	150	84.00	450	203.00	Medcinpriser.dk (2023)
Etoposide phosphate	IV	100	90.00	400	350.00	Medcinpriser.dk (2023)
Cyclophosphamide	IV	50 200	927.15 72.18	500	180.00	Medcinpriser.dk (2023)
Doxorubicin	IV	10 50	150.00 120.00	200	350.00	Medcinpriser.dk (2023)
Vincristine	IV	1	390.00	2	645.00	Medcinpriser.dk (2023)
Prednisolone	Oral	NA	NA	25	12.90	Medcinpriser.dk (2023)
Obinutuzumab	IV	NA	NA	1000	23,753.00	Medcinpriser.dk (2023)
Gemcitabine	IV	1,000	1,000.00	2000	1,200.00	Medcinpriser.dk (2023)
Oxalilplatin	IV	50	145.00	100	240.00	Medcinpriser.dk (2023)

*Pretreatment

Table 33 shows the drug doses and dosing schedule of the intervention and comparators considered in this health economic analysis. Information on the dose and treatment schedule were sourced from the NP30179 study, Odense University Hospitals treatment schedules, Danish clinical expert statement, and SmPCs (1, 38, 85, 87, 88). For treatments that are not administered with a fixed dose, IPD for baseline characteristics has been used using weight distribution from the safety population as mentioned in section 8.1.1.

Table 33: Dosing.

Drug	Dosing	Doses per model cycle (1, 38, 85, 87, 88) .
Glofitamab	2.5mg	1.00*
	10mg	0.33*

Drug	Dosing	Doses per model cycle (1, 38, 85, 87, 88) .
	30mg	0.33*
Obinutuzumab	1,000mg	1.00**
Rituximab	375mg, mg/m^2	Varies from 0.5 to 0.33
Dexamethasone	160mg, fixed	0.33
Cytarabine	4000mg, mg/m^2	0.33
Cisplatin	100mg, mg/m^2	0.33
Ifosfamide	5000mg, mg/m^2	0.33
Carboplatin	450mg, AUC	0.33
Etoposide phosphate	300mg, mg/m^2	0.33

*Step-up doses of 2.5 mg on day 8 of cycle 1 and 10 mg on day 15 of cycle 1, followed by 30 mg on day 1 of cycle 2 through 12 cycles with one cycle lasting 21 days

**Pretreatment: One single dose of obinutuzumab (1000 mg) as a pre-treatment to deplete B-cells 7 days prior to initiation of glofitamab

Abbreviations: R-DHAP - rituximab + dexamethasone + high-dose cytarabine + cisplatin; R-ICE - rituximab + ifosfamide + carboplatin + etoposide; AUC - area under the free carboplatin plasma concentration vs. time curve; mg - milligram, IV - intravenous

Treatment costs at subsequent lines of therapy

Once patients in the model discontinued their initial treatment line after progression, they were assumed to be eligible for all other treatments available at subsequent lines of DLBCL treatment. These are represented in the model as a pool of treatments that can be taken in any order after discontinuation from any arm. The post discontinuation therapy cost was applied once to the proportion of patients who move from the PFS to PPS health state each cycle. This takes into account the mean duration of treatment, the proportion assumed to use each treatment option and the associated cost. As per the statement of a Danish clinical expert it is observed that several patients may not receive further treatment upon experiencing progression in 3L+ treatment. Consequently, to investigate the potential impact of such a situation, a scenario assuming no patients receives subsequent therapy, and the influence on the result.

The mean duration on treatment and proportion of patients receiving different subsequent treatments upon progression on each induction treatment are listed in Table 34 and based on NP30179. The costs associated with each subsequent treatment is listed in Table 35, and shows total cost post discontinuation for glofitamab and R-chemotherapy. Drug acquisition costs for subsequent therapies are presented in Table 32.

Administration costs were assumed to be the same as for IV administration presented in Table 36, section 8.5.2 and are included in the treatment cost per week in Table 35. Subsequent treatment costs are assumed to not apply for patients in long-term remission (progression free after 24 months).

Table 34: Proportion assumed to take each subsequent therapy by arm.

Therapy	Proportion of patients receiving therapy	Mean duration in weeks	Source
R-GEMOX	2.68%	4,50	NP30179 trial
R-chemothearpy	2.68%	2,81	
Other R-chemotherapy regimens	8.93%	4,11	
Other chemo regimens (not including R)	22.32%	5,07	
Pola-BR	8.93%	4,71	
Radiotherapy	15.18%	1,00	
Allogeneic SCT	6,25%	1,00	
Autologous SCT	1,79%	1,00	

Abbreviations: R-GEMOX, rituximab + gemcitabine + oxaliplatin; R-chemotherapy , rituximab + cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone, R-chemotherapy , rituximab chemotherapy; Pola-BR, polatuzumab + vedotin + bendamustine + rituximab; STC, stem cell transplantation.

Table 35: Weekly treatment costs for post-discontinuation including administration (list price).

Therapy	Tx cost/week (incl. admin cost*) (DKK)	Source (81, 83)
R-GEMOX	11,129.33	Medicinpriser.dk, Interaktivdrg.dk, Assumption
R-chemotherapy	9,225.74	
Other R-chemotherapy regimens	10,177.53	
Other chemo regimens (not including R)	1,921.86	
Pola-BR	30,463.33	
Radiotherapy	2,230.00	DRG 2023, 27MP08 - Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedurer: (BWGC1) Konventionel ekstern strålebehandling
Allogeneic SCT	2,005.00	DRG 2023, 17MA98 - Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedurer: (BOQE1) Behandling med stamcellekoncentrat fra autolog knoglemarv
Autologous SCT	2,005.00	DRG 2023, 17MA98 - Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedurer: (BOQE3) Beh.m.stamcellekonc. fra allogen knoglemarv fra familiedonor, (BOQE5) Beh. m. stamcellekonc. fra allogen knoglemarv/fremmed donor
Total post-discontinuation (DKK)		**21,274.81**

Abbreviations: R-GEMOX - rituximab + gemcitabine + oxaliplatin; R-chemotherapy - rituximab chemotherapy; Pola-BR - polatuzumab + vedotin + bendamustine + rituximab; STC - stem cell transplantation.

8.5.2 Administration costs

Table 32, contains information regarding the costs of drugs and the mode of administration for each treatment regimen. Notably, the cost associated with the IV administration of 2,005 DKK (81). In contrast, the oral administration of dexamethasone does not involve any cost, see Table 36. To calculate the administration cost, the proportion of patients receiving each treatment regimen is multiplied by the corresponding price and the frequency of treatment administration within the weeks of treatment, as specified in the model based on the NP30179 trial, Odense University Hospitals treatment schedules, Danish clinical experts, and treatment SmPC, see Table 36 (1, 38, 85, 87, 88) .

Table 36: Administration costs.

Administration form	Unit cost (DKK)	Source (81)
Intravenous (outpatient)	2,005.00	DRG 2023, 17MA98 - 1-dagsgruppe, pat. Mindst 7 år, Diagnose: DC833) Diffust storcellet lymfom, Procedure BWAA6: Medicingivning intravenøst
Oral	0.00	Assumption
Cost per administration of each regime		
Glofitamab, first cycle	4,010.00	Glofitamab, obinutuzumab: IV
Glofitamab, subsequent cycles	2,005.00	Glofitamab: IV
R-DHAP	6,015.00	Rituximab, cytarabine, cisplatin: IV, dexamethasone: oral
R-ICE	8,020.00	Rituximab, ifosfamide, carboplatin, etoposide phosphate: IV

Abbreviations: R-DHAP - rituximab + dexamethasone + high-dose cytarabine + cisplatin; R-ICE - rituximab + ifosfamide + carboplatin + etoposide; mg - milligram; IV - Intravenous

Danish clinical experts estimated that patients will be admitted to the hospital after the first treatment administration with glofitamab. For subsequent doses, patients who experienced Grade ≥2 CRS (16.20%, average between rates according to Lee and ASTCT grading scales in the ITT population) with the previous infusion should be monitored for at least 22 hours after completion of the infusion. Consequently, a DRG tariff of 44,770 DKK was estimated as additional monitoring costs for patients treated with Glofitamab, see Table 37.

Table 37: Glofitamab monitoring cost.

	Value	Source
Glofitamab monitoring cost (DKK)	44,770.00	DRG 2023, 17MA98 - 1-dagsgruppe, pat. Mindst 7 år, Diagnose: (DC833) Diffust storcellet lymfom, Procedure: (ZZ0202) Observation af patient efter undersøgelse/behandling, >=12 timer (lang)
% pf patients experiencing Grade ≥2 CRS	16.20%	NP30179 CSR, taking average between rates according to Lee and ASTCT grading scales

Abbreviations: ASTCT - autologous stem cell transplantation; CRS - cytokine release syndrome

8.5.3 Supportive care costs

In each cycle that a patient remained alive, supportive care costs were implemented and varied between the PFS and PPS health states, regardless of the treatment arm utilized (as indicated in Table 38). These costs are indicative of healthcare resource consumption that is specific to the disease status, rather than the treatment arm employed.

To ascertain the resources included in supportive care for each health state or event, a combination of microcosting and tariff methods were applied. Resource use for both PFS and PPS states, which included one-time expenses for patient progression, were based on the statements of a Danish clinical expert and were deemed to be representative

of Danish R/R DLBCL patients. Subsequently, these resource approximations were priced using DRG tariffs or unit costs from the DMC official unit cost catalogue, labportalen.dk or laeger.dk.

It is postulated that patients who are undergoing treatment and in the PFS state will have 16 consultations with a haematologist that last for two hours each and six-hour consultations with a nurse throughout the course of a year. These 16 consultations are consistent with the number of blood tests and other examinations conducted as outlined in Table 38. Additionally, it is presumed that these patients will engage in four one-hour consultations with a radiologist each year, corresponding to the number of CT scans performed annually for these patients. Based on the clinical expert's assessment, patients in the PFS health state who receive treatment are anticipated to be hospitalized between two to four times in the first year due to AEs. In the model, it is estimated that patients in the PFS health state who are receiving treatment will be hospitalised approximately three times for a duration of three days each year (nine days in total assumed).

For patients who remain in the PFS state, it is assumed that they will have four half-hour consultations with a haematologist every year, which corresponds to the same amount of blood tests and other tests that are performed every three months, as stated by the Danish clinical expert.

In contrast, patients in the PPS state are primarily assumed to have 12 consultations with a haematologist that last for one hour each, as well as 1.5-hour consultations with a nurse throughout the course of a year. These 12 consultations correspond with the number of blood tests and other examinations conducted as outlined in Table 38. It is also presumed that these patients will engage in four one-hour consultations with a radiologist each year, corresponding to the number of PET-CT scans performed annually for these patients. Based on the clinical expert's assessment, patients in the PPS health state are expected to be hospitalized approximately six times per year.

The costs allocated for supportive care, including those related to the PFS and PPS health state, are shown in Table 38. Table 39 presents the one-time expenses associated with disease progression, which were applied in the cycle during which progression occurred.

Table 38: Supportive care costs and weekly resource use.

Supportive care	**Resource use of PFS on Tx (Yearly use)**	**Resource use of PFS off Tx (Yearly use)**	**Resource use of PPS (Yearly use)**	**Unit Cost (DKK)**	**Source** (82, 83, 102, 104)
Health care professionals and hospital resource use					
Haematologist (visit)	0.61 (16)	0.04 (4)	0.23 (12)	1,049	Værdisætning af enhedsomkostninger
Radiologist (visit)	0.08 (4)	0.00	0.04 (2)	1,049	Værdisætning af enhedsomkostninger
Nurse (visit)	0.31 (16)	0.00	0.23 (12)	441	Værdisætning af enhedsomkostninger
CT scan	0.08 (4)	0.00	0.04 (2)	2,440	DRG 2023, 30PR06, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (UXCF00)CT-skanning af hel overekstremitet,

					(UXCF00)CT-skanning af hel underekstremitet and Danish clinical expert
Inpatient day	0.17 (9)	0.00	0.11	2,240	Takstsystem 2023 and Danish clinical expert
Palliative care team	0.00	0.00	0.00	2,005	DRG 2023, 17MA98, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (BXBA) Specialiseret palliativ indsats
Treatment follow-up					
Full blood counts	0.31 (16)	0.08 (4)	0.23 (12)	21.63	Laeger.dk
LDH	0.31 (16)	0.08 (4)	0.23 (12)	14.00	Labportalen.dk
Liver function	0.31 (16)	0.08 (4)	0.23 (12)	54.00	Labportalen.dk
Renal function	0.31 (16)	0.08 (4)	0.23 (12)	57.00	Labportalen.dk
Immunoglobulin	0.31 (16)	0.08 (4)	0.23 (12)	24.00	RH Laboratorieundersøgelse
Calcium phosphate	0.31 (16)	0.08 (4)	0.23 (12)	88.00	Labportalen.dk
Total weekly supportive care costs (DKK)					
PFS "On Tx"					**1,511.69**
PFS "Off-Tx"					**60.03**
PPS					**793.46**

Abbreviations: PFS - progression-free survival; PPS - post-progressed survival; CT - computerized tomography; Tx - treatment; LDH - lactate dehydrogenase.

Table 39: One-off progression cost.

Resource	Unit cost (DKK)	Proportion of patients requiring resource	Time (hours)	Source (83, 85)
ECG	2,005.00	100.00%	0.17	DRG 2023, 17MA98 - 1-dagsgruppe, pat. Mindst 7 år, Diagnose: (DC833) Diffust storcellet lymfom, Procedure: (ZZ3925) EKG and Danish Clinical Expert
MUGA	1,975.00	5.00%	1.00	DRG 2023, 05PR04, Diagnose: (DC833) Diffust storcellet B-celle

				lymfom, Procedure: (UXUC80)Transtorakal ekkokardiografi and Danish Clinical Expert
MRI	2,447.00	20.00%	1.00	DRG 2023, 30PR02, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure:(UXMF00)MR-skanning af overekstremitet, (UXMG00)MR-skanning af underekstremitet and Danish Clinical Expert
PET-CT	3,488.00	100.00%	3.00	DRG 2023, 36PR07, Diagnose: (DC833) Diffust storcellet B-celle lymfom, Procedure: (WRACPXYXX)CT Underekstremiteter på PET/CT, (WDLBFXXXX)Billedfusionering (PET, SPECT, MRI, CT el. planar) and Danish Clinical Expert
Bone marrow biopsy	12,925.00	10.00%	0.50	DRG 2023, 17PR01, Diagnose: (DC833)Diffust storcellet B-celle lymfom, Procedure: (KTNE25A)Knoglemarvsbiopsi fra crista iliaca and Danish Clinical Expert
Blood transfusion	3,969.00	33.33%	1.50	DRG 2023, 16PR02, Diagnose: (DC833)Diffust storcellet B-celle lymfom, Procedure: (BOQA0)Blodtransfusion and Danish Clinical Expert
Tumour biopsy	5,484.00	33.33%	1.00	DRG 2023, 05PR02, Diagnose: (DC833)Diffust storcellet B-celle lymfom, Procedure: (KTPJ05)Nålebiopsi af lymfeknude and Danish Clinical Expert
Total one-off progression costs				
One-off progression cost (DKK)				**10,524.65**

Abbreviations: ERG - Electroretinogram; MUGA - multigated acquisition; MRI - magnetic resonance imaging; PET-CT - Positron Emissions Tomography – Computerized Tomography.

8.5.4 Adverse event costs

The model incorporates the costs related to the management of treatment-related AEs as outlined in Table 26 of section 8.2.2.5. AEs were applied as a one-off cost per treatment arm considering the frequency of their occurrence during the treatment period and the unit cost per AE.

As stated in the preceding section 8.2.2.5, the health economic assessment incorporates AEs of grade 3 or more, characterized by events that necessitate hospitalization or have the potential of resulting in life-threatening outcomes (96). Accordingly, all expenses associated with the AEs identified are estimated to reflect the long-term tariff of the DRG codes presented below (83). Table 40 presents the unit cost of AEs included in the assessment.

Table 40. Adverse event costs.

AEs	Unit cost (DKK)	Source (83)
Anaemia	40,106.00	DRG 2023, 16MA98, Diagnose: (DD592) Hæmolytisk ikke-autoimmun anæmi forårsaget af lægemiddel, lang
Anorexia	20,850.00	DRG 2023, 10MA98, Diagnose: (DR630) Appetitløshed, lang
Constipation	7,530.00	DRG 2023, 06MA11, Diagnose: (DK590) Forstoppelse
Diarrhoea	7,530.00	DRG 2023, 06MA11, Diagnose: (DK529B) Ikke-infektiøs diaré UNS, lang
Fatigue	4,728.00	DRG 2023, 23MA03, Diagnose: (DR539A) Udmattelse, lang
Febrile neutropenia	38,209.00	DRG 2023, 16MA03, Diagnose: (DD709A) Neutropeni og agranulocytose forårsaget af lægemiddel, lang
Hypokalaemia	28,368.00	DRG 2023, 10MA98, Diagnose: (DE876) Hypokaliæmi, lang
Hypomagnesemia	20,850.00	DRG 2023, 10MA04, Diagnose: (DE834B) Hypomagnesiæmi, lang
Hypophosphatemia	39,158.00	DRG 2023, 10MA98, Diagnose: (DE833A) Hypofosfatæmi, lang
Infection	30,146.00	DRG 2023, 18MA06, Diagnose: (DB348)Anden virusinfektion uden angivelse af lokalisation, lang
Insomnia	17,022.00	DRG 2023, 19MA98, Diagnose: (DF5100) Søvnløshed UNS, lang
Lymphopenia	26,179.00	DRG 2023, 16MA10, Diagnose: (DD728D) Lymfopeni, lang
Nausea	7,530.00	DRG 2023, 06MA11, Diagnose: (DR119B) Kvalme, lang
Neutropenia	38,209.00	DRG 2023, 16MA98, Diagnose: (DD709) Neutropeni UNS, lang
Renal faliure	35,456.00	DRG 2023, 11MA02, Diagnose: (DI120) Hypertensiv nyresygdom med nyresvigt
Thrombocytopenia	38,209.00	DRG 2023, 16MA98, Diagnose: (DD696) Trombocytopeni UNS, lang
Thrombosis/embolism	23,473.00	DRG 2023,05MA12, Diagnose: (DI744) Emboli eller trombose i arterie i ekstremitet UNS, lang
Tumor flare	44,770.00	DRG 2023, 17MA01, Diagnose: (DC833), lang
Vomiting	7,530.00	DRG 2023, 06MA11, Diagnose: (DR11C) Opkastning, lang

Abbreviations: DRG - Diagnose related groups

8.5.5 Patient time and travel costs

Patient and transportation costs are included in the model in line with the DMC method guidelines (75). 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 41 (75, 102). It is further assumed that patients would spend 30 minutes on transportation per visit (round-trip).

Table 41: Patient and transportation cost per unit

	Unit cost (DKK)	Source
Patient cost per hour	181.00	Danish method guidelines (75, 102)
Transport cost per visit	140.00	Danish method guidelines (75, 102)

Patient time and transportation costs are distributed based on the health states of PFS on/off treatment and PPS. The preceding section, specifically section 8.5.3, provides information on the resource use associated with R/R DLBCL patients in 3L+ treatment for both the PFS and PPS health state. Hence, the patient time and transportation costs incurred by a patient R/R DLBCL follow the same pattern of incurrence.

According to the Danish clinical expert, patients receiving glofitamab treatment will be hospitalized for one day following the initial administration. Consequently, 16 hours was assumed for patients being hospitalized reflecting the number of waken hours per day and will incur a cost of 2,986.50 DKK including transportation time. For the second and third administration, the clinical expert estimated a patient duration of six hours at a cost of 1,176.50 DKK. Subsequent treatment cycles (4-12) were approximated to take four hours of patient's time, at a cost of 814.50 DKK including transportation time per administration (85, 105). The patient time cost including transportation time is presented in Table 42.

As per the estimation of the Danish clinical expert, hospitalization of three days was expected for patients receiving R-chemotherapy treatment (R-DHAP and R-ICE), given that the administration of R-chemotherapy is spread across this duration (85, 87, 88, 105). Hence, a total of 48 hours per R-containing chemotherapy treatment was assumed and will incur a cost of 8,778.50 DKK, see Table 42.

Table 42: Patient time and transportation cost, PFS on treatment.

Patient time on treatment	Hours	Cost per administration (DKK)
Glofitamab, Patient time per treatment cycle incl. transportation time		
First administration	16.5	2,986.50
2nd and 3rd administration	6.5	1,176.50
4th – 12th administration	4.5	814.50
R-chemotherapy , Patient time per treatment cycle incl. transportation time		
R-DHAP	48.50	8,778.50
R-ICE	48.50	8,778.50
Transportation cost per treatment administration		
Transportation cost (All)		140.40

Abbreviations: R-DHAP - rituximab + dexamethasone + high-dose cytarabine + cisplatin; R-ICE - rituximab + ifosfamide + carboplatin + etoposide

Patients who remain free of progression after treatment cessation and those who experience progression, weekly costs for patient time and transportation are incurred and presented in Table 43. According to section 8.5.3, patients in the PFS health state are required to make four hospital visits annually for monitoring purposes. The estimated duration of each visit is half an hour, adding up to a total of two hours per year, equivalent to a weekly time consumption of 0.08 hours. The cost per week associated with this time use is 13.88 DKK and a transportation cost of 11.23 DKK (85, 105). Patients in the PPS health state are assumed to have 12 consultations yearly, resulting in a total

patient time consumption of 32 hours per year, equivalent to a weekly time use of 0.73 hours. The cost per week for this time use is 131.82 DKK and a transportation cost of 32.29 DKK (85, 105).

Table 43: Patient time and transportation costs, PFS and PPS.

Patient time incl. transportation time, Weekly use	Hours	Cost per weekly model cycle (DKK)
PFS "Off Tx"	0.08	13.88
PPS	0.73	131.82
Transportation cost per week		
PFS "Off Tx"		11.23
PPS		32.29

Abbreviations: PFS - progression-free survival; PPS - post-progressed survival; Tx – treatment.

Furthermore, the time spent by patients undergoing examination for those who progress was also factored in as a one-time cost. The patient time cost incurred as part of the aforementioned cost and time, as outlined in Table 39, was estimated to be 4.3 hours based on the statement provided by the Danish clinical expert. This has been presented in Table 44, leading to a one-time cost of patient time amounting to 778.18 DKK (85, 105).

Table 44: One-off progression time cost.

One-off hours used in PPS	Hours	One-off cost (DKK)
One-off progression time cost	4.30	778.18

Abbreviations: PPS - post-progressed survival

8.6 Results

8.6.1 Base case overview

Table 45: 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 (75)
Discount rate - costs	3.5% until year 35 then 2.5%	DMC methods guideline (75)
Data source	NP30179 and SCHOLAR-1	In line with relevant population in Denmark
Intervention	Glofitamab	NP30179, Only available evidence for R/R DLBCL patients treated with glofitamab
Comparator	R-chemotherapy	SCHOLAR-1, best available evidence reflecting Danish patient population and standard of care. Based on discussions with DMC and clinical experts.
Population parameters		
Age	63 years	NP30179 average age in safety population

Body weight	75 kg	NP30179 average weight in safety population
Height	171 cm	NP30179 average height in safety population
Body surface area	1.86 m^2	NP30179 average BSA in safety population
Efficacy and treatment duration		
PFS – Glofitamab	Log-normal	See section 8.3.1
PFS – R-chemotherapy	HR=0.65	See section 8.3.1
OS – Glofitamab	Log-normal	See section 8.3.2
OS – R-chemotherapy	HR=0.42	See section 8.3.2
Utilities		
PFS – On Tx	0.73	See section 8.4
PFS – Off Tx	0.77	See section 8.4
PPS	0.63	See section 8.4
Cost variables		
Drug cost	3L+ therapy applied to reflect the real administration	Reflects the drug costs accrued over the patient´s course of treatment
Administration cost	3L+ 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 PPS incidence cases per cycle	Reflecting number and cost of treatments patients receives after 3L+ 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 (75)

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, vs. R-chemotherapy .

Table 46 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. This can be explained by the significantly higher proportion of patients remaining alive in the glofitamab arm vs. the R-chemotherapy arm, underlining the new intervention's effectiveness. The deterministic Incremental cost-effectiveness ratio (ICER) is [redacted] per QALY gained, with incremental LYs gained of [redacted] and QALY gained at [redacted].

Table 46: Base case results.

Per patient	Intervention	Comparator	Difference
Life years gained			
Total life years gained			
PFS			
PPS			
Total QALYs			
PFS			
PPS			
Total costs			
Total PFS cost			
Treatment cost			
Diagnostic cost			
Administration cost			
AE management cost			
Supportive care			
Patient time cost			
Travel cost			
Total PPS cost			
Post-discontinuation therapy cost			
Supportive care			
Patient time cost			
Travel cost			
Incremental results			
ICER (per QALY)			
ICER (per life year gained)			
Net monetary benefit (NMB)*			

*Assuming a WTP threshold of 600,000 DK

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

8.7.2 Scenario analyses

Scenario analyses are performed to explore how changing some of the key model parameters will impact the model results. Table 47 below summarizes the scenario results. Based on the various parameter settings explored in the scenario analyses, the resulting ICERs are differentiating in glofitamab being cost-effective compared to R-chemo-therapy (i.e., max ICER ranging between [redacted] to [redacted]). The highest ICER is found when choosing a time horizon of 5 years, and the lowest ICER when choosing the Gompertz distribution for PFS in the glofitamab arm.

Table 47: Scenario analyses exploring changes to key parameters.

Parameter	Inc. cost per QALY Glofitamab vs R-chemotherapy average	DKK Δ ICER vs base case
Base case	[redacted]	
Assumptions		
Time horizon: 5 years		
Time horizon: 10 years		
Planned dose wo. vial sharing		
Planned dose w. vial sharing		
Actual dose wo. vial sharing		
Actual dose w. vial sharing		
Planned ind. dose w. vial sharing		
Long-term remission/survivorship scenario excluded		
Excess background mortaility risk data source (Marauer 2014)		
Excess background mortaility risk data source (Marauer 2014 (French pts)		
Excess background mortaility risk data source (Marauer 2014 (Howlader 2017)		
Treatment duration assumptions (Until progression)		
Treatment effect		
PFS approach	[redacted]	
Glofitamab		
Exponential		
Weibull		
Gen Gamma		
Log-logistic		
Gompertz		
Gamma		
KM with Exponential tail		
KM with Weibull tail		
KM with Log-normal tail		
KM with Gen Gamma tail		
KM with Log-logistic tail		
KM with Gompertz tail		
KM with Gamma tail		
Bayesian Average		

KM with Bayesian Average	[redacted]
R-chemotherapy	
HR from glofitamab PFS to R-chemotherapy PFS of 1	
HR from glofitamab PFS to R-chemotherapy PFS of from BR MAIC	
OS appraoch	
Glofitamab	
Exponential	
Weibull	
Gen Gamma	
Log-logistic	
Gompertz	
KM with Exponential tail	
KM with Weibull tail	
KM with Log-normal tail	
KM with Gen Gamma tail	
KM with Log-logistic tail	
KM with Gompertz tail	
KM with Gamma tail	
Bayesian Average	
KM with Bayesian Average	
Unweighted extrapolated OS curve from NP30179	
R-chemotherapy	
Extrapolated OS curve from MAIC (log-normal)	
Utility	
EORTC-QLQ-C30 Mapping (Direct)	
Adverse events	
Witzig et. al 2008	
Costs	
No subsequent treatments	
70% on R-DHAP	
70% on R-ICE	

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 22 and Figure 23 below using list prices. This represents the joint distribution of costs and effect for the intervention (glofitamab), and the comparator included in the model (R-chemotherapy) 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.

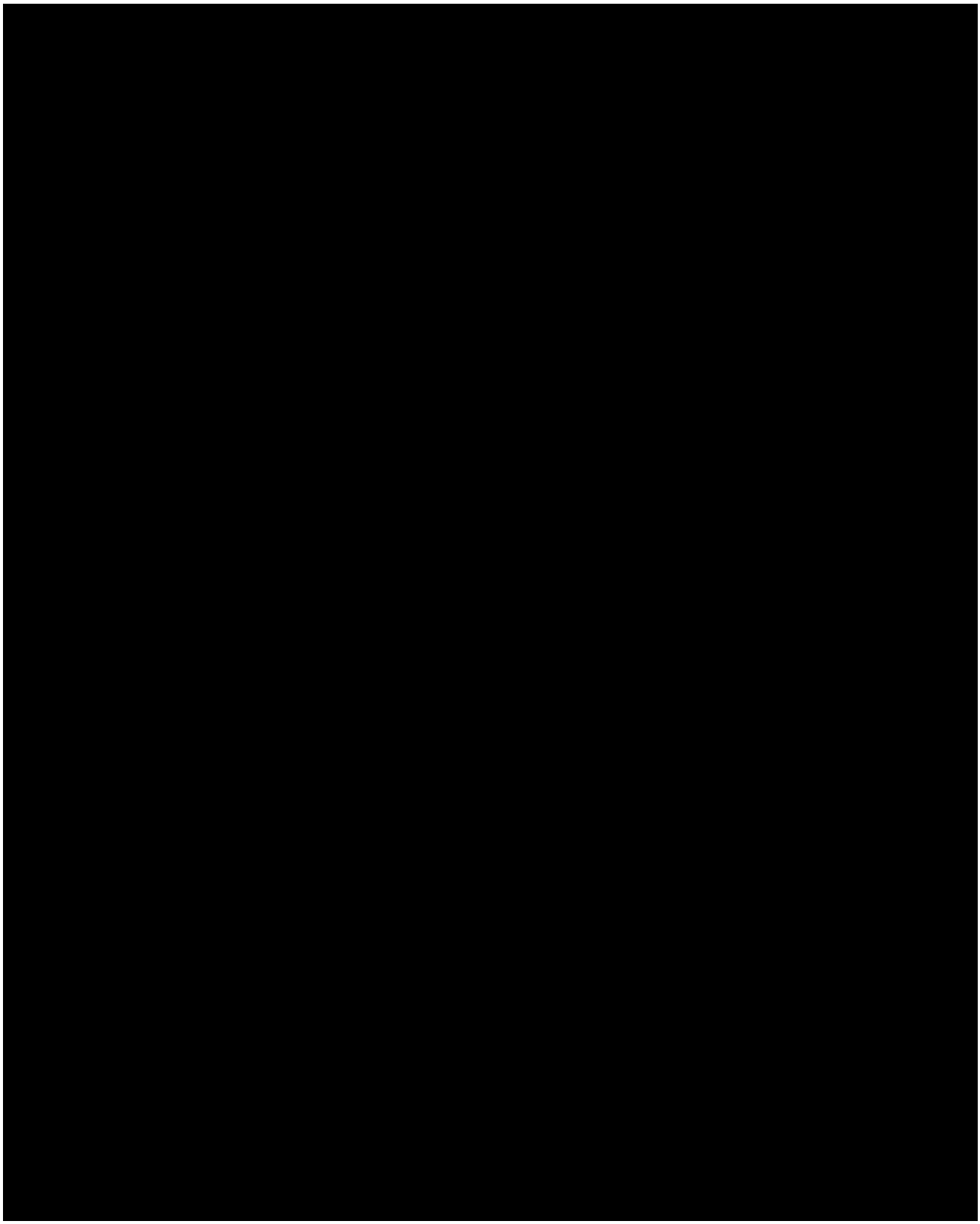


Figure 23: Incremental cost-effectiveness plane Glofitamab vs. R-chemotherapy.

In total the sensitivity analyses illustrate that the results of the base case cost effectiveness analysis is solid to changes in assumptions and possible variations in data.

9. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending glofitamab 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 Glofitamab is recommended as a standard treatment and the scenario where glofitamab 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

It is anticipated that approximately 20 patients are expected to be eligible for treatment with glofitamab the first year. For the budget impact analysis, the assumed number of new patients over a period of 5 years are reported in Table 48.

Future market shares depend on multiple factors such as possible new treatment alternatives and available capacity and economic resources. Regardless, the estimates will be associated with uncertainty. The potential market share for glofitamab with or without a recommendation is reported in Table 48.

Table 48: Number of patients expected to be treated over the next five-year period.

	Year 1	Year 2	Year 3	Year 4	Year 5
Total number of new eligible patients	20	21	21	22	22
Scenario where Glofitamab is not recommended					
Glofitamab	0%	0%	0%	0%	0%
R-chemotherapy	100%	100%	100%	100%	100%
Scenario where Glofitamab is recommended					
Glofitamab	100%	100%	100%	100%	100%
R-chemotherapy	0%	0%	0%	0%	0%

Abbrevations: R-chemotherapy - (R-DHAP (rituximab + dexamethasone + high-dose cytarabine + cisplatin) or R-ICE (rituximab + ifosfamide + carboplatin + etoposide))).

9.2 Budget impact result

[redacted]

10. Discussion on the submitted documentation

Discussion of the clinical data

The presentation of the efficacy and safety of glofitamab in this application, is based on a phase I/II study, NP30179. While it is a limitation that this study is a single arm study and thus without a comparator arm, a large group of patients with NHL histology (n=503) have been enrolled, of which 287 patients were of the DLBCL histology. The first patients were enrolled in the beginning of 2017, and the follow-up time on a subset of the patients is therefore very long. As presented in the results section, the 24-month event-free rate for DOCR was determined for a supporting cohort. With [redacted] still in CR after 24 months, more than half of the patients in the supporting cohort achieved lasting remissions for at least two years, and it is thus reasonable to consider these patients as cured at this point. From the full population enrolled in NP30179, 41 Danish patients participated in the clinical study, of which 11 patients were part of the ITT population (n=155). Therefore, Danish clinicians already have experience with glofitamab.

Validation of emerging therapies for third line treatment in DLBCL is impeded by the low number of eligible patients. Therefore, randomized clinical trials are not always feasible within a realistic time frame, and time-to-access is often weighted higher in indications where there is an unmet medical need. Oncology therapies in high treatment lines are therefore sometimes approved based on phase/II studies. In a study published in Journal of Clinical Oncology from 2009, the authors investigated anticancer drugs approved from 1973 through 2006 by the FDA. Of the 68 approved oncology drugs, 31 were approved without a randomized trial. For these 31 drugs, ORR was the most common endpoint with a median response rate of 33% (range, 11% to 90%). Importantly, thirty drugs are still fully approved. This information is important to keep in mind considering the primary endpoint being CR in NP30179.

To evaluate glofitamab against Danish standard of care, chemotherapy +/- R, in an appropriate way considering NP30179 being a single-arm study, a MAIC analysis was conducted. MAIC analyses are very useful as the method adjusts for between-trial differences in baseline characteristics. Treatment outcomes can therefore be compared across balanced trial populations. To conduct a MAIC, data needs to be available from trials with the comparator of interest. This was indeed a challenge in this application, since there is no dominant standard of care for third line DLBCL. Therefore, when limiting our search for relevant literature to R-DHAP/R-ICE and R-GDP, current Danish clinical practice, very few studies were available. Additionally, when assessing the identified relevant literature for suitability for conducting a MAIC, only the SCHOLAR-1 study was deemed suitable as this was the only study that reported relevant endpoints with sufficient baseline characteristics to adjust for. The advantage, however, of using SCHOLAR-1, is that it is one of the largest patient-level pooled analyses. Furthermore, SCHOLAR-1 has been used in previous assessments of CAR-T in the same indication by HTA bodies in CANADA, Norway and the UK, and it is therefore a widely accepted study when comparing new treatments to chemotherapy in third line DLBCL.

The conducted MAIC analysis in this application strongly favored glofitamab vs. chemotherapy in SCHOLAR-1. The calculated odds ratio (OR) for CR and ORR as well as the HR for OS in both the unadjusted [redacted] base-case models, demonstrated superiority of glofitamab. Though these results are convincing, they should be interpreted in the light of the limitations of the MAIC analysis. It was not possible to adjust for all baseline characteristics as some were unmeasured or unavailable. Hence, differences in patient baseline characteristics between trials could not be entirely excluded, and this could introduce a potential bias. Additionally, in our case, a filtering procedure was adopted on the ITT population based on the SCHOLAR-1 eligibility criteria. The filtering criteria consisted of excluding patients who did not have refractory disease according to the SCHOLAR-1 criteria (progressive or stable disease as the best response to first line or to the most recent chemotherapy regimen or disease progression or relapse within 12 months after autologous stem-cell transplantation). Furthermore, patients with HGBCL histology or with 4 or more prior lines of therapy were also excluded, to align with the population included in SCHOLAR-1.

Overall, this meant that the variation between the populations in NP30179 and SCHOLAR-1 was reduced, but it also meant that the total number of patients from NP30179 included in the MAIC was reduced to 74. Nevertheless, despite differences in baseline characteristics, the favorable HR obtained with glofitamab seems to be robust enough to overcome variations across different populations.

The comparative analysis evaluating the endpoints PFS, safety and HRQoL was limited by the availability of data in the SCHOLAR-1 study. The endpoints were not reported in SCHOLAR-1, and the data was therefore extracted from the individual studies that were part of the SCHOLAR-1 study, and compared narratively. However, for those endpoints the presented data was very scarce which made proper comparisons difficult. Additionally, in the narrative analysis, it was not possible to adjust for differences in baseline characteristics which may have biased the results.

While it is important to consider differences in baseline characteristics within a population when comparing interventions from different trials, it is noteworthy that the OS in the SCHOLAR-1 study and the OS in the Danish population-based study (9) were very similar despite differences in baseline characteristics such as age and ECOG status. In SCHOLAR-1 the median OS was 6.1 months (95% CI 5.2-7.0) for patients who were refractory to second-line or later line therapy, and similarly the median OS was reported to be 6 months (95% CI 5-9) in the Danish population-based study. The poor OS in both studies indicate that there is a need for novel effective therapies in this indication, but at the same time it also suggests that the intrinsic disease biology may be the major driver of OS.

Although Danish patients have participated in the NP30179 study, the enrollment has been carried out globally including patients from 13 different countries, including Australia, New Zealand, the US, Canada, Taiwan and Europe. However, the comparability of the ITT population in NP30179 to Danish patients was good. The comparability was assessed using the data available in the Danish population-based study reporting data from LYFO where the main differences were in regards to ECOG-PS and prior number of therapies. The Danish population is of a poorer ECOG-PS, but the ITT population in NP30179 was more heavily pre-treated. Additionally, 33.5% of the ITT population in NP30179 have received prior CAR-T cell therapy, which is in contrast to the Danish patients where none have received this. Taken together, it is likely that glofitamab will demonstrate high effectiveness in Danish patients in a real-world setting.

Conclusively, glofitamab has shown to be effective and with a manageable safety profile favourable for DLBCL patients after two or more lines of therapies as compared to chemotherapy regimens. Currently, there is no standard therapy for this population in Denmark, and as Danish clinicians already have experience with glofitamab due to the relatively large number of Danish patients in NP30179, its use in a Danish setting is promising.

Discussion of the health economics analysis

A cost-utility analysis was performed, resulting in a base case ICER of [redacted] and incremental QALYs of [redacted] and LYs of [redacted] Glofitamab has both a higher efficacy and costs compared to R-chemotherapy, for patients with R/R DLBCL. The differences in QALY is driven by patients treated with glofitamab having a lower risk of dying while at the same time remain progression-free for a longer time than patients treated with chemotherapy (+/- R). The differences is costs is mainly driven by the drug costs of glofitamab, but administration of glofitamab also contributes to some extent. Probability analyses were also performed to inform about decision uncertainty at various WTP threshold levels. Assuming a WTP of [redacted], treatment with glofitamab is cost-effective in the majority of the simulations, showcased by ICERs located in the north east (NE) quadrant of the cost-effectiveness plane (CE-plane). This indicates that even though there is a degree of uncertainty due to the single-arm trial design there is much less decision uncertainty – even at much higher thresholds glofitamab remains cost-effective.

The budget impact of a positive recommendation of glofitamab is only [redacted] due to the low number of patients that reach third line treatment.

Conclusively, glofitamab has shown to be effective and with a manageable safety profile favourable for DLBCL patients after two or more lines of therapies as compared to chemotherapy regimens, while at the same time being very cost-effective and with a low budget impact. Currently, there is no standard therapy for this population in Denmark, and as Danish clinicians already have experience with glofitamab due to the relatively large number of Danish patients in NP30179, its use in a Danish setting is promising.

11. List of experts

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Version log		
Version	**Date**	**Change**
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.
1.1	9 February 2022	Appendix K and onwards have been deleted (company specific appendices) Color scheme for text highlighting table added after table of contents Section 6: Specified requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described Section 8.3.1: Listed the standard parametric models Section 8.4.1: Added the need for description of quality of life mapping Appendix A: Specified that the literature search needs to be specific for the Danish context and the application Appendices B and D: Stated it explicitly that statistical methods need to be described in the tables in the appendices
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in excel files has been added, see page 1.

Appendix A Literature search for efficacy and safety of glofitamab and comparator(s)

No direct evidence comparing glofitamab with standard treatment of care used in Danish clinical practice is available. In order to identify relevant studies for the indirect treatment comparisons a systematic literature review was conducted.

The Medicines Council methods guide for assessing new pharmaceuticals version 1.2 has provided guidance for the literature search. Electronic searches were carried out in PubMed and in CENTRAL (via Cochrane Library) on March 12, 2023. The searches were based on the defined PICOs described Table 50. In addition, the searches contain terms descriptive of the area as described in the search strings.

Table 50: Inclusion and exclusion criteria for the search in DLBCL.

	Inclusion criteria	Exclusion criteria
Population	Adult patients with relapsed or refractory DLBCL, after two or more lines of systemic therapy	Pediatric patients, adult patients treated at 1L or 2L setting only
Intervention	Glofitamab	Pharmacological interventions not listed in the "include" column
Comparators	• GDP (gemcitabin, dexamethason, cisplatin) +/- rituximab • DHAP (cisplatin, cytarabin, dexamethason) +/- rituximab • ICE (ifosfamid, carboplatin, etoposid) +/- rituximab	• Pharmacological interventions not listed in the "include" column • On-pharmacological interventions (e.g. surgery, radiotherapy, diagnostic/screening)
Outcomes	• Complete response • Progression-free survival • Overall survival • HRQoL assessed by EORTC QLQ-C30 and FACT-Lym • Incidence of adverse events (AEs) • Treatment-related AEs • Serious AEs • Serious treatment-related AEs • Discontinuations due to AEs	Outcomes not listed in the "include" column
Design	• RCTs (Phase 1/2/3) • Prospective clinical trials (non-RCTs, non-comparative) • Extension phases of trials • Observational/registry studies (prospective/retrospective)	• Case-control studies • Cross-sectional surveys • Case series • Case reports • Pharmacokinetic studies • Animal/in vitro studies • Editorials • Opinion pieces • Reviews • Treatment guidelines • SLR, meta-analyses, and narrative review publications of interventional and/or observational studies

		(for citation-chasing and baseline data gap filling only) • Economic evaluations
Language	English, Scandinavian	Other language
Publication data (date limits)	No date limits	Not applicable
Human/animal	Human only	Veterinary (not human)

Table 51: Bibliographic databases included in the literature search.

Database	Platform	Relevant period for the search	Date of search completion
PubMed	MEDLINE	No date limits	12.03.2023
CENTRAL	Cochrane Library	No date limits	12.03.2023

Search strategy

The search strategy and search strings have been prepared based on the PICOs. The inclusion and exclusion criteria for the searches are presented in Table 52. Because it was suspected that limited evidence for the comparators of interest would be available, the scope of the review was broadened so that the population included DLBCL as a whole. Also, no restriction were applied in terms of treatment lines. In addition, no strict restrictions were applied to the study design, which included interventional and observational studies. The search strings and results for each database are presented below (Table 52,
Table 53 and screen shots). In the comment field of the tables it is stated, which search term applies to what part of the PICO.

Table 52: Search strategy, PubMed - March 12, 2023.

Search #	Query	Comments on search strategy
1	"Lymphoma, Large B-Cell, Diffuse"[mh]	Population
2	(diffuse[tiab] AND (large cell[tiab] OR large-cell[tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab]	
3	#1 OR #2	
4	"glofitamab"[nm]	Intervention
5	glofitamab[tiab] OR RG6026[tiab]	
6	#4 OR #5	
7	"GDP protocol"[nm] OR ("gemcitabine"[mh] AND "Dexamethasone"[mh] AND "Cisplatin"[mh])	Comparators: GDP +/- rituximab (gemcitabine, dexamethasone, cisplatin, rituximab)
8	GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab]))	
9	"DHAP protocol"[nm] OR ("Dexamethasone"[nm] AND "Cytarabine"[mh] AND "Cisplatin"[mh])	DHAP +/- rituximab (dexamethasone, cytarabine, cisplatin, rituximab)

10	DHAP[tiab] OR RDHAP[tiab] OR R-DHAP[tiab] OR (dexamethason*[tiab] AND cytarabin*[tiab] AND (cisplatin*[tiab] OR cisplatin*[tiab]))	
11	"ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh])	ICE +/- rituximab (ifosfamide, carboplatin, etoposide, rituximab)
12	((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab]	
13	#7 OR #8 OR #9 OR #10 OR #11 OR #12	
14	#6 OR #13	Combination of intervention and comparator
15	#3 AND #14	Combination of population, intervention and comparator
16	"case reports"[pt] OR "comment"[pt] OR "editorial"[pt] OR "guideline"[pt] OR "systematic review"[pt] OR "review"[pt]	Exclusion of non-relevant publication types
17	case report[ti] OR review of the literature[tiab]	
18	#15 NOT (#16 OR #17)	Final search

Search	Actions	Details	Query	Results	Time
#18	•••	›	Search: **#15 NOT (#16 OR #17)**	113	14:15:06
#17	•••	›	Search: **case report[ti] OR review of the literature[tiab]**	400,656	14:14:50
#16	•••	›	Search: **"case reports"[pt] OR "comment"[pt] OR "editorial"[pt] OR "guideline"[pt] OR "systematic review"[pt] OR "review"[pt]**	6,831,460	14:14:34
#15	•••	›	Search: **#3 AND #14**	178	14:14:16
#14	•••	›	Search: **#6 OR #13**	90,182	14:14:00
#13	•••	›	Search: **#7 OR #8 OR #9 OR #10 OR #11 OR #12**	90,161	14:13:46
#12	•••	›	Search: **((iphosphamid*[tiab] OR isophosphamid*[tiab] OR isofosfamid*[tiab]) AND Carboplat*[tiab] AND (eposi*[tiab] OR etopos*[tiab] OR VP-16*[tiab] OR VP16[tiab])) OR R-ICE[tiab] OR RICE[tiab]**	70,117	14:13:23
#11	•••	›	Search: **"ICE protocol 1"[nm] OR "ICE protocol 2"[nm] or "ICE protocol 3"[nm] or "ICE protocol 4"[nm] or "ICE protocol 5"[nm] or "ICE protocol 6"[nm] OR ("Ifosfamide"[mh] AND "Carboplatin"[mh] AND "Etoposide"[mh])**	674	14:13:06
#10	•••	›	Search: **DHAP[tiab] OR RDHAP[tiab] OR R-DHAP[tiab] OR (dexamethason*[tiab] AND cytarabin*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab]))**	853	14:12:51
#9	•••	›	Search: **"DHAP protocol"[nm] OR ("Dexamethasone"[nm] AND "Cytarabine"[mh] AND "Cisplatin"[mh])**	181	14:12:36
#8	•••	›	Search: **GDP[tiab] OR RGDP[tiab] OR R-GDP[tiab] OR (gemcitabin*[tiab] AND dexamethason*[tiab] AND (cisplatin*[tiab] OR cis-platin*[tiab]))**	18,584	14:12:18
#7	•••	›	Search: **"GDP protocol"[nm] OR ("gemcitabine"[mh] AND "Dexamethasone"[mh] AND "Cisplatin"[mh])**	73	14:11:59
#6	•••	›	Search: **#4 OR #5**	21	14:11:41
#5	•••	›	Search: **glofitamab[tiab] OR RG6026[tiab]**	21	14:11:28
#4	•••	›	Search: **"glofitamab"[nm]**	6	14:11:12
#3	•••	›	Search: **#1 OR #2**	34,065	14:10:57
#2	•••	›	Search: **(diffuse[tiab] AND (large cell[tiab] OR large-cell[tiab] OR b-cell[tiab] OR b cell[tiab] OR histiocytic[tiab]) AND lymphoma*[tiab]) OR DLBCL[tiab]**	22,565	14:10:41
#1	•••	›	Search: **"Lymphoma, Large B-Cell, Diffuse"[mh]**	23,148	14:10:02

Table 53: Search strategy, CENTRAL via Cochrane Library – March 12, 2023.

Search #	Query	Comments on search strategy
1	[mh "Lymphoma, Large B-Cell, Diffuse"]	Population
2	((diffuse AND (large cell OR large-cell OR b-cell OR b cell OR histiocytic) AND lymphoma*) OR DLBCL):ti,ab,kw	
3	#1 OR #2	
4	(glofitamab OR R6026):ti,ab,kw	Intervention
5	(GDP OR RGDP OR R-GDP OR (gemcitabin* AND (dexamethason* OR [mh "Dexamethasone"]) AND ([mh "Cisplatin"] cisplatin* OR cis-platin*))):ti,ab,kw	Comparators: GDP +/- rituximab (gemcitabine, dexamethasone, cisplatin, rituximab)
6	(DHAP OR RDHAP OR R-DHAP OR ((dexamethason* OR [mh "Dexamethasone"]) AND (cytarabin* OR [mh "Cytarabin"]) AND ([mh "Cisplatin"] cisplatin* OR cis-platin*))):ti,ab,kw	DHAP +/- rituximab (dexamethasone, cytarabine, cisplatin, rituximab)
7	[mh "Ifosfamide"] AND [mh "Carboplatin"] AND [mh "Etoposide"]	ICE +/- rituximab (ifosfamide, carboplatin, etoposide, rituximab)
8	(((iphosphamid* OR isophosphamid* OR isofosfamid*) AND Carboplat* AND (eposi* OR etopos* OR VP-16* OR VP16)) OR R-ICE OR RICE):ti,ab,kw	
9	#5 OR #6 OR #7 OR #8	
10	#4 OR #9	Combination of intervention and comparator
11	#3 AND #10	Combination of population, intervention and comparator
12	("conference abstract" OR review):pt	Exclusion of non-relevant publication types
13	NCT*:au	
14	("clinicaltrials.gov" OR trialsearch):so	
15	#12 OR #13 OR #14	
16	#11 NOT #15	Final search

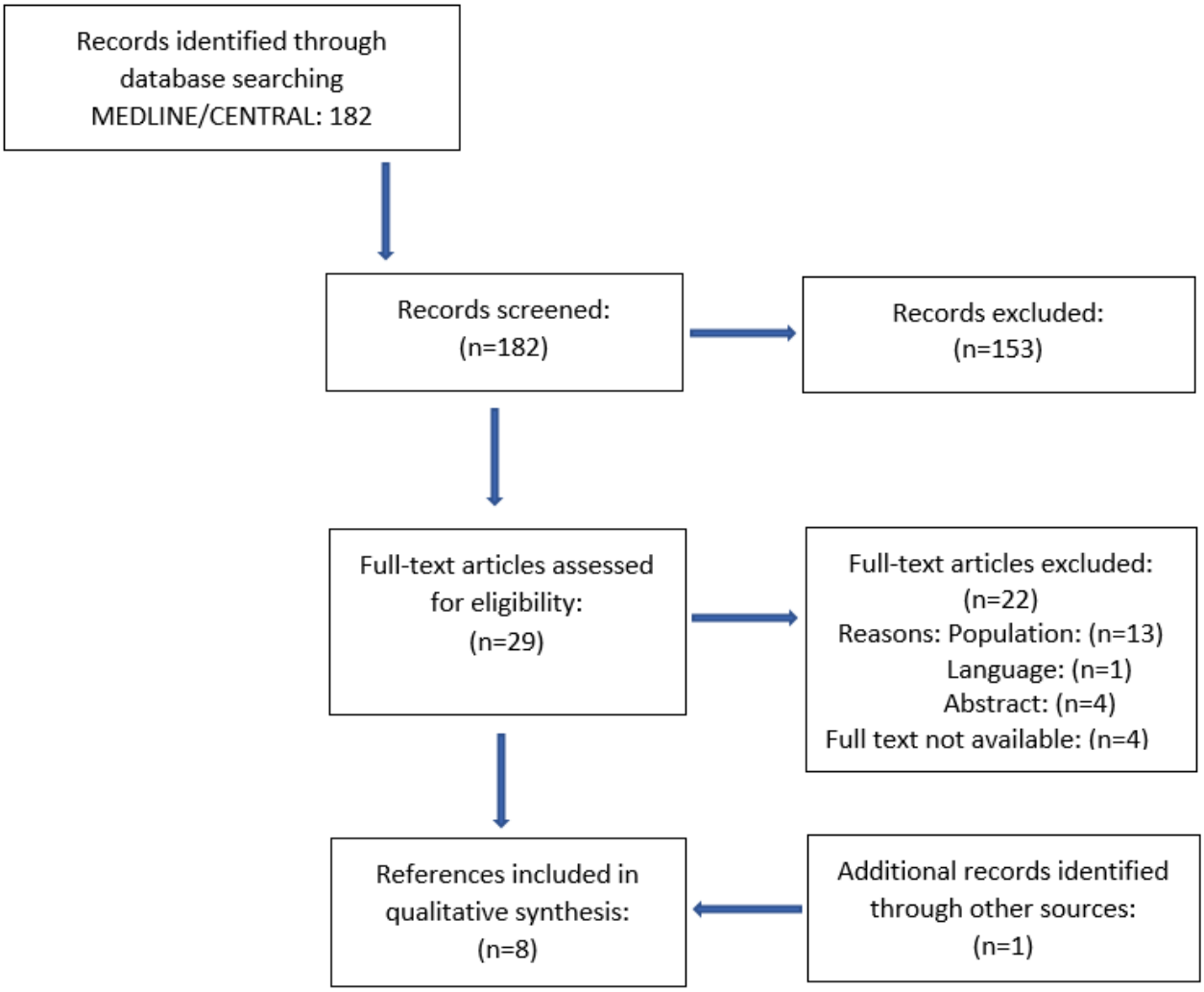
− +	#1	[mh "Lymphoma, Large B-Cell, Diffuse"]	Limits	571
− +	#2	((diffuse AND (large cell OR large-cell OR b-cell OR b cell OR histiocytic) AND lymphoma*) OR DLBCL):ti,ab,kw	Limits	2053
− +	#3	#1 OR #2	Limits	2054
− +	#4	(glofitamab OR R6026):ti,ab,kw	Limits	7
− +	#5	(GDP OR RGDP OR R-GDP OR (gemcitabin* AND (dexamethason* OR [mh "Dexamethasone"]) AND ([mh "Cisplatin"] cisplatin* OR cis-platin*))):ti,ab,kw	Limits	391
− +	#6	(DHAP OR RDHAP OR R-DHAP OR ((dexamethason* OR [mh "Dexamethasone"]) AND (cytarabin* OR [mh "Cytarabin"]) AND ([mh "Cisplatin"] cisplatin* OR cis-	Limits	226
− +	#7	[mh "Ifosfamide"] AND [mh "Carboplatin"] AND [mh "Etoposide"]	Limits	90
− +	#8	(((iphosphamid* OR isophosphamid* OR isofosfamid*) AND Carboplat* AND (eposi* OR etopos* OR VP-16* OR VP16)) OR R-ICE OR RICE):ti,ab,kw	Limits	2560
− +	#9	#5 OR #6 OR #7 OR #8	Limits	3191
− +	#10	#4 OR #9	Limits	3198
− +	#11	#3 AND #10	Limits	100
− +	#12	("conference abstract" OR review):pt	Limits	0
− +	#13	NCT*:au	Limits	241117
− +	#14	("clinicaltrials.gov" OR trialsearch):so	Limits	450433
− +	#15	#12 OR #13 OR #14	Limits	450679
− +	#16	#11 NOT #15	Limits	69

Supplementary manual searches

- Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study; M. Crump et al; Blood (2017) 130 (16): 1800–1808

Systematic selection of studies

Figure 25: PRISMA Flow Diagram - PubMed and CENTRAL search combined.



List of excluded full-text papers

Based on the title and abstract screening, a total of 29 references were selected for full-text review. Following review, 22 references were excluded due to the reasons stated in Table 54.

Table 54: List of excluded full text papers.

Reference	Reason for exclusion
Treatment of relapsed non-Hodgkin's lymphomas with dexamethasone, high-dose cytarabine, and cisplatin before marrow transplantation; O. W. Press et al; Journal of Clinical Oncology; 1991	Population, Outcome not reported separately for relevant subpopulation
Outpatient-based ifosfamide, carboplatin and etoposide (ICE) chemotherapy in transplant-eligible patients with non-Hodgkin's lymphoma and Hodgkin's disease; M. S. Hertzberg et al; Annals of Oncology; 2003	Population, Only 2L
Gemcitabine, dexamethasone, and cisplatin in patients with recurrent or refractory aggressive histology B-cell non-Hodgkin lymphoma: a Phase II study by the National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG); M. Crump et al; Cancer; 2004	Population, Only 2L
Efficacy of rituximab-containing salvage regimens on relapsed or refractory B-cell non-Hodgkin's lymphoma; H. Q. Huang et al; Ai Zheng; 2006	Language, Chinese
Dexamethasone, high-dose cytarabine, and cisplatin in combination with rituximab as salvage treatment for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma; U. J. Mey et al; Cancer Investigation; 2006	Population, Outcome not reported separately for relevant subpopulation
DHAP in combination with rituximab vs DHAP alone as salvage treatment for patients with relapsed or refractory diffuse large B-cell lymphoma: a matched-pair analysis; U. J. Mey et al; Leukemia & Lymphoma; 2006	Population
Outpatient fractionated ifosfamide, carboplatin and etoposide as salvage therapy in relapsed and refractory non-Hodgkin's and Hodgkin's lymphoma; M. S. Hertzberg et al; Annals of Oncology; 2006	Population, Only 2L
Randomised phase III study of R-ICE vs. R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by high-dose therapy and a second randomisation to maintenance treatment with rituximab or not: an update of the CORAL study; H. Hagberg and C. Gisselbrecht; Annals of Oncology; 2006	Population
R-ICE vs. R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by stem cell transplantation and maintenance treatment with rituximab or not: first interim analysis on 200 patients. CORAL study; C. Gisselbrecht et al; Blood; 2007	Abstract
Salvage chemotherapy with rituximab DHAP for relapsed non-Hodgkin lymphoma: a phase II trial in the North Central Cancer Treatment Group; T. E. Witzig et al; Leukemia & Lymphoma; 2008	Population, Outcome not reported

R-ICE vs. R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma (DLBCL) followed by autologous stem cell transplatation: CORAL study; C. Gisselbrecht et al; Journal of clinical oncology; 2009	Abstract
A phase 2b trial comparing dacetuzumab 1 R-ICE vs placebo 1 R-ICE in patients with relapsed diffuse large B-cell lymphoma; L. Fayad et al; Annals of oncology; 2011	Full text not available
Salvage regimen with autologous stem cell transplantation with or without rituximab maintenance for relapsed diffuse large B-cell lymphoma (DLBCL): coral final report; C. Gisselbrecht et al; Annals of Oncology; 2011	Full text not available
Rituximab, gemcitabine, cisplatin, and dexamethasone in patients with refractory or relapsed aggressive B-cell lymphoma; Y. Hou et al; Medical Oncology; 2012	Population, Outcome not reported separately for relevant population
The efficacy and safety of gemcitabine, dexamethasone, and cisplatine (GDP) therapy for relapsed/refractory lymphoma; K. Nozawa et al; Annals of oncology; 2015	Full text not available
A randomized, phase 2 trial of denintuzumab mafodotin and RICE vs RICE alone in the treatment of patients (pts) with relapsed/refractory (r/r) diffuse large B-cell lymphoma (DLBCL) who are candidates for autologous stem cell transplant (ASCT); R. W. Chen et al; Journal of clinical oncology; 2016	Abstract
Long term survival after 2 years event free survival in relapsed DLBCL after autologous transplantation in the two randomized trials ly.12 and coral; S. Assouline et al; Bone marrow transplantation; 2020	Population, Only 2L
A Phase 2/3, Multicenter Randomized Study of Rituximab-Gemcitabine-Dexamethasone-Platinum (R-GDP) with or without Selinexor in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (RR DLBCL); S. T. Lee et al; Blood; 2021	Abstract
Effectiveness and safety of R-GCD (rituximab, gemcitabine, carboplatin, and dexamethasone) for transplant-ineligible relapse/refractory diffuse large B-cell lymphoma and grade 3a follicular lymphoma: a retrospective analysis comparing with R-GDP (rituximab, gemcitabine, cisplatin, and dexamethasone); R. Naka et al; Leukemia & Lymphoma; 2022	Population, Only 2L
Glofitamab Treatment in Relapsed or Refractory DLBCL after CAR T-Cell Therapy; V. Rentsch et al; Cancers (Basel); 2022	Population, CAR-T not approved in Denmark
Pola-R-ICE: open-label, prospective phase III clinical study to compare polatuzumab vedotin + rituximab, ifosfamide, carboplatin + etoposide(Pola-R-ICE) with rituximab, ifosfamide, carboplatin + etoposide(R-ICE) alone as salvage-therapy in patients with primary refractory or relapsed diffuse large B-cell-lymphoma (DLBCL); R. Greil et al; Memo - magazine of european medical oncology; 2022	Full text not available

Augmented ICE in Patients With Poor-Risk Refractory and Relapsed Lymphomas; Loo S et al; Clinical Lymphoma Myeloma Leukemia; 2023	Population, Only 2L

Selection criteria used in the MAIC Feasibility Assessment:

- Exclude studies related to glofitamab (Roche has access to full trial data, Individual Patient Data (IPD))
- DLBCL histologies (those aligned with the glofitamab trial to be ≥ 80%)
- At least 45% of patients have received 2 or more lines of previous therapy
- More than one publication based on the same study, incl. only the publication with the most recent CCOD
- ECOG PS (0–1 vs ≥2)
- Age (mean, or median if mean not reported, or % ≥60 years, if neither reported)
- Prioritize phase III over phaseI/II
- Number of included patients greater than 40
- Baseline characteristics reported**:** ≥ 5 relevant co-variables available including refractory/relapse status
- Outcomes reported: at a minimum CR and OS

Table 55: Overview of study design for studies included in the MAIC feasibility assessment.

Reference	Intervention Comparator	Type of clinical study	No. of DLBCL-patients: n	DLBCL histology: n (%)	No of prior lines of therapy: n (%)	ECOG PS: n (%)	Median age: n (range)	No of baseline characteristics reported for patients with DLBCL: n	Roche study	CCOD	Outcomes reported for DLBCL-patients	Excluded	Rationale for exclusion/inclusion
Bieker et al., 2003 (106)	R-CHOP/R-CHAP	Retrospective	10	Not specified	0: 3 (30) 1: 4 (40) 2: 2 (20) 3: 1 (10)	Not reported	52 (32-74)	3	-	Not relevant (Only one publication)	ORR, CR, PR, DOR, duration of survival, survival rate (but the follow up is not clear)	Yes	Sample size, lack of information on baseline characteristics
Chiu et al., 2022 (107)	GDP/GDCarboP +/- R	Retrospective	18	Not specified	Not specified for DLBCL-patients	Not reported	Not specified for DLBCL-patients	Not specified for DLBCL-patients	-	Not relevant (Only one publication)	ORR, CR, PR	Yes	Histology; missing information on DLBCL-patients, sample size, outcomes
Crump et al., 2017 (6)		Retrospective	636	DLBCL*: 87 % PMBCL: 2% tFL: 4% Missing: 7% **Not defined as "NOS" since inclusion criteria in CORAL was "DLBCL"*	1: 28% 2-3: 49 % ≥4: <1%	0-1: 73% 2-4: 14 % Missing: 13 %	55 (19-81)	8	-	Not relevant (Only one publication)	CR, PR, OS	No	Included
Dickinson et al., 2022 (1)	Glofitamab	Phase I/II	155	DLBCL NOS: 110 (71) tFL: 27 (18) HGBCL: 11 (7) PMBCL: 6 (4)	2: 62 (40) ≥3: 92 (60)	0: 69 (45) 1: 84 (55)	66 (21–90)	10	NP30179 Glofitamab	March 15, 2022	CR, ORR, DOCR, DOR, PFS, OS	Yes	Roche study, data reported from an earlier CCOD compared to data on file

M. Hutchings et al., 2021 (3)	Glofitamab	Phase I/II	171** **B-NHL	DLBCL NOS: 73 (42.7) tFL: 29 (17.0) PMBCL: 3 (1.8) FL grade 1-3A: 44 (25.7) Richter's transformation: 10 (5.8) Others: 12 (7.0)	Median: 3 Range (1-13)	0: 87 (51.2) 1: 83 (48.8)	64 (22-85)	14	NP30179 Glofitamab	August 3, 2020	CR, PR, ORR, PFS	Yes	Roche study, data reported from an earlier CCOD compared to data on file
Kong et al., 2022 (108)	R-DHAP	Prospective, phase IV	21	All had histology confirmed DLBCL. Of these: 33% had double-expression DLBCL and 10% were double-hit DLBCL. However, these data were for patients who had received only 1 line or more lines of previous therapy	1: 12 (57) >1: 9 (43)	0-1: 11 (52) 2-3: 10 (48) 4-5: -	51 (14-70)	approximately 7	-	Not relevant (Only one publication)	ORR, DOR, toxicity, PFS and OS	Yes	Sample size, outcomes, no of prior lines of therapy
Moccia et al., 2017 (109)	GDP	Retrospective	152	Not specified	Primary refractory: 57 (37) Relapse/progression: 1st: 144 (95) 2nd/3rd: 8 (5)	Not reported	56 (16–79)	11	-	Not relevant (Only one publication)	PFS, OS	Yes	Unclear exactly how many patients who have received two or more lines of therapy.
Neste et al., 2017 (47)	ICE, DHAP, gemcitabine-containing, CHOP-like and other	Extension of a phase III study	75	Not specified	2	Not reported	56.1 (20.9-67.7)	3	-	Not relevant (Only one publication)	CR, PR, OS	Yes	Lack of relevant baseline characeristics

Table 56: Overview of included studies in SCHOLAR-1.

Reference	Study NCT	Patient population	Intervention and comparator (sample size (n))	Primary and secondary outcome and follow-up period
Crump, M., et al., Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood, 2017. **130**(16): p. 1800-1808 (6)	SCHOLAR-1 (multicohort retrospective):	Adult patients with refractory DLBCL (including the subtypes PMBCL and trFL)	Chemotherapy N=636	- CR - PR - ORR - OS
	LY.12 (13) *(NCT 00078949)*	*Adult patients with aggressive non-Hodgkin's lymphoma who were refractory or relapsed after first-line treatment*	*R-GDP or R-DHAP* *N=619*	*- Response rates* *- PFS* *- OS* *- Safety* *- QoL*
	CORAL (11, 12) *(NCT 00137995)*	*Adult patients with DLBCL who were in their first relapse or who were refractory after first-line therapy.*	*R-DHAP or R-ICE* *N=396*	*- Response rates* *- PFS* *- OS* *- Safety*
	MDACC (observational cohort) (14)	*Adult patients with R/R DLBCL or trFL who had received initial R-CHOP/CHOP-like therapy, had failed salvage chemotherapy and who had received a second salvage therapy*	*Rituximab-containing chemotherapy* *N=191*	*- Response rates* *- PFS* *- OS*
	IA/MC (15, 16) *(observational cohort)*	*Newly diagnosed patients with lymphoma who entered prospective documentation of primary and subsequent treatments and outcomes*	*Chemotherapy* *US data sets: MER cohort: N=680 of which 552 entered into post-treatment observations. Of the 552, 112 suffered a relapse.*	*- OS*

Quality assessment

The described literature searches have been performed based on the fact that no direct evidence comparing glofitamab with standard treatment of care used in Danish clinical practice is available. Since it was anticipated that limited evidence would be available, there was a need to broaden the scope of the review so that the population included DLBCL as a whole. In addition, no strict restrictions were applied to the study design which included interventional and observational studies. Also, because of the sparse evidence for the comparators of interest, the review was broadened to include treatment regimens such as

- GDP +/- R (gemcitabine, dexamethasone, cisplatin, rituximab)
- DHAP +/- R (dexamethasone, cytarabine, cisplatin, rituximab)
- ICE +/- R (ifosfamide, carboplatin, etoposide, rituximab)

Furthermore, no restrictions were applied in terms of treatment lines and no outcome search terms were included to ensure that the searches reflect a broad search.

To ensure that every literature article in the search result was assessed with a first and second opinion, two reviewers independently screened the references by title and abstract according to the defined in- and exclusion criteria using a reference management tool.

With the above-mentioned search parameters and strategies in mind - and looking at the output of the searches where it is seen that the references which were expected to be found actually are included - it reasonable to conclude that the search strings are strong.

Unpublished data

The unpublished data reported from the NP30179 study from the CCOD June 15, 2022 is currently not published. However, the data will be available in the EMA assessment report which will be available after commission decision.

Further, unpublished data presented in section 5 and Appendix C are derived from the unpublished manuscript by AL-Mashadi et al. (9), which reports data from the Danish lymphoma database (LYFO). The planned submission of these data is 2023.

Appendix B Main characteristics of included studies

Table 57: Study characteristics of NP30179.

Trial name: NP30179	NCT number: NCT03075696
Objective	To evaluate the efficacy, safety, tolerability and pharmacokinetics (PK) of a novel T-Cell bispecific (TCB), glofitamab, administered by intravenous (IV) infusion as a single agent and in combination with obinutuzumab, following pre-treatment with a one-time, fixed dose of obinutuzumab.
Publications – title, author, journal, year	Glofitamab for Relapsed or Refractory Diffuse Large B-Cell Lymphoma, Michael J. Dickinson, MJ et al, The New England Journal of Medicine, 2022.
Study type and design	Phase I/II, multicenter, open-label, dose-escalation study divided in 3 parts: dose escalation (Parts I and II) and dose expansion (Part III). Single-participant dose-escalation cohorts will be used in Part I, followed by conversion to multiple participant dose-escalation cohorts (Part II), in order to define a tentative maximum tolerated dose (MTD) or optimal biological dose (OBD). The expansion cohorts (Part III) will be initiated when the tentative MTD/OBD is defined, to further evaluate the safety, PK and therapeutic activity of glofitamab.
Sample size (n)	CCOD of June 15, 2022: ITT population, n= 155, Safety-evaluable population, n=154 Supporting cohort, n=101 CCOD of September 14, 2021: Pivotal cohort, n=108, Safety-evaluable pivotal cohort, n=107

Main inclusion and exclusion criteria	Inclusion Criteria: • Depending upon study part, a history or status of: 1) a histologically-confirmed hematological malignancy that is expected to express cluster of differentiation (CD)20; 2) relapse after or failure to respond to at least one prior treatment regimen; and 3) no available treatment options that are expected to prolong survival (e.g., standard chemotherapy or autologous stem cell transplant [ASCT]) • Measurable disease, defined as at lease one bi-dimensionally measurable nodal lesion, defined as > 1.5 cm in its longest dimension, or at least one bi-dimensionally measureable extranodal lesion, defined as > 1.0 cm in its longest dimension • Able to provide a fresh biopsy from a safely accessible site, per investigator determination, providing the patient has more than one measurable target lesion • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Life expectancy of >/=12 weeks • AEs from prior anti-cancer therapy must have resolved to Grade less than or equal to (</=) 1 • Adequate liver, hematological and renal function • Negative serologic or polymerase chain reaction (PCR) test results for acute or chronic Hepatitis B virus (HBV) infection • Negative test results for Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) • Negative serum pregnancy test within 7 days prior to study treatment in women of childbearing potential. Women who are not of childbearing potential who are considered to be postmenopausal (at least 12 months of non-therapy amenorrhea) or surgically sterile (absence of ovaries and/or uterus) are not required to have a pregnancy test Exclusion Criteria: • Inability to comply with protocol mandated hospitalizations and restrictions • Participants with chronic lymphocytic leukemia (CLL), Burkitt lymphoma and lymphoplasmacytic lymphoma • Participants with a known or suspected history of hemophagocytic lymphohistiocytosis (HLH) • Participants with acute bacterial, viral, or fungal infection at baseline, confirmed by a positive blood culture within 72 hours prior to obinutuzumab infusion or by clinical judgment in the absence of a positive blood culture • Participants with known active infection, or reactivation of a latent infection, whether bacterial, viral, fungal, mycobacterial, or other pathogens or any major episode of infection requiring hospitalization or treatment with IV antibiotics within 4 weeks of dosing • Prior treatment with systemic immunotherapeutic agents, including, but not limited to, radioimmunoconjugates, antibody-drug conjugates, immune/cytokines and monoclonal antibodies (e.g., anti-cytotoxic T-lymphocyte-associated protein 4 [anti-CTLA4], anti-programmed death 1 [anti-PD1] and anti-programmed death ligand 1 [anti-PDL1]) within 4 weeks or five half-lives of the drug, whichever is shorter, before obinutuzumab infusion on Cycle 1 Day -7 • History of treatment-emergent immune-related AEs associated with prior immunotherapeutic agents • Documented refractoriness to an obinutuzumab-containing regimen • Treatment with standard radiotherapy, any chemotherapeutic agent, or treatment with any other investigational anti-cancer agent, including chimeric antigen receptor therapy (CAR-T) within 4 weeks prior to obinutuzumab infusion • Prior solid organ transplantation • Prior allogeneic SCT • Autologous SCT within 100 days prior to obinutuzumab infusion • Participant with history of confirmed progressive multifocal leukoencephalopathy (PML) • Current or past history of central nervous system (CNS) lymphoma • Current or past history of CNS disease, such as stroke, epilepsy, CNS vasculitis, or neurodegenerative disease. Participants with a past history of stroke that have not experienced a stroke or transient ischemic attack in the past 2 years and have no residual neurologic deficits are allowed • Evidence of significant, uncontrolled concomitant diseases that could affect compliance with the protocol or interpretation of results, including diabetes mellitus, history of relevant pulmonary disorders and known autoimmune diseases

Trial name: NP30179	NCT number: NCT03075696
	• Participants with another invasive malignancy in the last 2 years (with the exception of basal cell carcinoma and tumors deemed by the Investigator to be of low likelihood for recurrence) • Significant or extensive history of cardiovascular disease such as New York Heart Association Class III or IV or Objective Class C or D cardiac disease, myocardial infarction within the last 6 months, unstable arrhythmias, or unstable angina • Administration of a live, attenuated vaccine within 4 weeks before obinutuzumab infusion or anticipation that such a live attenuated vaccine will be required during the study • Received systemic immunosuppressive medications (including but not limited to cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor agents) within two weeks prior to obinutuzumab infusion. Treatment with corticosteroid </= 25 mg/day prednisone or equivalent is allowed. Inhaled and topical steroids are permitted. • Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that would contraindicate the use of an investigational drug • History of autoimmune disease, including but not limited to myocarditis, pneumonitis, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus, erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. Participants with a remote history of, or well controlled autoimmune disease, may be eligible to enroll after consultation with the Medical Monitor • In Part III DLBCL dexamethasone cohort, patients with a history of hypersensitivity to dexamethasone or systemic corticosteroids will be excluded
Intervention	Participants received glofitamab monotherapy after a fixed, single-dose pre-treatment of obinutuzumab. Glofitamab was administered in step-up doses of 2.5 mg on day 8 of cycle 1 and 10 mg on day 15 of cycle 1, followed by 30 mg on day 1 of cycle 2 through 12 cycles.
Comparator(s)	N/A
Follow-up time	13.4 months (CCOD June 15, 2022)
Is the study used in the health economic model?	Yes

Trial name: NP30179	NCT number: NCT03075696
Primary, secondary and exploratory endpoints	Endpoints included in this application: The primary endpoint was complete response (CR) rate according to assessment by an independent review committee (IRC). Key secondary endpoints included IRC-assessed duration of CR (DOCR), IRC-assessed progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQoL) as assessed by EORTC QLQ-C30 v3.0 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: • Part I and II: Percentage of Participants With Dose Limiting Toxicities (DLTs) [Time Frame: From Baseline up to 4 weeks] • Part II: MTD or OBD of Glofitamab [Time Frame: From Baseline up to 4 weeks] • Part II: Recommended Phase II Dose (RP2D) of Glofitamab [Time Frame: From Baseline up to 5 years] • Part I, II and III: Area Under the Serum Concentration Vs. Time Curve (AUC) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 to Day 71] • Part I, II and III: Maximum Serum Concentration (Cmax) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 to Day 198] • Part I, II and III: Minimum Serum Concentration (Cmin) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 up to Day 198] • Part I, II and III: Clearance (CL) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 to Day 71] • Part I, II and III: Volume of Distribution at Steady-State (Vss) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 to Day 71] • Part I, II and III: Half-Life (t1/2) of Glofitamab [Time Frame: At pre-defined intervals from Cycle 1 Day 1 to Day 71] • Part I, II and III: Cmax of Obinutuzumab [Time Frame: Pre-dose of obinutuzumab on Day -7; pre-dose (Hr 0) of glofitamab on Day 1 of Cycle 1] • Part I, II and III: Cmin of Obinutuzumab [Time Frame: Pre-dose of obinutuzumab on Day -7; pre-dose (Hr 0) of glofitamab on Day 1 of Cycle 1] • Part I, II and III: Anti-Drug Antibodies (ADA) to Glofitamab [Time Frame: Pre-dose of obinutuzumab on Day -7; pre-dose (Hr 0) of glofitamab on Day 1 of each cycle from Cycle 2 onwards for a maximum of 8-12 cycles, and at EOT/follow-up visit (up to 5 years)] • Parts I and II: Percentage of Participants With Overall Response (Partial Response [PR] or Complete Response [CR]) as Determined by the Lugano Classification [Time Frame: From Baseline up to end of study or discontinuation due to disease progression (up to 5 years)] • Part I, II and III: Percentage of Participants With PR or CR (Overall Response Rate) as Determined by the Lugano Classifications [Time Frame: From Baseline up to end of study or discontinuation due to disease progression (up to 5 years)] • Part I, II and III: Duration of Response (DOR) as Determined by the Lugano Classification [Time Frame: From first occurrence of documented objective response until disease progression, relapse or death due to any cause (up to 5 years)] • Part III: Investigator-assessed Complete Response (CR) Rate as Assessed by Independent Review Committee (IRC) According to Standard Non-Hodgkin's Lymphoma (NHL) Response Criteria (Lugano Classification) [Time Frame: From treatment start up to 5 years] • Part I, II and III: Investigator-assessed Duration of Complete Response (DOCR) as Determined by the Lugano Classification [Time Frame: From the first occurrence of a documented, complete response, until the time of relapse or death from any cause (up to 5 years)] • Part I, II and III: Investigator-assessed Progression-Free Survival (PFS) as Determined by the Lugano Classification [Time Frame: From first study treatment to the first occurrence of disease progression or death due to any cause (up to 5 years)] • Time to First Overall Response (TFOR) [Time Frame: From time of treatment start to first documented response (up to 5 years)] • Time to First Complete Response (TFCR) [Time Frame: From treatment start to first documented complete response (up to 5 years)]

Trial name: NP30179	NCT number: NCT03075696
Method of analysis	CR and ORR was assessed by the IRC and INV and based on assessment of PET-CT scans by using the Lugano classification. A comparison of CR between the pivotal cohort and historical controls was conducted using an exact binomial test with two-sided α level of 5% based on data from the initial CCOD of September 14, 2021. The historical CR rate for patients in the R/R DLBCL cohort was assumed to be 20% and the 95% CIs for the CR rate was calculated based on the Clopper-Pearson method. DOCR was assessed by the IRC and INV using the Lugano criteria. The extent of follow-up for DOCR was estimated using the reverse Kaplan-Meier method, where censors and events were reversed from DOCR. The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOCR. PFS was assessed by the IRC and INV using the Lugano criteria. The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS. The Kaplan-Meier method was used to estimate 6-month PFS and 12-month PFS, along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula. Likewise, the Brookmeyer-Crowley method was used to construct the 95% CI for the median OS. The Kaplan-Meier method was used to estimate 6-month and 12-month survival rates, along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula. PRO was assessed using both EORTC QLQ-C30 and FACT-Lym LymS.
Subgroup analyses	No subgroup analysis are presented in this application. However, subgroup analyses were performed on IRC- and INV-assessed CR rate for the ITT population and separately for the pivotal cohort. Forest plots showing the proportions of CRs with 95% CIs within each subgroup were produced on the basis of the primary endpoint subgrouped by e.g. demography data prior therapy including CAR-T, NHL subtype at study entry and relapse and refractory status. The subgroup analyses were not adjusted for multiplicity, and all subgroup analyses were exploratory only.
Other relevant information	-

Table 58: Study characteristics of SCHOLAR-1.

Trial name: SCHOLAR-1	NCT number:
Objective	To evaluate response rates and OS in patients with refractory NHL including DLBCL-trFL and PMBCL
Publications – title, author, journal, year	Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR1 study. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C, Blood, 2017
Study type and design	SCHOLAR-1 is an international, multicohort, retrospective NHL research study retrospectively evaluating outcomes in patients with refractory y NHL, including DLBCL, trFL and PMBCL. SCHOLAR-1 pooled patient-level data from 4 sources; 2 large phase 3 clinical trials (CORAL and LY.12) and 2 observational cohorts (MDACC and IA/MC).
Sample size (n)	861 patient records were extracted from the 4 studies with 636 patients (CORAL, n=170; LY.12, n=219; MDACC, n=165, and IA/MC, n=82.) included in the analysis on the basis of the refractory inclusion criteria (see below). 523 patients were evaluated for responses. 603 patients were evaluated for survival.

Trial name: SCHOLAR-1	NCT number:
Main inclusion and exclusion criteria	Inclusion Criteria: • Patients with refractory DLBCL, including trFL and PMBCL, who had received subsequent therapy. Refractory DLBCL (including subtypes PMBCL and trFL) was defined as progressive disease (received ≥4 cycles of first-line therapy) or stable disease (received 2 cycles of later-line therapy) as best response to chemotherapy or relapse ≤12 months after ASCT. Transformed FL and PMBCL were included because they are histologically similar and are clinically treated as large-cell lymphoma. • Patients must have received an anti-CD20 monoclonal antibody and an anthracycline as one of their qualifying regimens. • For IA/MC, LY.12, and CORAL, patients were included at first instance of meeting refractory criteria, whereas for MDACC, patients who first met refractory criteria from second-line therapy onward were included. Exclusion Criteria: • Patients with primary central nervous system lymphoma
Intervention	CORAL: R-ICE or R-DHAP LY.12: GDP or DHAP MDACC: Rituximab-containing salvage therapies included: HyperCVAD (17%), ICE (15%), DHAP (14%), ESHAP (12%), Gem-Ox (9%) and methotrexatecytarabine (4%), other chemotherapies (14%) and therapies on clinical trials (15%) IA/MC: Anthracycline-based immunotherapy
Comparator(s)	-
Follow-up time	OS: Unclear (up to 108 months)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	Not directly stated but as indicated in the objectives response rate and OS were endpoint

Trial name: SCHOLAR-1	NCT number:
Method of analysis	Patient-level data were extracted and submitted to a central database from which the pooled analysis was performed. Response to therapy (CR, PR and ORR) for refractory disease was determined by the 1999 International Working Group response criteria per local review for randomized studies (11, 13, 51). In the observational cohorts response to therapy was determined by investigator assessment also using International Working Group response criteria. For the randomized studies CORAL and LY.12, responses/CR were prospectively assessed as per the study schedule of assessments while responses for the observational cohorts MDACC and IA/MC were determined at the time of patient treatment or management as per institution standard procedures. Responses were obtained from an electronic medical record or patient medical record. Higgin's Q statistic with a pre-specified value of $P > 0.1$ was used to evaluate the heterogeneity of response rate between the source databases(54). Higgin's Q statistic describes the percentage of variability in the effect estimates as a result of heterogeneity rather than sampling error. A non-significant *P* value suggests that the heterogeneity does not have a strong influence on the variability in the analysis and that the data can be combined for analysis without further adjustment. Data were pooled at patient level and response rates/CR were estimated with a random effects model (55). Covariates for response were evaluated with a Cochran-Mantel-Haenszel test stratified by institution. Survival was estimated, and covariates were assessed by a Cox proportional hazards model stratified by data source. When covariates assessed after the start of therapy for refractory status were used in survival models, survival time was calculated from the day of covariate assessment. A nominal *P* value of .05 from the Cochran-Mantel-Haenszel tests and Cox models was used to evaluate the effect of covariates on response and survival.
Subgroup analyses	No subgroup analysis are presented in this application. However, response rates were evaluated across subgroups namely, age, refractory status, disease stage and IPI while OS was evaluated separately for age, ECOG, disease stage, IPI and refractory status.
Other relevant information	-

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

Comparability of patients across studies

See also section 7.1.3.

Table 59: Baseline characteristics of the ITT population in NP30179 and the overall population in SCHOLAR-1.

	NP30179	SCHOLAR-1
	ITT Population (n=155)	Overall population (n=636)
Age, years		
Mean (SD)	63.1 (14.5)	-
Median	66	55
Min - max	21-90	19-81
Sex, n (%)		
Female	-	-
Male	64.5%	64 %
ECOG PS at Baseline, n (%)		
0	69 (44.5)	-
1	84 (54.2)	-
0-1	-	73 %
2	1 (0.6)	-
2-4	-	14 %
Missing	1 (0.6)	13 %
Ann Arbor Staging at study entry, n (%)		
Stage I	10 (6.5)	-
Stage II	25 (16.1)	-
Stage I-II	-	27 %
Stage III	31 (20.0)	-
Stage IV	85 (54.8)	-
Stage III-IV	-	72 %
Unknown	4 (2.6)	-
Missing	-	< 1 %
High LDH, n (%) [>ULN]		
High	101 (65.2)	-

Low-Normal	52 (33.5)	-
Missing	2 (1.3)	-
Extranodal disease, n (%)		
Yes	95 (61.3)	-
No	60 (38.7)	-
IPI score		
0	5 (3.2)	
1	24 (15.5)	
0-1		25 %*
2	45 (29.0)	24 %*
3	55 (35.5)	
4	26 (16.8)	
3-5	-	33 %*
Missing or incompletely assessed	-	18 %*
Histology at Baseline, n (%)		
DLBCL	110 (71.0)****	87 %†
HGBCL	10 (6.5)	-
PMBCL	6 (3.9)	2 %
trFL	29 (18.7)	4 %
No. of Prior Treatment Lines, n (%)**		
Mean (SD)	3.08 (1.19)	-
1	-	28 %
2	61 (39.4)	-
3	49 (31.6)	-
2-3	-	49 %
$\geq$ 4	45 (29.0)	< 1 %
Relapse or Refractory category		
Relapse or Refractory to First Line of Prior Therapy		
Refractory	91 (58.7)	28 %
Relapse	64 (41.3)	-
Refractory to last line of prior therapy		
Refractory	131 (84.5)	50 %***
Relapse	24 (15.5)	-
Relapse or Refractory to Any Line of Prior Therapy		

Refractory	139 (89.7)	100 %
Relapse (No Refractory)	16 (10.3)	-
Refractory to prior ASCT		
Refractory	7 (4.5)	-
Relapsed ≤ 12 months post-ASCT	-	22 %
Relapse (No Refractory)	21 (13.5)	-
Unknown	127 (81.9)	-
Prior CAR-T		
Yes	52 (33.5)	-
No	103 (66.5)	100 %
Prior ASCT		
Yes	29 (18.7)	-
No	126 (81.3)	-

Abbreviations: DLBCL - diffuse large B-cell lymphoma; ECOG PS - Eastern Cooperative Oncology Group performance status; HGBCL - high-grade B-cell lymphoma; IPI - International Prognostic Index; LDH - lactate dehydrogenase; PMBCL - primary mediastinal large B-cell lymphoma; SCT - stem-cell transplantation; SD - standard deviation; trFL - transformed FL.
*IPI was determined at diagnosis for MDACC and IA/MC and at randomization for LY.12 and CORAL study patients.
†CORAL: The disease subtype for 96 patients was not available: per the study inclusion criteria, patients were reported to have DLBCL. **SCHOLAR-1: Includes the 78% of patients who were refractory to chemotherapy and excludes those who relapsed post-ASCT. ***Refractory to ≥ 2nd line of therapy. ****DLBCL NOS

Table 60: Baseline characteristics of the populations in the individual studies included in SCHOLAR-1; CORAL, LY.12 and MDACC.

	CORAL		LY.12		MDACC
	R-ICE population (n=202)	R-DHAP population (194)	GDP population (n=310)	DHAP population (n=309)	Overall population n=191
Age, years					
Median	54	55	55.2	54.6	56
Min - max	19-65	19-65	18.7-71.2	22.6-74.3	20-80
> 60, n (%)	-	-	88 (29.4)	89 (28.8)	
Sex, n (%)					
Female	77	76	122 (39.4)	118 (38.2)	
Male	125	118	188 (60.0)	191 (61.8)	
ECOG PS, n (%)					
0	-	-	127 (41.0)	130 (42.1)	
1	-	-	141 (45.5)	137 (44.3)	
≥2	-	-	42 (13.5)	42 (13.6)	
Ann Arbor Staging, n (%)					

Stage I-II	81	66	-	-	
Stage III	-	-	79 (25.5)	76 (24.6)	
Stage IV	-	-	138 (44.5)	134 (43.4)	
Stage III-IV	119	121	-	-	
Histology, n (%)					
DLBCL	*+	*+	216 (71)	203 (67)	179
trFL	-	-	-	-	19
HGBCL	-	-	-	-	
PMBCL	-	-	6 (2)	12 (4)	
FL	**	**	-	-	
Peripheral T-cell	-	-	12 (4)	15 (5)	
Anaplastic large cell	-	-	10 (3)	13 (5)	
Hodkin's Lymphoma	***	***	-	-	
T-cell Lymphoma	****	****	-	-	
Transformed indolent	-	-	42 (14)	45 (15)	
IPI score					
0-1	-	-	115 (38)	117 (38)	
2	-	-	88 (29)	89 (29)	
≥ 3	-	-	100 (33)	98 (32)	

Abbreviations: DLBCL - diffuse large B-cell lymphoma; ECOG PS - Eastern Cooperative Oncology Group performance status; HGBCL - high-grade B-cell lymphoma; IPI - International Prognostic Index; PMBCL - primary mediastinal large B-cell lymphoma; SCT - stem-cell transplantation; SD - standard deviation; FL - follicular lymphoma; trFL – transformed FL.
*383 DLBCL patients in total, + The disease subtype for 96 patients was not available; per the study inclusion criteria, patients were to have DLBCL, **9 FL patients in total, ***2 Hodkin's Lymphoma patients in total, ****2 T-cell Lymphoma patients in total

Comparability of the study populations with Danish patients eligible for treatment

To describe the comparability between the study population in NP30179 and the Danish population, the un-published manuscript by Ludvigsen AL-Mashadi et al. (9), which reports data from the Danish lymphoma database (LYFO) describing the baseline characteristics of 3L+ DLBCL patients in a population-based setting in Denmark will be referred to. It has to be noted, however, that patient reports collected in AL-Mashadi et al were from 2015 to 2019, and some baseline characteristics are therefore eight years old.

Table 61: Baseline characteristics of the ITT population in NP30179 and the overall population in AL-Mashadi et al.

	NP30179	Ludvigsen AL-Mashhadi et al (9)
	ITT Population (n=155)	Overall population (n=190)
Age, years		
Mean (SD)	63.1 (14.5)	-

Median	66	71
Min - max	21-90	20.0-90.0
Sex, n (%)		
Female	35.5%	-
Male	64.5%	-
ECOG PS at Baseline, n (%)		
0	69 (44.5)	-
1	84 (54.2)	-
0-1	-	90 (47.4)
2	1 (0.6)	-
2-4	-	55 (28.9)
Missing/unknown	1 (0.6)	45 (23.7)
Ann Arbor Staging at study entry, n (%)		
Stage I	10 (6.5)	-
Stage II	25 (16.1)	-
Stage I-II	-	51 (26.8)
Stage III	31 (20.0)	-
Stage IV	85 (54.8)	-
Stage III-IV	-	123 (64.7)
Missing/Unknown	4 (2.6)	16 (8.4)
LDH, n (%) [>ULN]		
High	101 (65.2)	108 (56.8)
Low-Normal	52 (33.5)	73 (38.4)
Missing	2 (1.3)	9 (4.8)
Extranodal disease, n (%)		
Yes	95 (61.3)	115 (60.5)
No	60 (38.7)	61 (32.1)
Unknown		14 (7.4)
IPI score		
0	5 (3.2)	
1	24 (15.5)	
2	45 (29.0)	
3	55 (35.5)	
4	26 (16.8)	

1-2	-	30 (15.8)
2-3	-	114 (60.0)
4-5	-	41 (21.6)
Unknown	-	5 (2.6)
Histology at Baseline, n (%)		
DLBCL	110 (71.0)*	95 (50.0)
HGBCL	10 (6.5)	7 (3.7)
PMBCL	6 (3.9)	-
trFL	29 (18.7)	-
Unknown	-	88 (46.3)
No. of Prior Treatment Lines, n (%)		
Mean (SD)	3.08 (1.19)	
2	61 (39.4)	183 (96.3)
3	49 (31.6)	5 (2.6)
≥ 4	45 (29.0)	2 (1.0)
Relapse or Refractory category		
Relapse or Refractory to First Line of Prior Therapy		
Refractory	91 (58.7)	-
Relapse	64 (41.3)	-
Refractory to last line of prior therapy		
Refractory	131 (84.5)	-
Relapse	24 (15.5)	-
Relapse or Refractory to Any Line of Prior Therapy**		
Refractory	139 (89.7)	145 (76.3)
Relapse (No Refractory)	16 (10.3)	45 (23.7)
Prior CAR-T		
Yes	52 (33.5)	-
No	103 (66.5)	100%
Prior ASCT		
Yes	29 (18.7)	Second line ASCT: 33 (17.3) Third line ASCT: 9 (4.7)
No	126 (81.3)	

Abbreviations: DLBCL - diffuse large B-cell lymphoma; ECOG PS - Eastern Cooperative Oncology Group performance status; HGBCL - high-grade B-cell lymphoma; IPI - International Prognostic Index; PMBCL - primary mediastinal large B-cell lymphoma; SCT - stem-cell transplantation; SD - standard deviation; FL - follicular lymphoma; trFL – transformed FL.
*DLBCL NOS, ** In AL-Mashadi et al., refractory status is defined as “refractory to prior line of therapy”.

As seen from Table 61, the median age was lower in NP30179 compared to the Danish population, 66 years vs 71 years. ECOG-PS was also better in NP30179 where the majority (98.7%) was ECOG PS 0-1 compared to 47.4% in the Danish population, and only one patient in NP30179 had an ECOG of 2 and above, whereas in the Danish population, 28.9% had an ECOG PS of 2-4. However, 23.7% in the Danish population had an unknown status meaning that the numbers reported in the 0-1 and 2-4 categories in the AL-Mashadi et al manuscript could be higher. According to Danish clinical experts (36), 40% of Danish 3L+ patients are ECOG PS of 2. The IPI score was comparable between the two populations if one assumes that IPI 2 is included in the 2-3 category rather than the 1-2 category for the Danish population. Differences in histologies is difficult to assess since 46.3% was reported as unknown in the Danish population. However, a minimum of 50% had a DLBCL histology in the Danish population, compared to 71% in NP30179 (DLBCL NOS). The two populations differ in the number of prior treatment lines. In the Danish population, the majority (96.3%) had received two prior treatments, whereas in NP30179 this number was much lower (39.4%) since 60.6% had received three or more prior treatments. The population in NP30179 is therefore more heavily pre-treated. When comparing the refractory status, more patients in NP30179 were refractory to any line of prior therapy (89.7%) compared to the Danish population (76.3%). In NP30179 33.5% of the patients had received a prior CAR-T therapy whereas none had received this in the Danish population.

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 62: Definition, validity and clinical relevance of outcomes presented in this application.

Outcome measure	Definition	Validity	Clinical relevance
CR	NP30179: The proportion of patients whose BOR was a CR based on IRC-assessment of PET-CT) scans by using the Lugano criteria (50). SCHOLAR-1: Response to therapy for refractory disease were determined by the 1999 International Working Group response criteria (51).	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.
ORR	NP30179: The proportion of patients whose BOR was a CR or partial response (PR) based on either IRC- or INV-assessment of PET-CT scans by using the Lugano classification (50). SCHOLAR-1: Response to therapy for refractory disease were determined by the 1999 International Working Group response criteria (51).	ORR is an important endpoint to demonstrate the response to treatment. In previous Medicines Council assessments, ORR has been defined as an important clinical endpoint.	To our knowledge, published information on minimal important differences is not available.
DOCR	NP30179: The time from the initial occurrence of a documented CR until documented disease progression or death due to any cause, whichever occurred first.	DOCR is an important endpoint to demonstrate the duration of response to treatment, especially in the case of DLBCL patients whom may be considered cured after complete remission beyond 24 months (56).	To our knowledge, published information on minimal important differences is not available

Outcome measure	Definition	Validity	Clinical relevance
PFS	NP30179: The time from the first study treatment (obinutuzumab or glofitamab if obinutuzumab was not taken) to the first occurrence of disease progression or death from any cause, whichever occurred first. CORAL: The time from study entry until disease progression or death.	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 (110, 111). 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.	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.
OS	NP30179: The time from the first study treatment (obinutuzumab or glofitamab if obinutuzumab was not taken) to the date of death from any cause. SCHOLAR-1: In CORAL patients with refractory disease were assessed for survival approximately every 3 months for 1 year and then every 6 months for 3 years while patients in LY.12 were assessed at least once a year. In IA/MC and MDACC, patients were followed up for survival per institution standard procedures. Patients who were alive at the time of data extraction were censored at the date of last contact.	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).

Outcome measure	Definition	Validity	Clinical relevance
AEs	NP30179: The incidence, nature and severity of adverse events (AEs) were recorded by the investigator. AEs were coded according to the Medical Dictionary for Regulatory Activities, version 24.0, and AEs were evaluated according to National Cancer Institute–Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Investigators graded cytokine release syndrome (CRS) by consensus criteria of Lee et al and managed according to protocol guidance. LY.12: Adverse events were graded according to CTCAE version 2.0 CORAL: Adverse events were graded according to CTCAE version 3.0	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	NP30179: 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 (57, 112).	To our knowledge, published information on minimal important differences is not available.

Outcome measure	Definition	Validity	Clinical relevance
FACT-Lym LymS	NP30179: 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 (58).	To our knowledge, published information on minimal important differences is not available.

Results per study

Table 63: Outcomes from NP30179

NP30179			Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	[redacted]	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CR rate (IRC-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	CR was assessed by the IRC using the Lugano criteria (50). 95% CIs for the CR rate was calculated based on the Clopper-Pearson method.	CCOD: June 15, 2022

CR rate (INV-assessed)	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
CR rate (IRC-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	CR was assessed by the IRC using the Lugano criteria (50). Comparisons of CR between the pivotal cohort and historical controls was conducted using an exact binomial test with two-sided α level of 5%. The historical CR rate for patients in the R/R DLBCL cohort is assumed to be 20%. 95% CIs for the CR rate was calculated based on the Clopper-Pearson method.	CCOD: September 14, 2021
CR rate (IRC-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	CR was assessed by the IRC using the Lugano criteria (50). 95% CIs for the CR rate was calculated based on the Clopper-Pearson method.	CCOD: June 15, 2022
CR rate (INV-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	CR was assessed by the IRC using the Lugano criteria (50).	CCOD: June 15, 2022

		[redacted]								95% CIs for the CR rate was calculated based on the Clopper-Pearson method.	
ORR (IRC-assessed)	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	ORR was assessed by the IRC using the Lugano criteria (50). 95% CIs for the CR rate was calculated based on the Clopper-Pearson method.	CCOD: June 15, 2022
ORR (INV-assessed)	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
Median DOCR, months (IRC-assessed)	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	DOCR was assessed by the IRC using the Lugano criteria (50). The Brookmeyer-Crowley method was used to construct the 95% CI for the median DOCR.	CCOD: June 15, 2022

DOCR, 6-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
DOCR, 12-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
DOCR, 24-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
Median DOCR, months (INV-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022

DOCR, 6-month event-free rate (INV-assessed) n=patients at risk	Glofitamab	[redacted]		N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
DOCR, 12-month event-free rate (INV-assessed) n=patients at risk	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
DOCR, 24-month event-free rate (INV-assessed) n=patients at risk	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
Median DOCR, months Supporting cohort (IRC-assessed)	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	DOCR was assessed by the IRC using the Lugano criteria (50). The Brookmeyer-Crowley method was used to construct	CCOD: June 15, 2022

n=patients at risk		[redacted]								the 95% CI for the median DOCR.	
DOCR, 6-months Supporting cohort (IRC-assessed) n=patients at risk	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
DOCR, 12-months Supporting cohort (IRC-assessed) n=patients at risk	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
DOCR, 24-months Supporting cohort (IRC-assessed) n=patients at risk	Glofitamab			N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022

Median DOCR, months Supporting cohort (INV-assessed)	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
DOCR, 6-months Supporting cohort (INV-assessed) n=patients at risk	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
DOCR, 12-months Supporting cohort (INV-assessed) n=patients at risk	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
DOCR, 24-months	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022

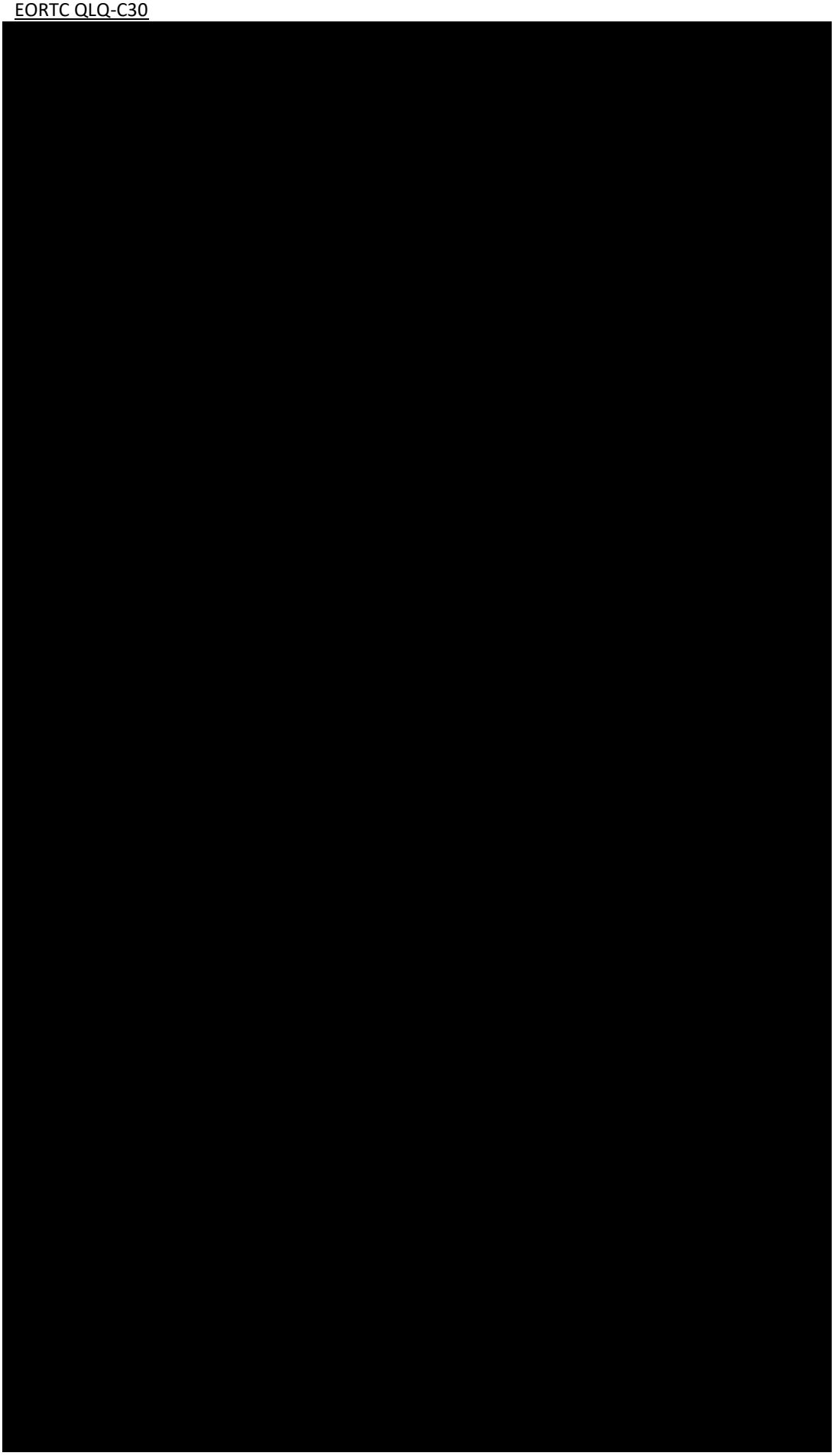
Supporting cohort (INV-assessed) n=patients at risk		[redacted]								
Median OS	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	The Brookmeyer-Crowley method was used to construct the 95% CI for the median OS	CCOD: June 15, 2022
OS, 6-month survival rate n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022
OS, 12-month survival rate n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022
OS, 24-month survival rate n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022

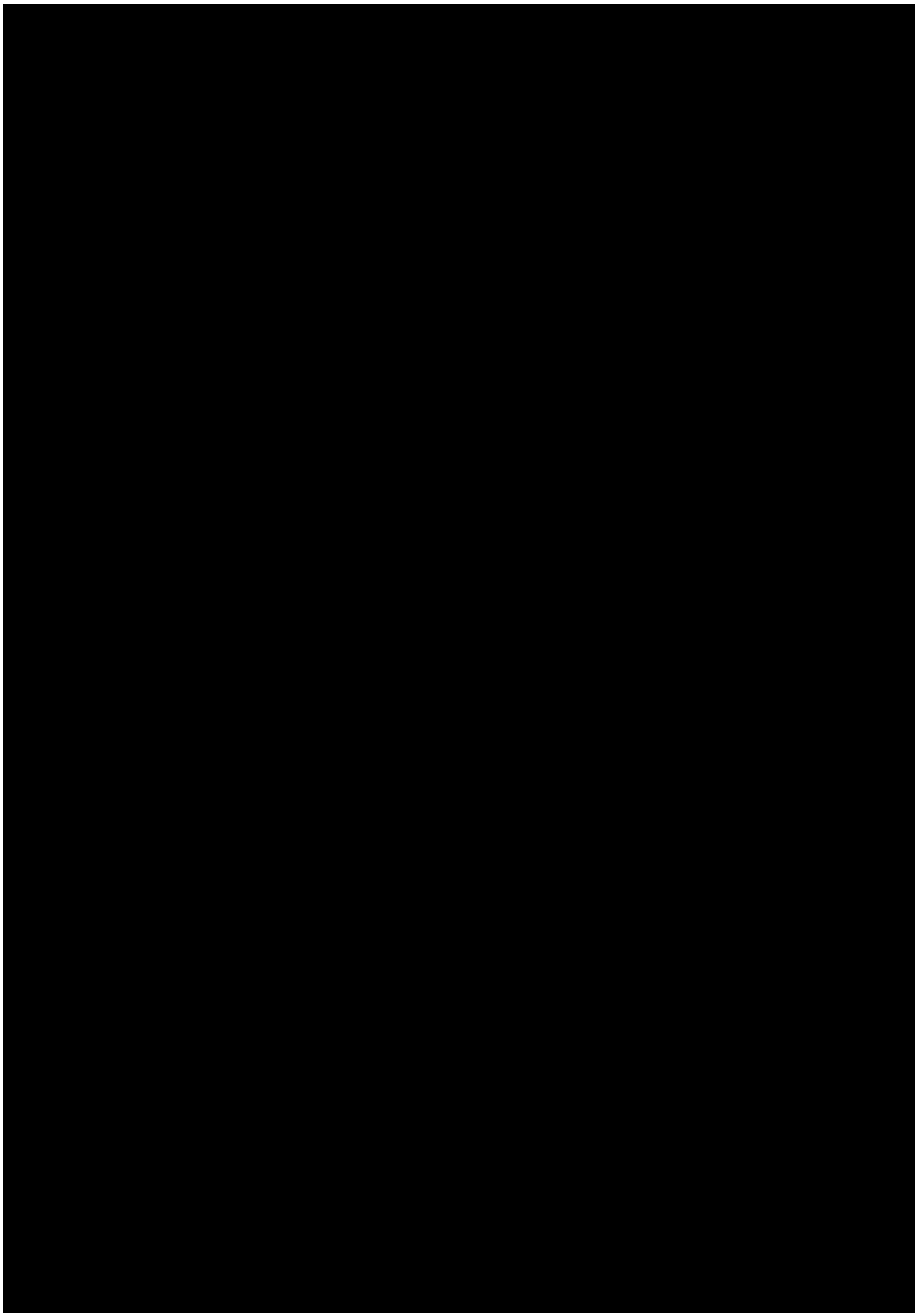
No. patients with PFS event (IRC-assessed)	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis.	CCOD: June 15, 2022
Median PFS (IRC-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	The Brookmeyer-Crowley method was used to construct the 95% CI for the median PFS.	CCOD: June 15, 2022
PFS, 6-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022
PFS, 12-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022
PFS, 24-month event-free rate (IRC-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Estimated by Kaplan–Meier analysis along with the standard error and the corresponding 95% CIs, with use of Greenwood's formula.	CCOD: June 15, 2022

No. patients with PFS event (INV-assessed)	Glofitamab	[redacted]	N/A	N/A	N/A	N/A	N/A	PFS was assessed by the investigator using the Lugano criteria (50).	CCOD: June 15, 2022
Median PFS (INV-assessed)	Glofitamab		N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
PFS, 6-month event-free rate (INV-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
PFS, 12-month event-free rate (INV-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022
PFS, 12-month event-free rate (INV-assessed) n=patients at risk	Glofitamab		N/A	N/A	N/A	N/A	N/A	Same as for IRC-assessed	CCOD: June 15, 2022

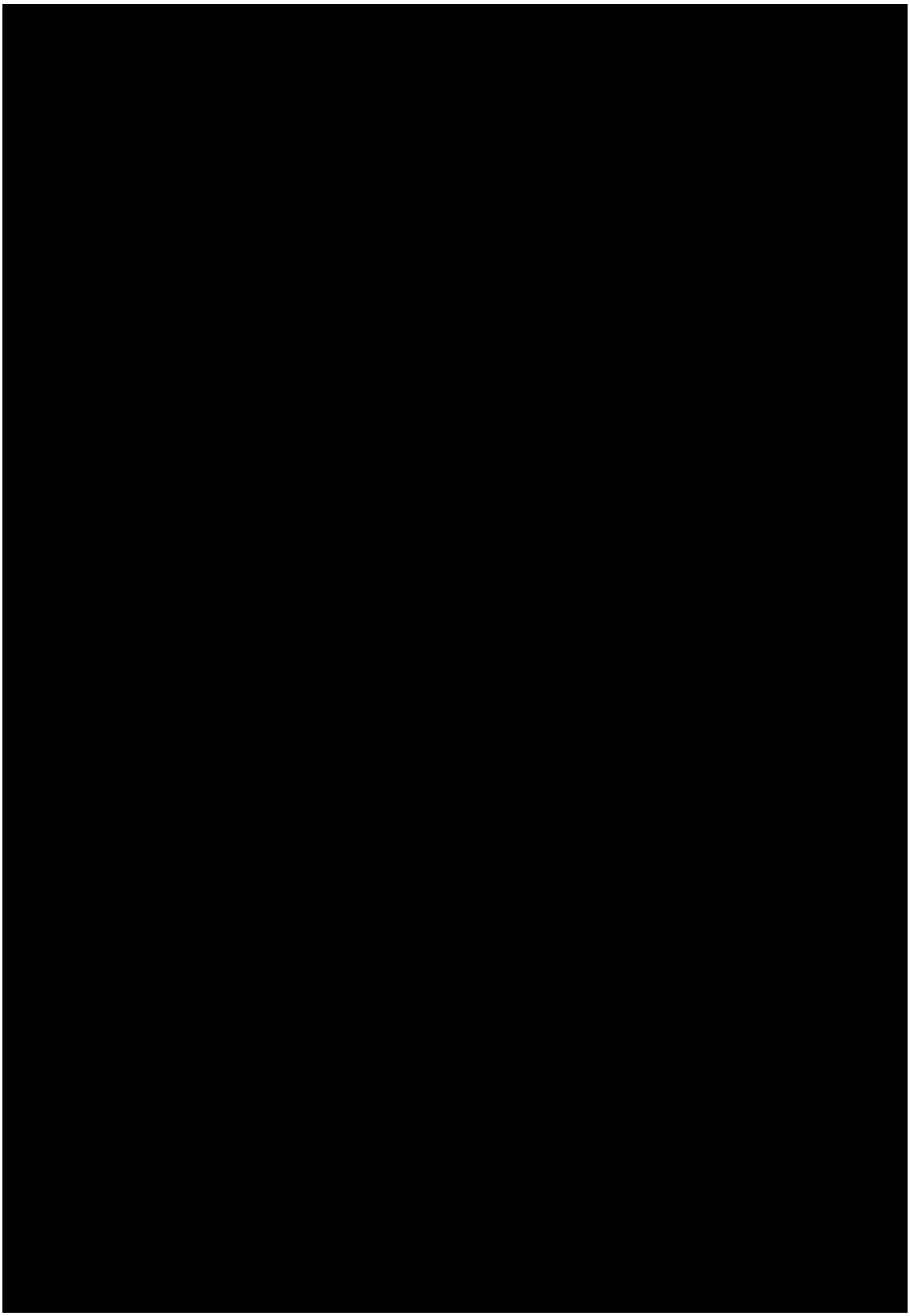
HRQoL

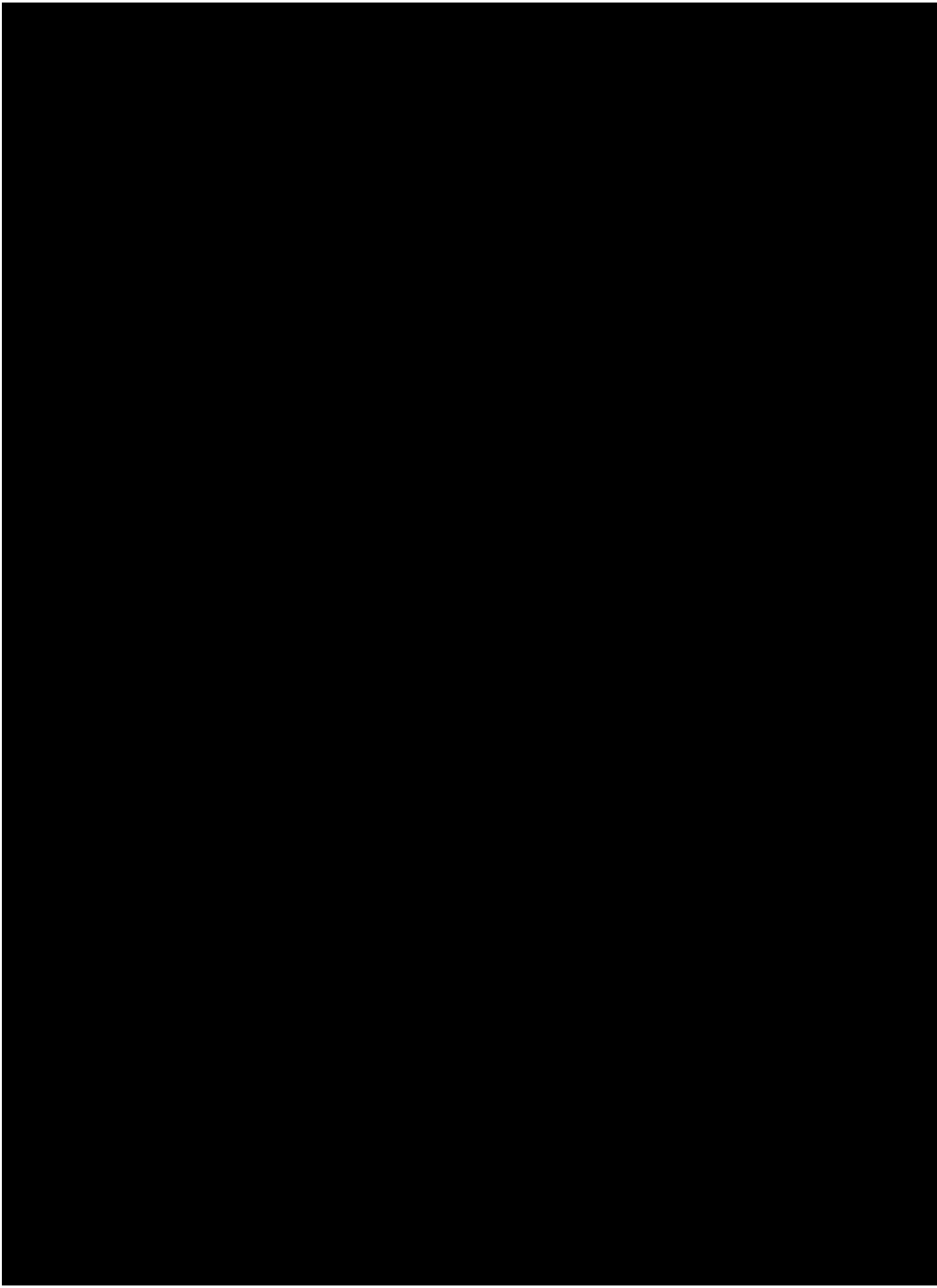
EORTC QLQ-C30

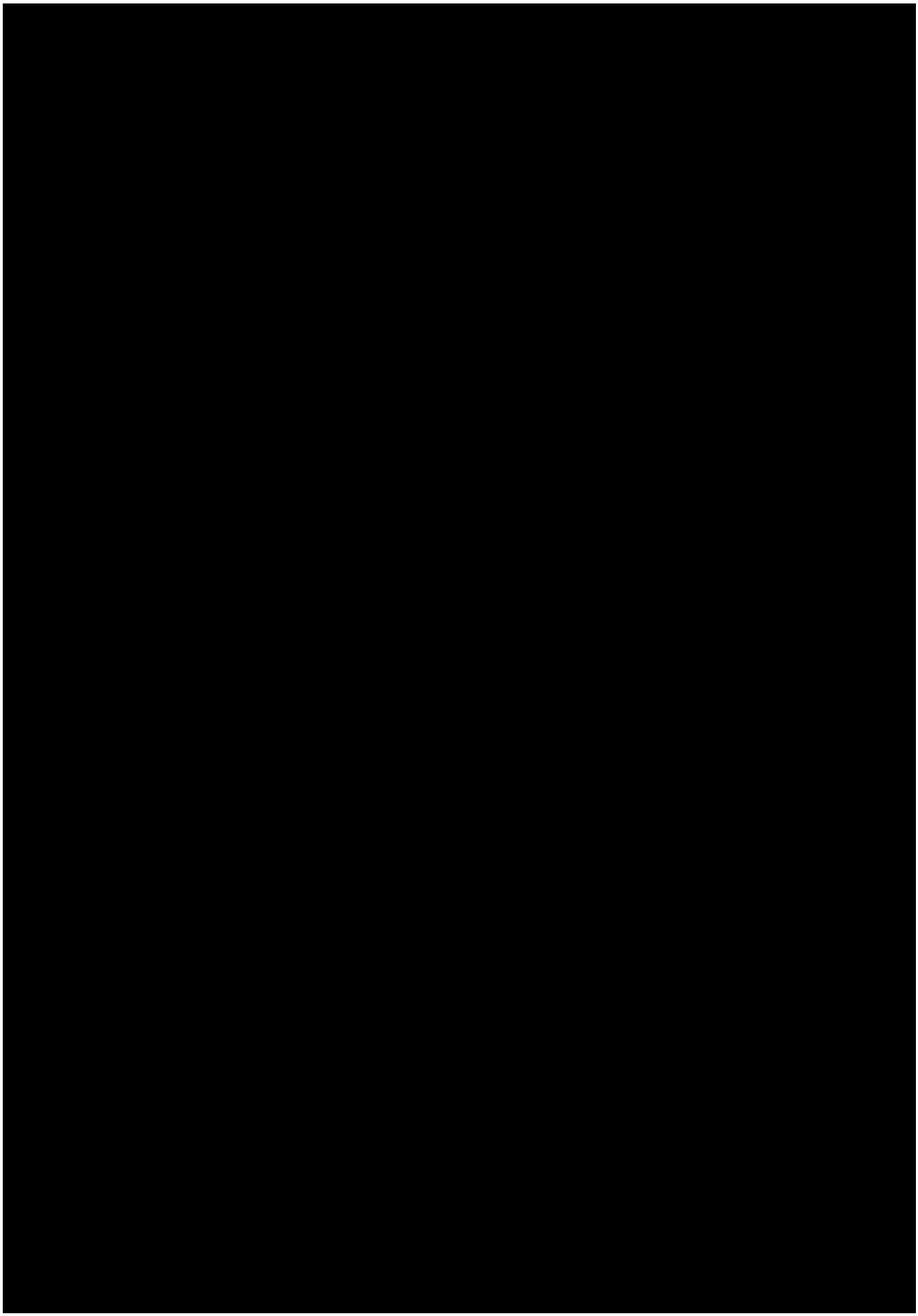


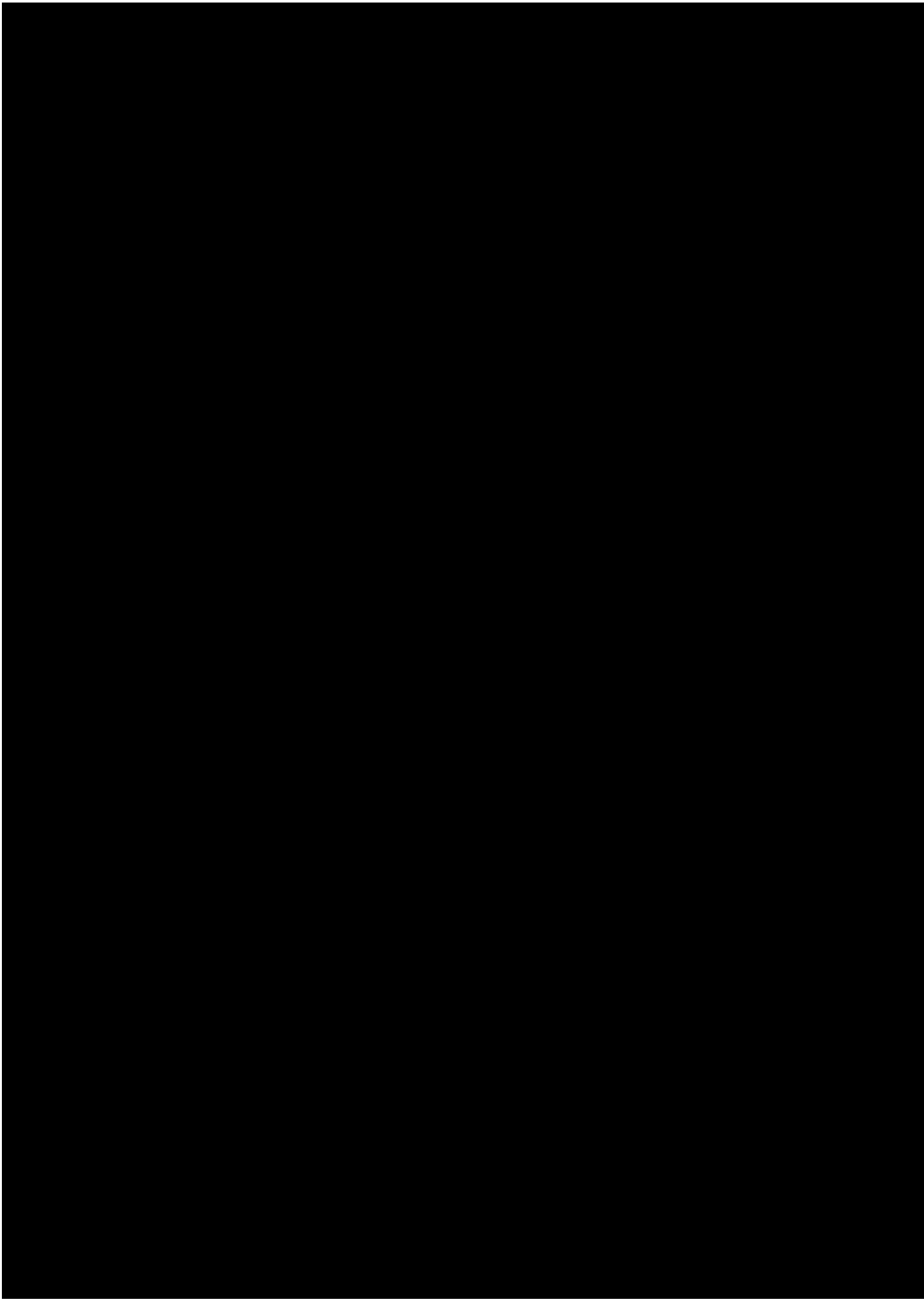


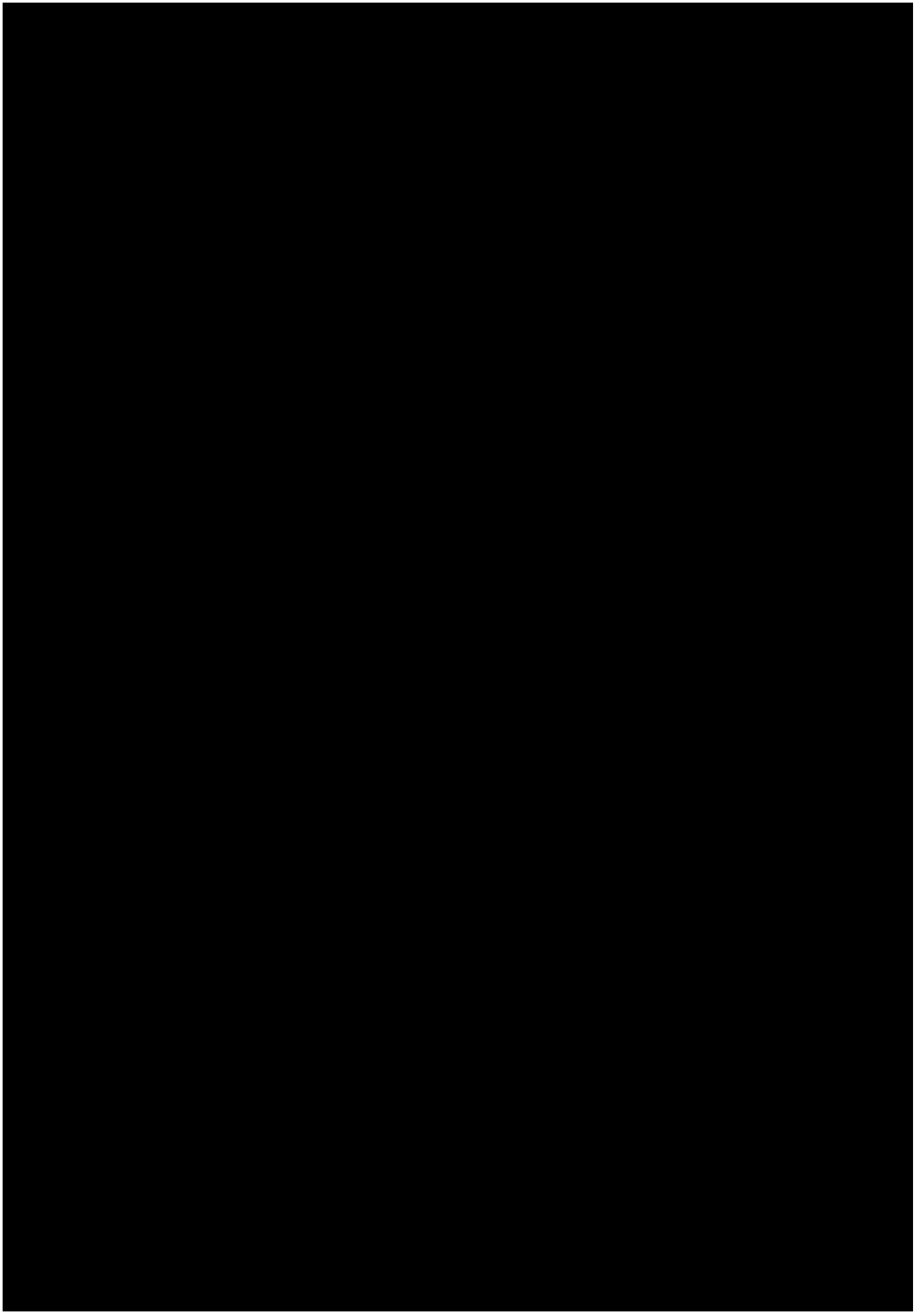
GHS/QoL











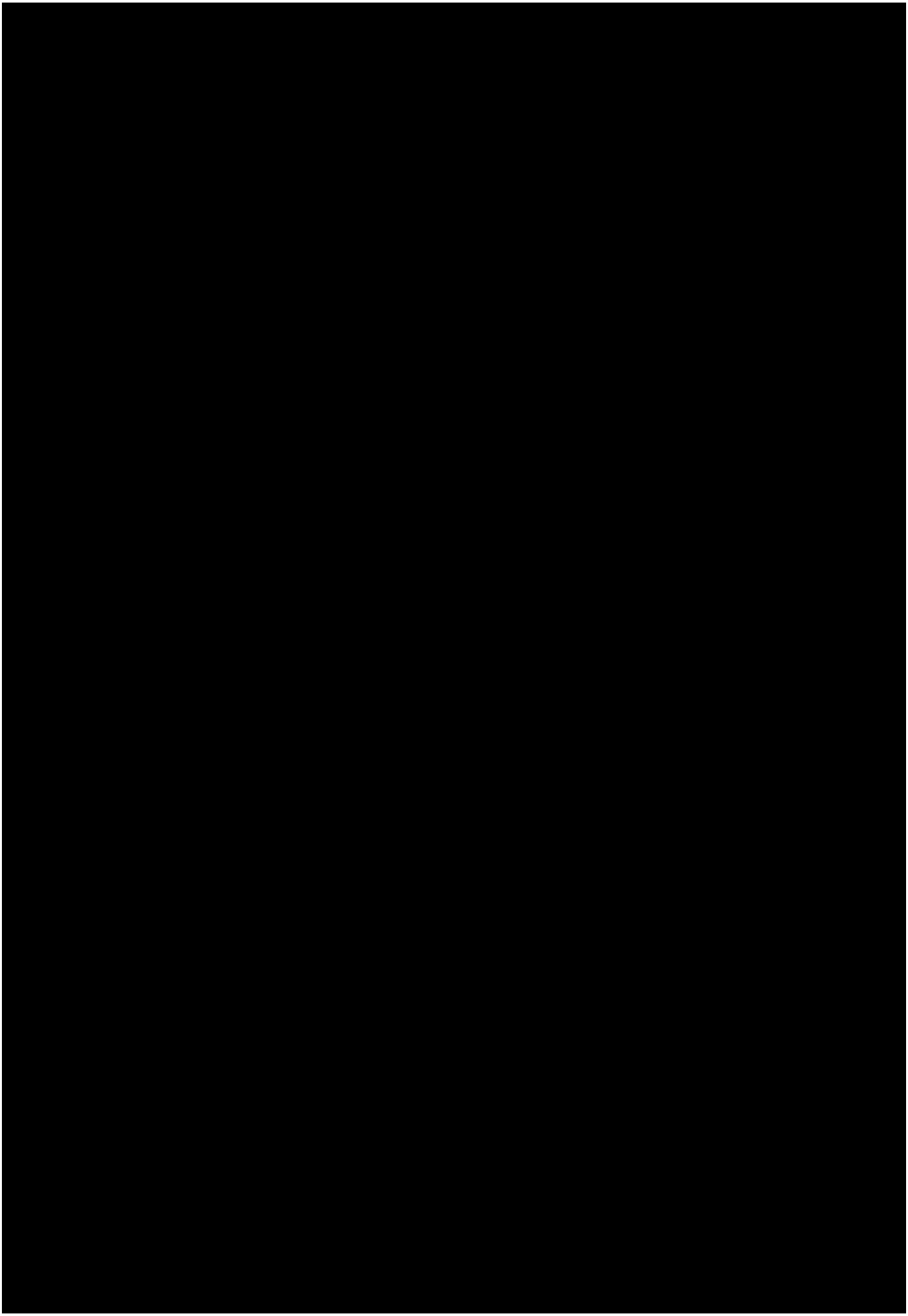


Table 64: Outcomes from SCHOLAR-1.

SCHOLAR				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CR rate	Pooled*	523	7% (3-15)	N/A	N/A	N/A	N/A	N/A	N/A	CR were assessed by the 1999 International Working Group response criteria per local review for randomized studies. In the observational cohorts response to therapy was determined by investigator assessment also using International Working Group response criteria. Higgin's Q statistic with a prespecified value of $P > 0.1$ was used to evaluate the heterogeneity of response rate between the source databases. The pooled analysis was performed and CR was estimated with a random effects model.	Crump et al., 2017 (6)
ORR	Pooled*	523	26% (21-31)	N/A	N/A	N/A	N/A	N/A	N/A	Same as for CR	Crump et al., 2017

Median OS	Pooled*	603	6.3 mo. (5.9-7.0)	N/A	N/A	N/A	N/A	N/A	N/A	Survival was estimated, and covariates were assessed by a Cox proportional hazards model stratified by data source. When covariates assessed after the start of therapy for refractory status were used in survival models, survival time was calculated from the day of covariate assessment. A nominal *P* value of .05 from the Cochran-Mantel-Haenszel tests and Cox models was used to evaluate the effect of covariates on response and survival.	Crump et al., 2017

*Pooled data from four sources: CORAL (R-ICE or R-DHAP), LY.12 study (GDP or DHAP), IA/MC (anthracycline-based immunotherapy) and MDACC (R-containing salvage therapies: HyperCVAD (17%), ICE (15%), DHAP (14%), ESHAP (12%), Gem-Ox (9%) and methotrexatecytarabine (4%), other chemotherapies (14%) and therapies on clinical trials (15%).

Table 65: Outcomes from CORAL.

CORAL				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
3-year PFS	Full population	388	37% (31%-42%)							Kaplan-Meier method	Gisselbrecht et al., 2010 (11)

3-year PFS	R-ICE	191	31%						0.4	Kaplan-Meier method	Gisselbrecht et al., 2010
3-year PFS	R-DHAP	197	42%						0.4	Kaplan-Meier method	Gisselbrecht et al., 2010

[redacted]

Table 66: Outcomes from MDACC.

MDACC				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (95% CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Median PFS	Salvage rituximab-containing chemotherapies including Hyper-CVAD (17%), ICE (15%), DHAP (14%), SHAP (12%), Gem-Ox (9%), methotrexate–cytarabine (4%), other chemotherapies (14%), and therapies on clinical trials (15%).	191	2.8 months (2.4-3.3)	-	-	-	-	-	-	-	Ahmed et al., 2015 (14)

For safety results per study, refer to Appendix E.

Appendix E Safety data for intervention and comparator(s)

Additional safety information can be found in section 7.2.7

Table 67: Incidence of safety outcomes in the safety-evaluable population in NP30179, LY.12 and CORAL.

Safety parameter	NP30179	LY.12		CORAL	
	Safety-evaluable pop-ulation	R-GDP n=306	R-DHAP n=304	R-ICE n=202	R-DHAP n=194
Any AE, n (%)	[redacted]	-	-	-	-
Grade 3-4 AEs	[redacted]	143 (47)+	183 (61)+	-	-
Grade 5 AEs	[redacted]	-	-	-	-
Treatment-related AE, n (%)	[redacted]	-	-	-	-
Grade 3-4 treatment-related AEs	[redacted]	-	-	-	-
Grade 5 treatment-related AEs	[redacted]	2 (0.7)	6 (2.0)	1 (0.5)	3 (1.5)
Any SAE, n (%)	[redacted]	-	-	58 (29)	68 (35)
Treatment-related SAEs	[redacted]	-	-	-	-

Appendix F Comparative analysis of efficacy and safety

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

Effect Modifiers

High priority[2]

- International prognostic index (IPI) (0–2 vs 3–5)/AA-IPI (0–1 vs 2–3) and/or any of its components:
    - Age (mean, or median if mean not reported, or % ≥60 years, if neither reported)
    - ECOG PS (0–1 vs ≥2) [0 vs 1 not that important prognostically]
    - Ann Arbor Stage (I–II vs. III–IV)
    - High lactate dehydrogenase (LDH) levels
    - Presence of extranodal disease (yes/no or number of lesions reported)
- Refractoriness (definition may vary across studies) to first line of treatment
- Refractoriness (definition may vary across studies) to last line of treatment
- Refractoriness (definition may vary across studies) to any line of treatment
    - Some advisors ranked this as lower priority compared to the previous two and as somewhat lower priority compared with early relapse/refractory status to individual agents
- Histological subtype (DLBCL NOS, HGBCL, PMBCL or trFL)
- Double/triple hit lymphoma[3] (to be prioritised over histological subtype, if both reported)
    - This has a similar importance to histological subtype, as double/triple hit lymphoma typically corresponds to having HGBCL (their definitions can vary across studies, though), so controlling for both may not always be needed and only one may be prioritised
- Early relapse after SCT (e.g. defined as duration of response [DOR] or time since completion of transplant to next treatment line <12 months)
    - Not many patients had this condition in NP30179 D3 cohort; if controlling for this was not feasible as resulting in low ESS, consider controlling for prior autologous SCT (ASCT) instead, as a proxy
- Number of prior treatment lines (e.g. 3 vs >3 [no clinically established threshold], or median)

Medium priority

- Bulky disease (definition can vary across studies [no clinically established threshold])[4]

[2] Note that CNS involvement was also flagged as an important prognostic factor, however, it was not included since it was an exclusion criteria in NP30179.

[3] Tumours with double-/triple-hit rearrangements, which do not correspond to double-/triple-expressor tumours, whose actual prognostic value is unclear.

[4] Bulky disease is generally constructed from the size of largest lymph node lesion (longest dimension) involved; as none of the thresholds typically used to define bulky disease have been established as being superior prognostically over the others (based on medical feedback), then adjusting for bulky disease in the MAICs should be de-prioritized in favour of size of largest lymph node lesion when information on both is available.

- Chemotherapy refractoriness
- Prior treatment with (or refractoriness to) rituximab and an anthracycline therapy
    - This has likely a slightly lower (or similar) importance to chemotherapy refractoriness, so when both are reported there is likely no need to control for both and chemotherapy refractoriness can be prioritized, otherwise they can be used as proxies for one another
- Rituximab refractoriness
- Early relapse from last line of treatment (e.g. defined as DOR or time since last completion of therapy treatment <12 months), or, alternatively, time since completion of last therapy)

<u>Low priority</u>

- Primary diagnosis (DLBCL vs. non-DLBCL/indolent lymphoma)
- Cell type of origin of the disease (by immunohistochemistry [IHC] or gene expression profiling [GEP]; when both reported, GEP to be prioritised)
    - If values like germinal centre B cell (GCB), non-GCB and activated B cell (ABC) are reported, then non-GCB and ABC can be pooled; this somewhat applies also to the "unclassified" category, though it is not clear
    - If ABC is reported as a category, then the method of assessment is by definition GEP
    - This variable can have a lot of missing values, particularly for GEP results. In those cases, prioritise the variable definition featuring <50% missing
- Bone marrow involvement
- Primary bone marrow transplant
    - Occurs very rarely and is also very rarely reported, plus only one patient with this in the NP30179 trial, so most likely it cannot be controlled for
- Prior SCT

Table 68: Summary of baseline characteristics grouped according to priority across the NP30179 and SCHOLAR-1 cohorts.

Covariate High priority	NP30179 Total (N=155)	SCHOLAR-1 (n=636)
IPI, n (%)	0: 5 (3.2%) 1: 24 (15.5%) 2: 45 (29.0%) 3: 55 (35.5%) 4: 26 (16.8%)	Low risk (0–1): 25%* Low-intermediate risk (2): 24%* High-intermediate to high risk (3–5): 33%* Missing or incompletely assessed: 18%*
Mean (SD) age, years	63.1 (14.7)	Median: 55 (19–81)
ECOG PS, n (%)	0: 77 (49.7%) 1: 78 (50.3%) 2: 1 (0.6%)	0–1: 73% 2–4: 14% Missing: 13%
Ann Arbor Stage, n (%)	I: 10 (6.5%) II: 25 (16.1%) III: 31 (20.0%) IV: 85 (54.8%) Unknown: 4 (2.6%)	Disease stage: I–II: 27% III–IV: 72% Missing: <1%
High LDH, n (%) [>ULN]	High: 101 (65.2%) Low-Normal: 52 (33.5%) Missing: 2 (1.3%) [at screening]	NR
Extranodal disease, n (%) [yes, or number of sites]	95 (61.3%)	NR
Refractory to 1st line, n (%)	91 (58.7%)	Primary refractory: 28% (Defined as best response of PD or SD to first chemotherapy regimen)

Covariate	NP30179 Total (N=155)	SCHOLAR-1 (n=636)
	(Failure to respond to first treatment or progression within 6 months)	
Refractory to last line, n (%)	131 (84.5%) (Failure to respond to previous treatment or progression within 6 months)	Refractory to ≥ 2nd line of therapy: 50% (Defined as best response of PD or SD to last chemotherapy regimen)
Refractory to any line, n (%)	139 (89.7%) (Failure to respond to any treatment or progression within 6 months)	All patients had to be refractory to be enrolled in the study
Histological subtype: HGBCL, PMBCL or DLBCL/trFL, n (%)	DLBCL: 110 (71.0%) HGBCL: 10 (6.5%) PMBCL: 6 (3.9%) FL: 29 (18.7%)	Primary diagnosis:† DLBCL: 87% PMBCL: 2% trFL: 4% Indeterminate/missing: 7%
Double/triple hit lymphoma, n (%)	19 (12.3%)	NR
Refractory to prior SCT/Early relapse after SCT (<12 months), n (%)	7 (4.5%)	Relapsed within 12 months after prior ASCT: 22%
Number of prior treatment lines, n (%) and median (range)	2: 61 (39.4%) 3: 49 (31.6%) 4: 27 (17.4%) 5: 10 (6.5%) 6: 5 (3.2%) 7: 3 (1.9%) ≥3: 94 (60.6%)	Total no. of lines of chemotherapy and ASCT received:** 1: 28% 2-3: 49% ≥4: <1%
Medium priority		

Covariate	NP30179 Total (N=155)	SCHOLAR-1 (n=636)
Bulky disease, n (%)	>6 cm: 64 (41.6%) >10 cm: 19 (12.3%) Missing: 1 (0.6%)	NR
Refractory to chemotherapy, n (%)	133 (85.8%)	NR
Refractory to rituximab and anthracycline, n (%)	88 (56.8%)	NR
Refractory to rituximab, n (%)	129 (83.2%)	NR
Time since last treatment, mean (SD) [months]	6.49 (15.41)	NR
Low priority		
Primary diagnosis, n (%)	DLBCL: 112 (72.3%) FL: 28 (18.1%) HGBCL: 8 (5.2%) PMBCL: 6 (3.9%) trFL: 1 (0.6%)	NR
Cell type of origin, n (%)	ABC: 17 (11.0%) GCB: 66 (42.6%) Mis-/unclassified: 38 (24.5%) Non-GCB: 34 (21.9%)	NR
Bone marrow involvement, n (%)	18 (11.6%)	NR
Prior SCT, n (%)	29 (18.7%)	NR

Abbreviations: GCB, germinal centre B cell; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; IPI, International Prognostic Index; LDH, lactate dehydrogenase; NOS, not otherwise specified; NR, not reported; PMBCL, primary mediastinal large B-cell lymphoma; SCT, stem-cell transplantation; SD, standard deviation; trFL, transformed FL. * IPI was determined at diagnosis for MDACC and IA/MC and at randomization for LY.12 and CORAL study patients. † In the CORAL (LYSARC) study, the disease subtype for 96 patients was not available; per the study inclusion criteria, patients were to have DLBCL. ** Includes the 78% of patients who were refractory to chemotherapy and excludes those who relapsed post-ASCT.

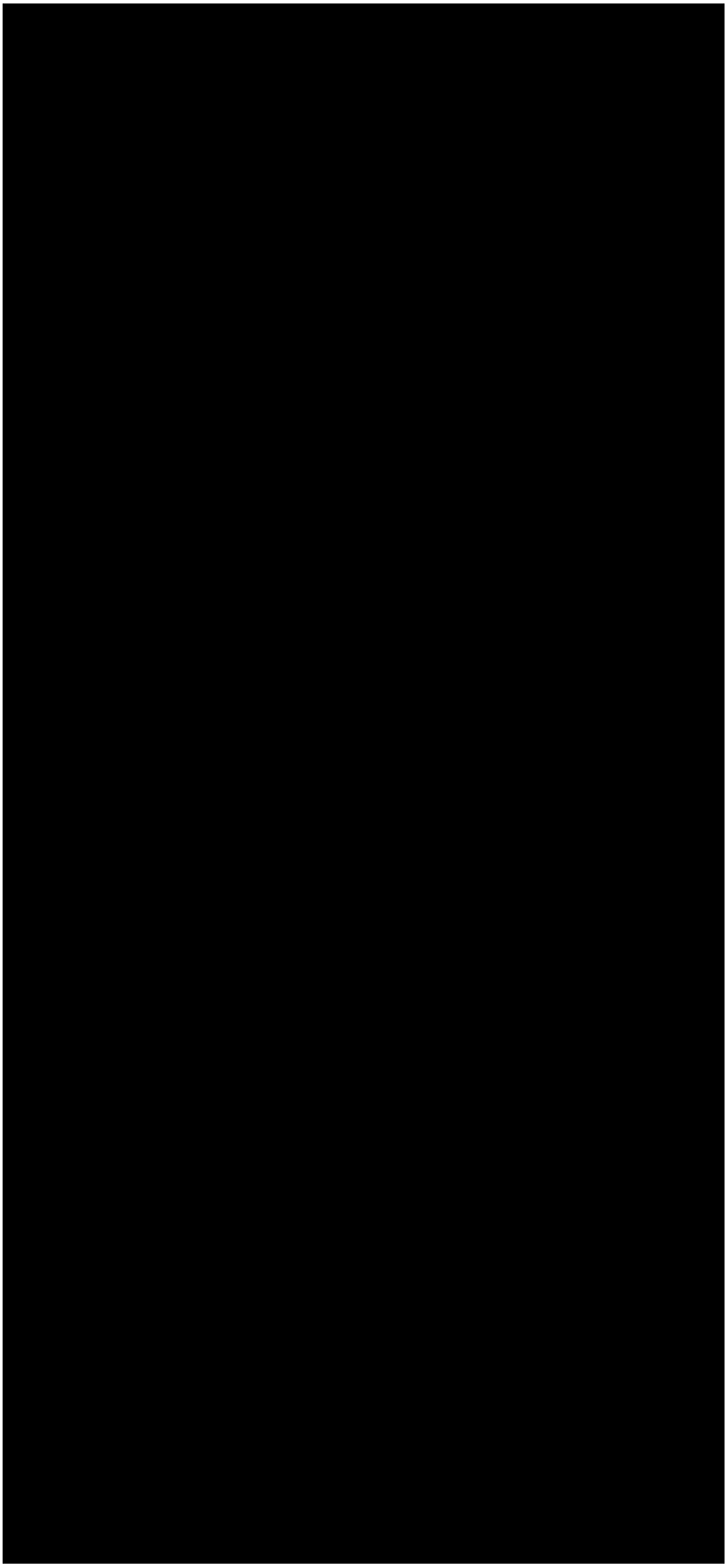
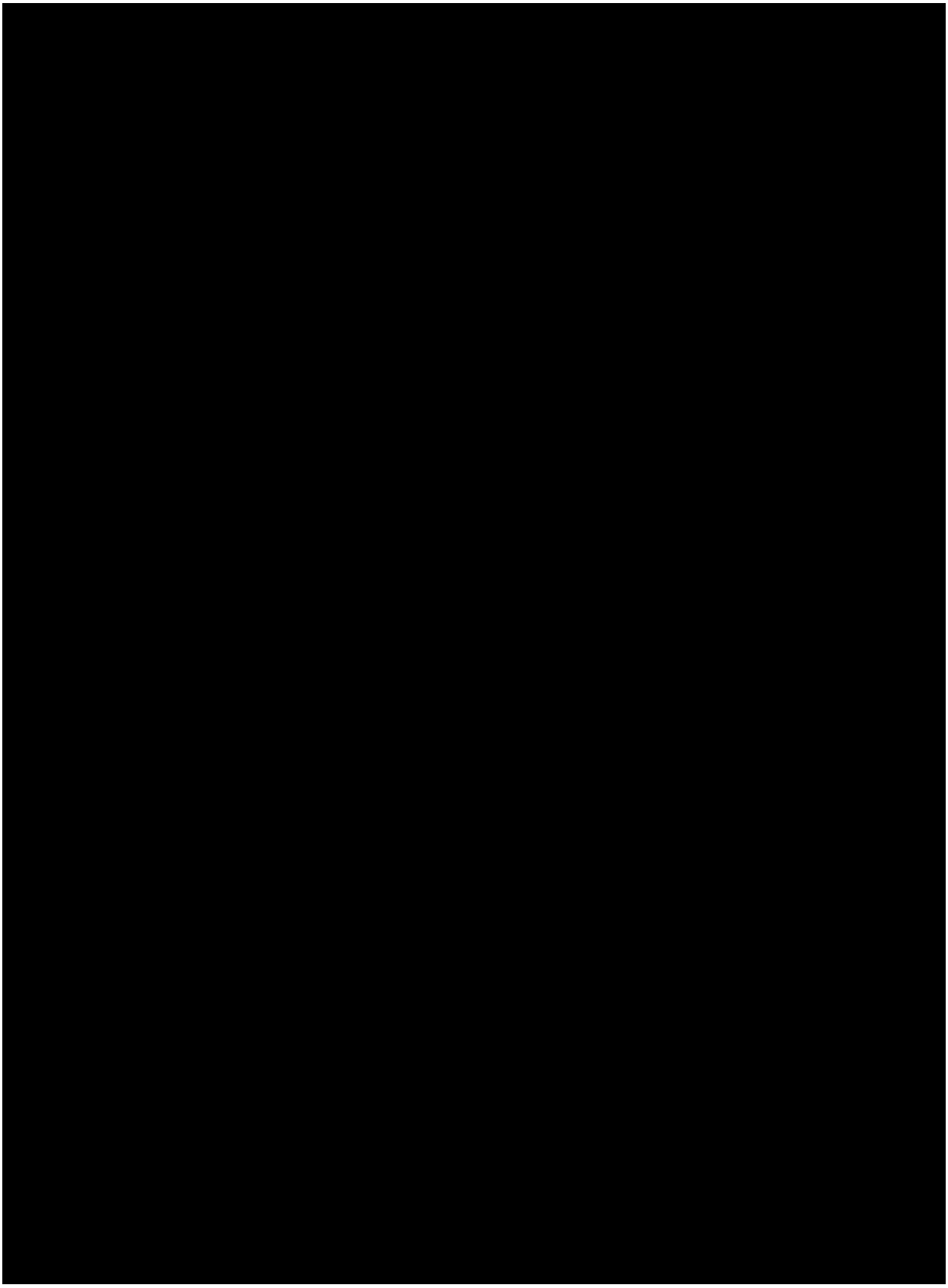


Table 69: MAIC analysis comparing glofitamab to chemotherapy (+/- R) for patients with 3L+ DLBCL.

MAIC analysis comparing glofitamab to chemotherapy (+/- rituximab) for patients with 3L+ DLBCL									
Outcome	Studies included in the analysis	Absolute difference in effect			Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
		Difference	CI	*P* value	Difference	CI	*P* value		
Overall survival	NP30179	NA	NA	NA	[redacted]			Unadjusted Cox model	*Yes*
	SCHOLAR-01	NA	NA	NA				Bootstrap median OR (95% percentile CI) weighted Cox model	*Yes*
		NA	NA	NA				Bootstrap median OR (95% BCa CI) weighted Cox model	*No*
(INV-assessed) Objective response rate	NP30179	NA	NA	NA				Unadjusted Cox model	*No*
	SCHOLAR-01	NA	NA	NA				Bootstrap median OR (95% percentile CI) weighted Cox model	*No*
		NA	NA	NA				Bootstrap median OR (95% BCa CI) weighted Cox model	*No*
(INV-assessed)	NP30179	NA	NA	NA				Unadjusted Cox model	*No*

MAIC analysis comparing glofitamab to chemotherapy (+/- rit					[redacted]		
Complete response	SCHOLAR-01	NA	NA	NA		Bootstrap median OR (95% percentile CI) weighted Cox model	*No*
		NA	NA	NA		Bootstrap median OR (95% BCa CI) weighted Cox model	*No*



Appendix G Extrapolation

Scenario analysis with extrapolated OS curve for R-chemotherapy

Table 70 provides the rationale for the choice of the OS extrapolation curve for R-chemotherapy in a scenario analysis (scenario 2).

Table 70: Parametric distribution selected for OS for chemotherapy (+/- R).

PH-Assumption	PH assumption is assumed, log-log (cumulative) hazard plots are relatively parallel and does not cross.
Distribution selected – R-chemotherapy	Log-normal
AIC-rank	4th
BIC-rank	4th
Visual Inspection	Good visual fit of the extrapolated curves to the observed KM data
Smooth Hazards plot	Demonstrates the behaviour of hazards that the clinical expert considers clinically plausible (The hazard rise due to the mortality of non-responders, but the composition of the patient group may also shift as long-term responders and survivors become a more significant portion of the cohort, resulting in a decrease in hazard, see Figure 67)
Clinically plausibility	Danish clinical expert assessed that, based on biology, the hazard function should have an initial increase followed by a decrease. This translates to a log-normal or log-logistic parametric function, however, the clinical experts assessed that a log-normal distribution would be most reasonable and clinical plausible for patients with R/R DLBCL (17). This is consistent with the log-normal parametric function previously chosen by the professional committee of the DMC for both PFS and OS in the Pola+BR submission as this was assessed clinical realistic (73, 85). Log-normal was likewise chosen for PFS and OS in the base case of the NICE assessment for tisagenlecleucel (Kymriah) (78)
Comments	Choosing log-normal for extrapolation generates a realistic and clinical plausible result, considering the expected hazard profile and statistical fit. This distribution has been used to long-term extrapolation in previous submission for Pola+BR, R/R DLBCL (73, 85).

Abbreviations: PH, proportional hazards, R-chemotherapy , rituximab + cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone; Pola-BR, polatuzumab + vedotin + bendamustine + rituximab; AIC, Akaike information criterion; BIC, Bayesian information criterion; KM, Kaplan Meier; DMC, the Danish Medicines Council; PFS , progression free survival; OS, overall survival; R/R, refractory or relapsed; DLBCL – diffuse large B-cell lymphoma.

Table 71: AIC and BIC for OS with ranks in brackets.

Parametric distribution	R-chemotherapy	
	AIC (rank)	BIC (rank)
Exponential	3,974.60 (7)	3,979.00 (7)
Weibull	3,793.29(5)	3,802.09 (5)
Log-normal	3,642.19 (4)	3,650.99 (4)
Gen Gamma	3,619.04 (3)	3,632.25 (3)
Log-logistic	3,615.94 (2)	3,624.74 (2)
Gompertz	3,571.06 (1)	3,579.87 (1)
Gamma	3,862.77 (6)	3,871.57 (6)

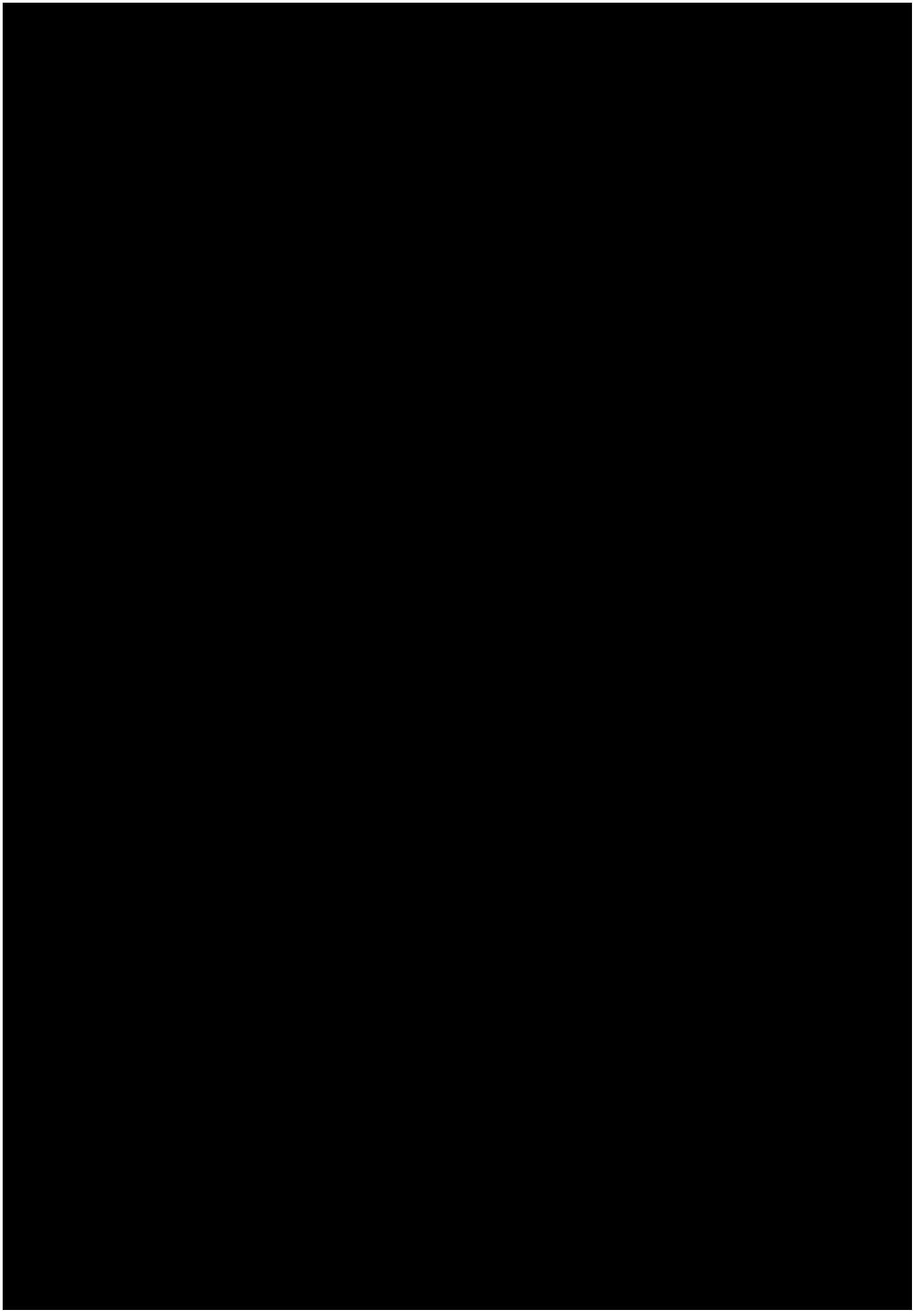
Abbreviations: AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; Gen, generalised

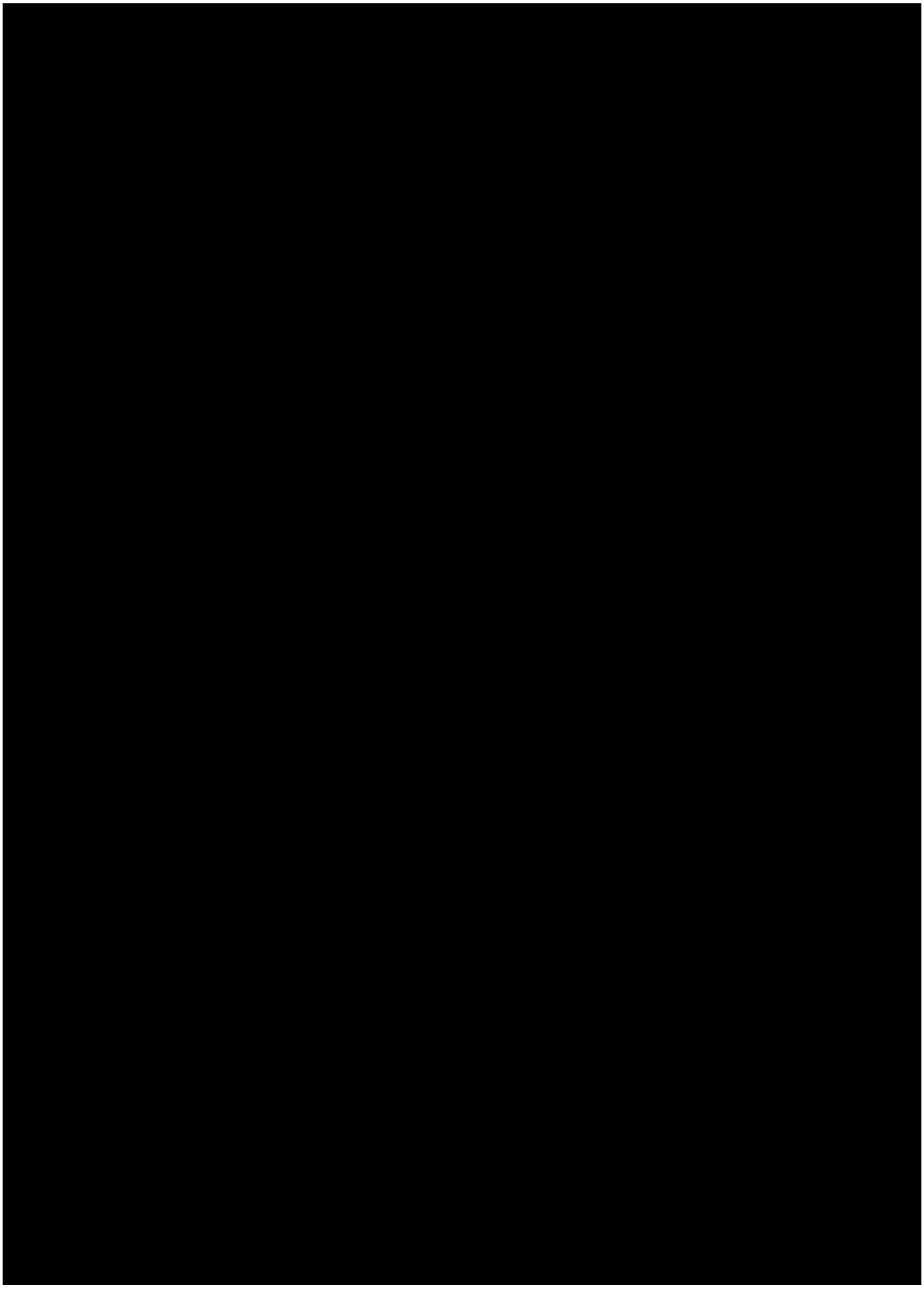
Plots

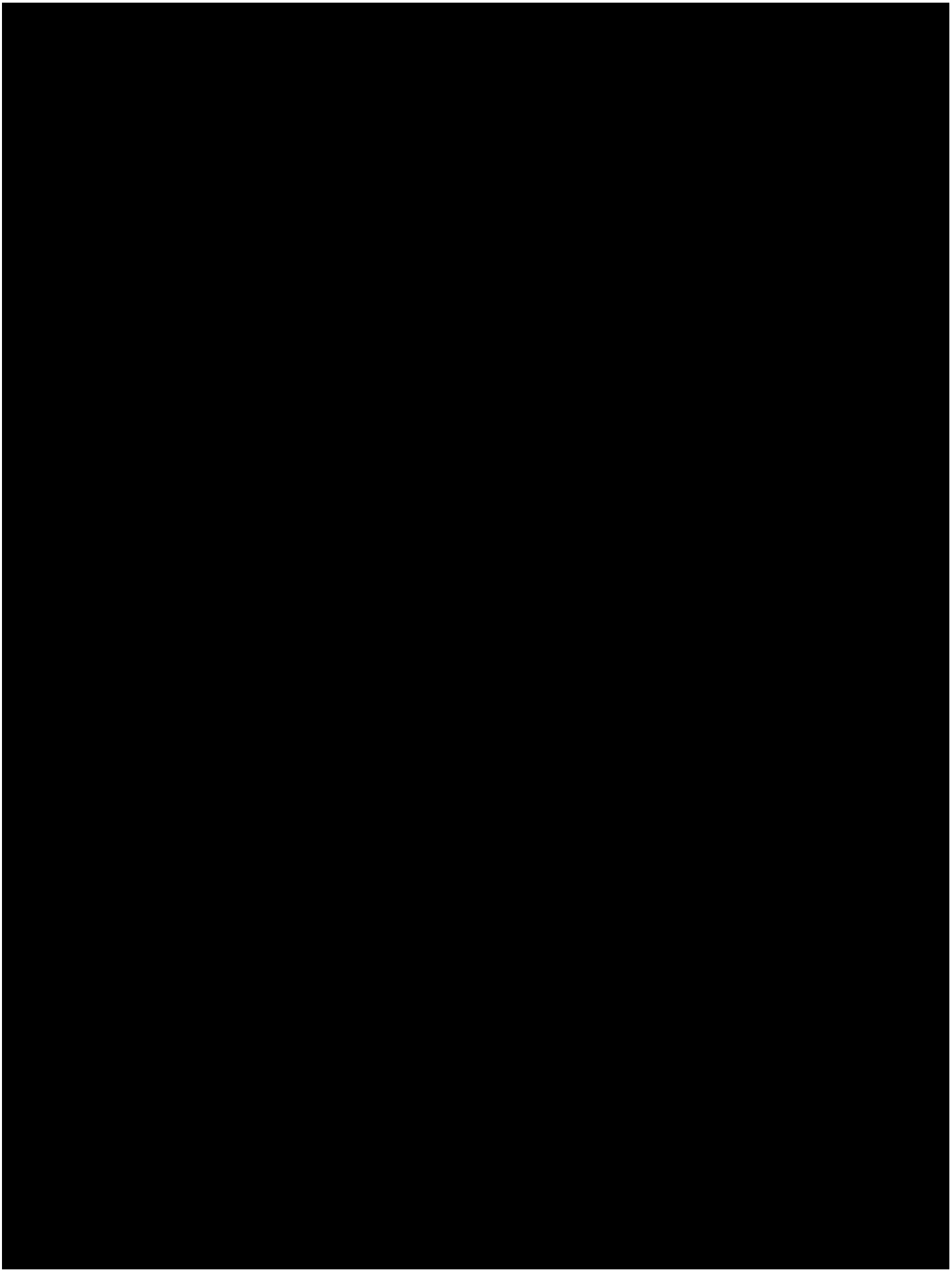
The plots of the parametric extrapolation fits performed over subpopulations and the comparators. Program generated using R 4.0.3. Extrapolations were generated using the package flexsurv. For visualization purposes, the upper confidence interval of the hazard plots for each distribution has been set to a maximum of the estimated hazard value plus 0.1. These extrapolations are obtained independently for each arm using the weights from the ITC (either MAIC or PSM, depending on the reference case).

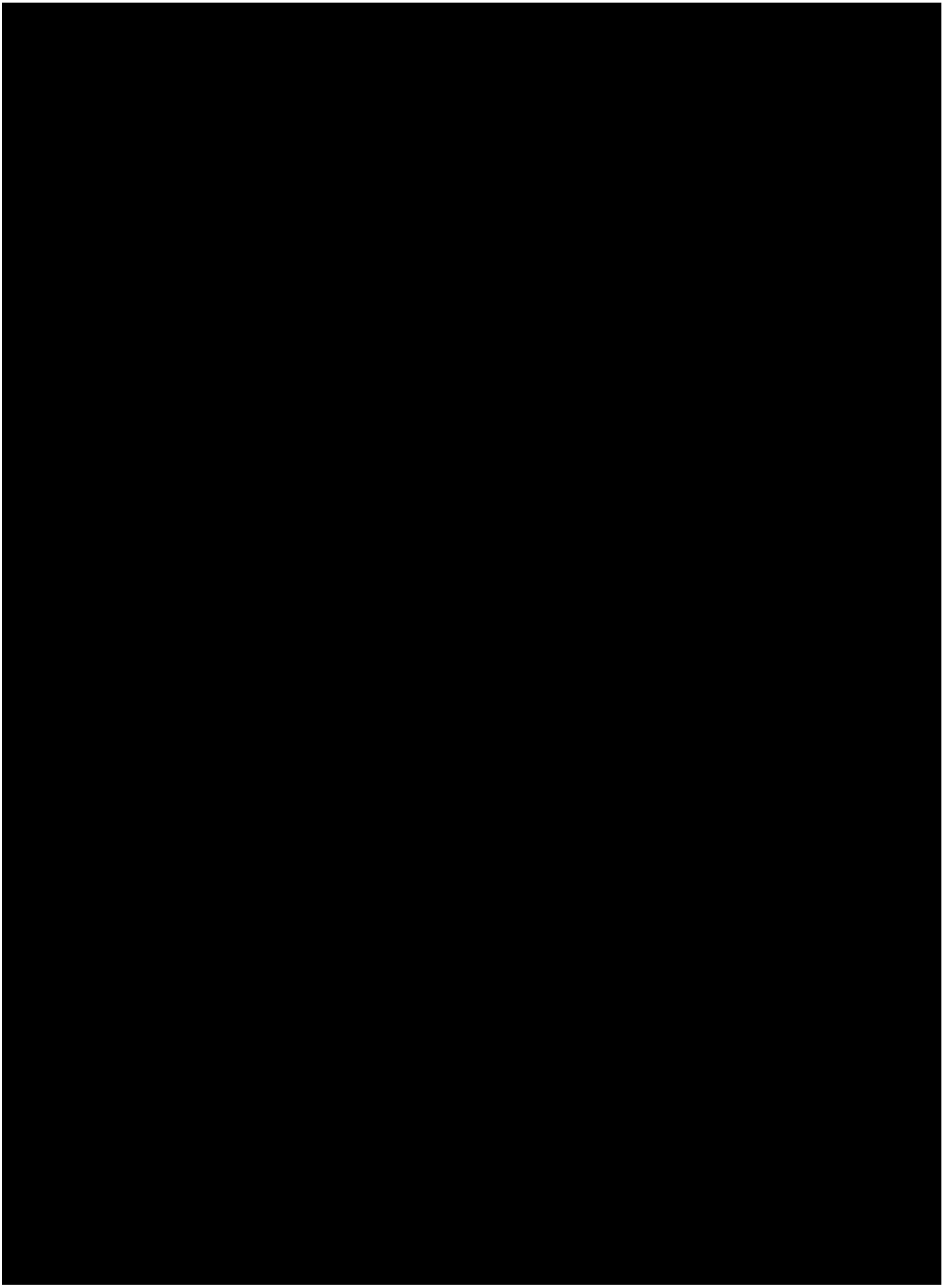
The smoothed hazard plots use the muhaz package. Note that the empirical hazard is sensitive to the smoothing parameters, especially when not much data is available.

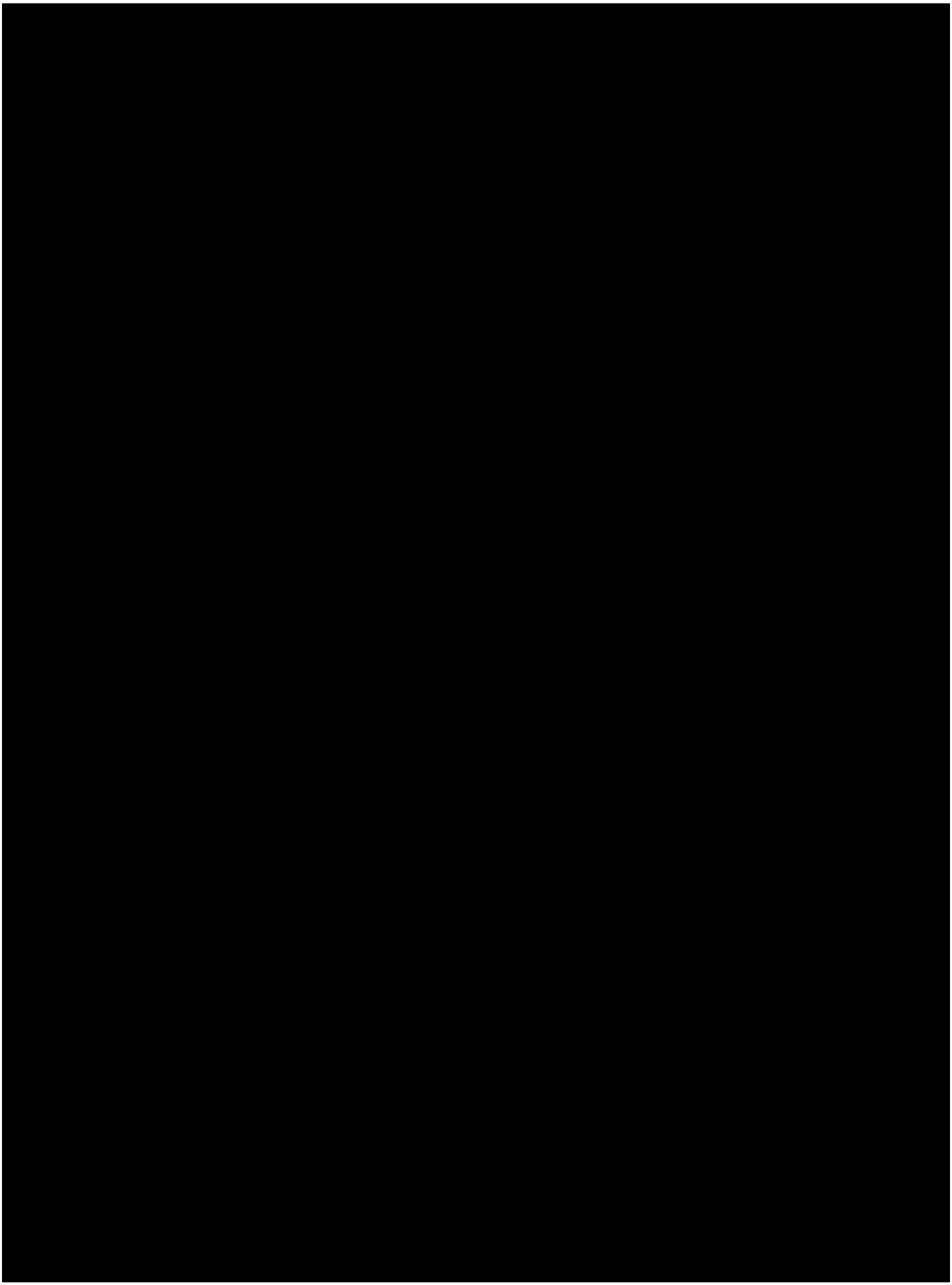
OS-Curves

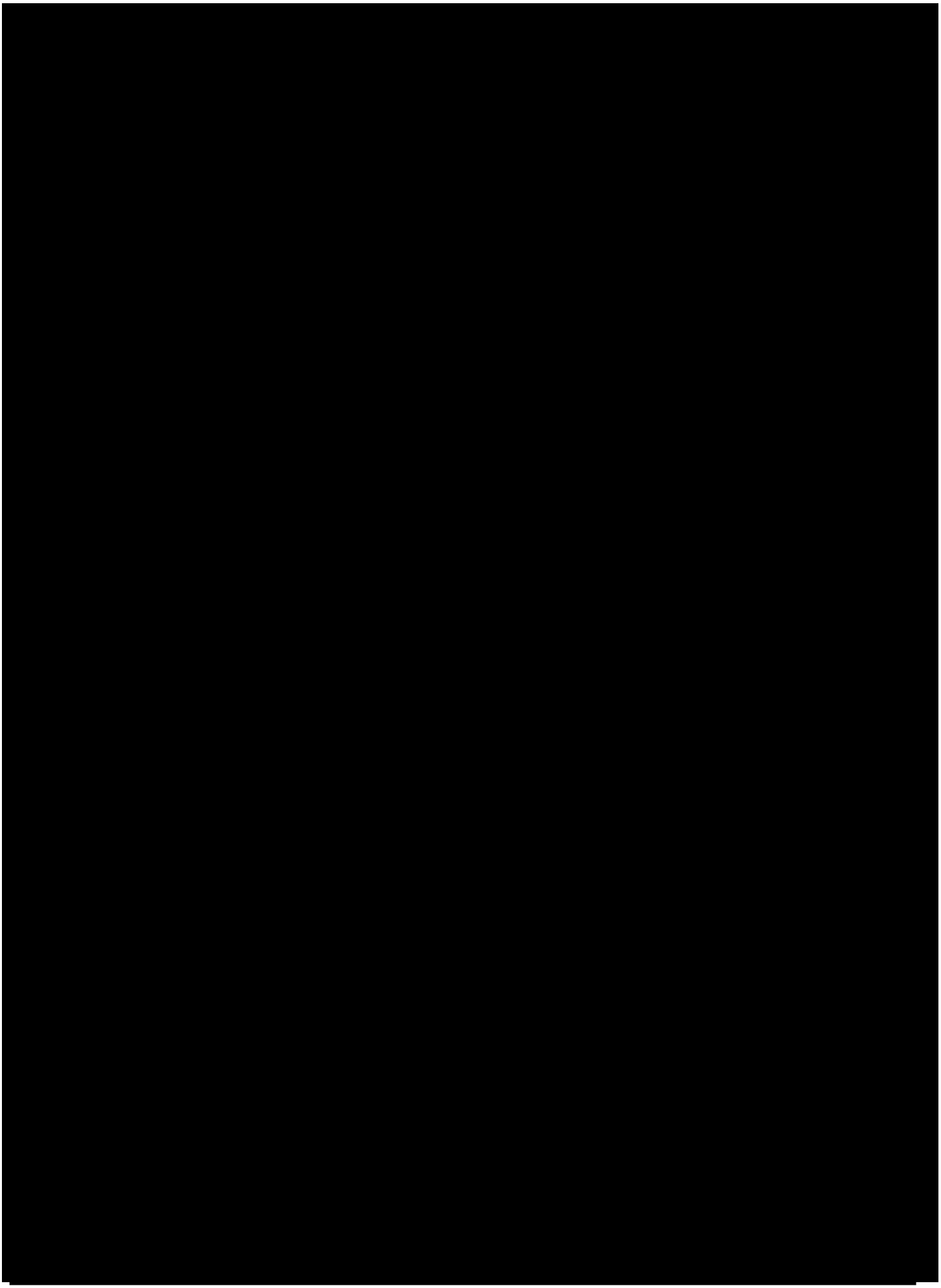


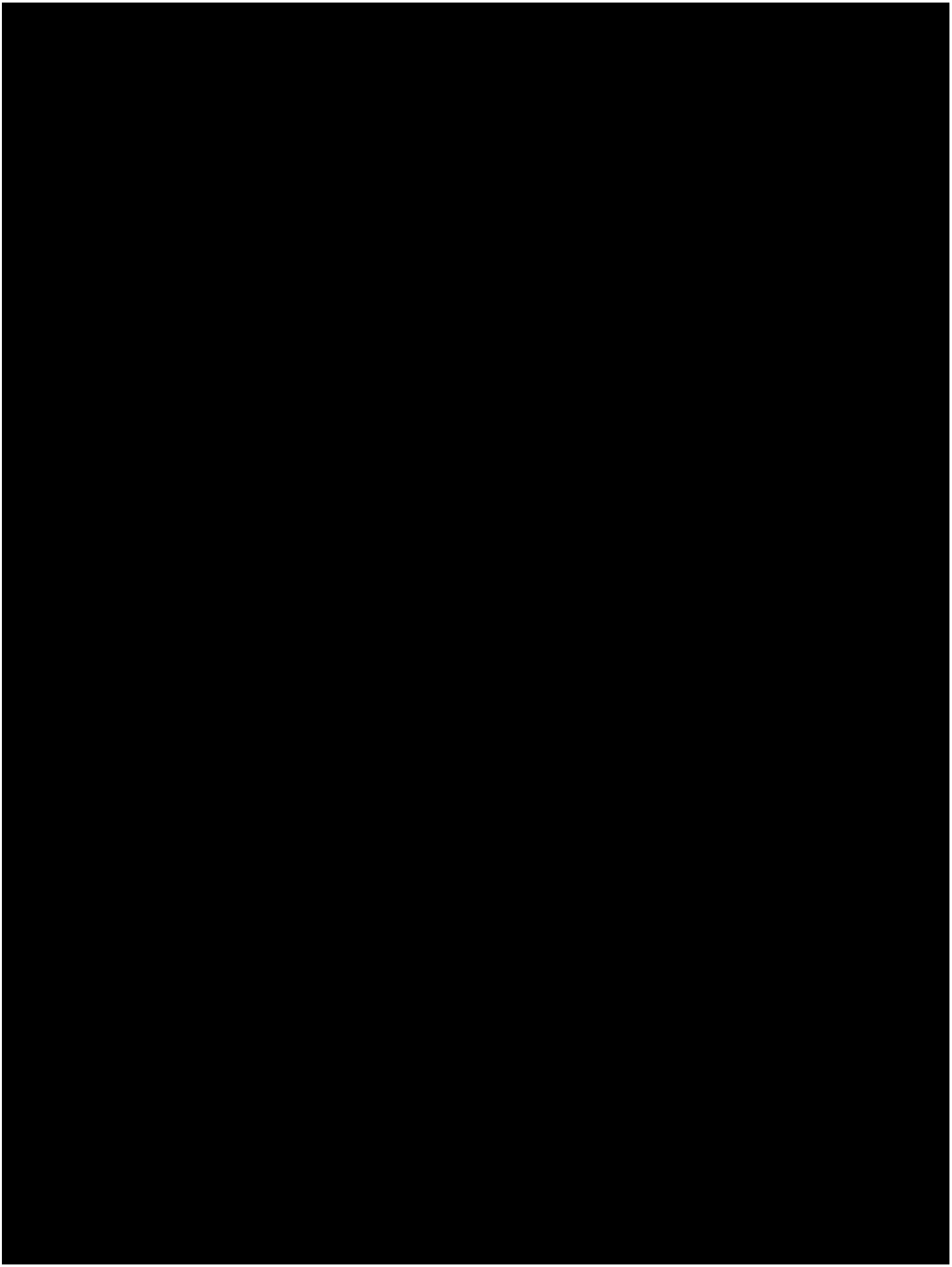


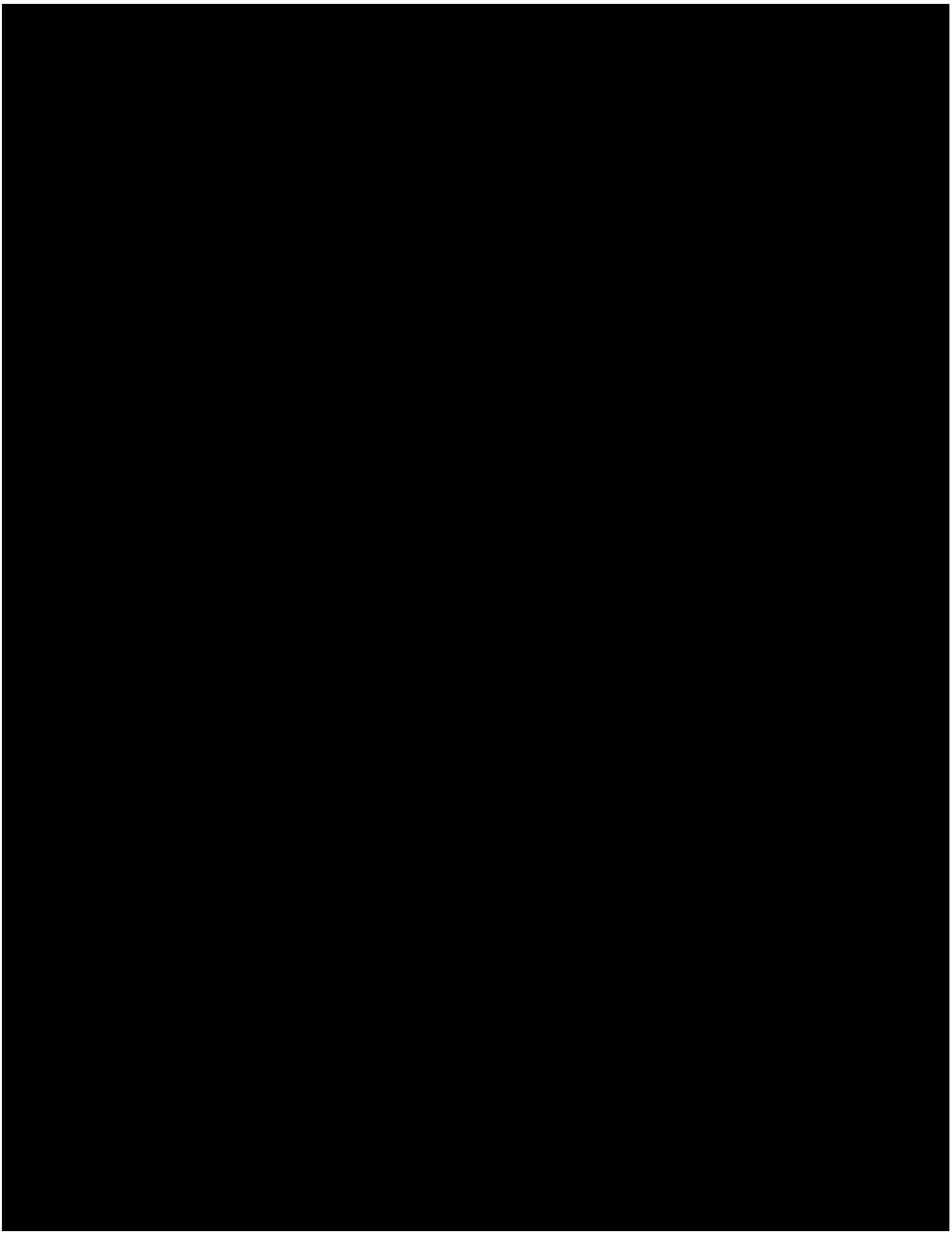


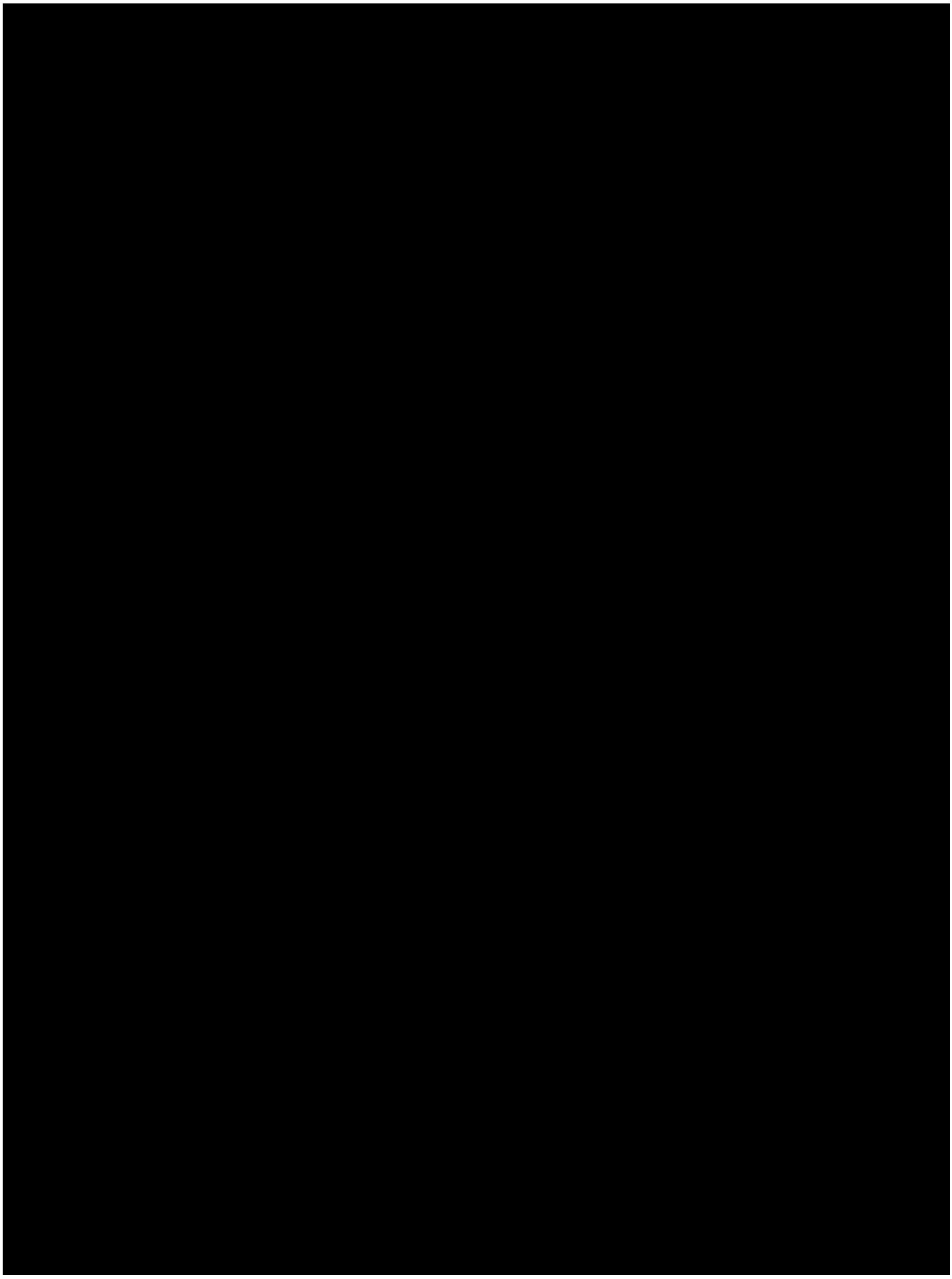


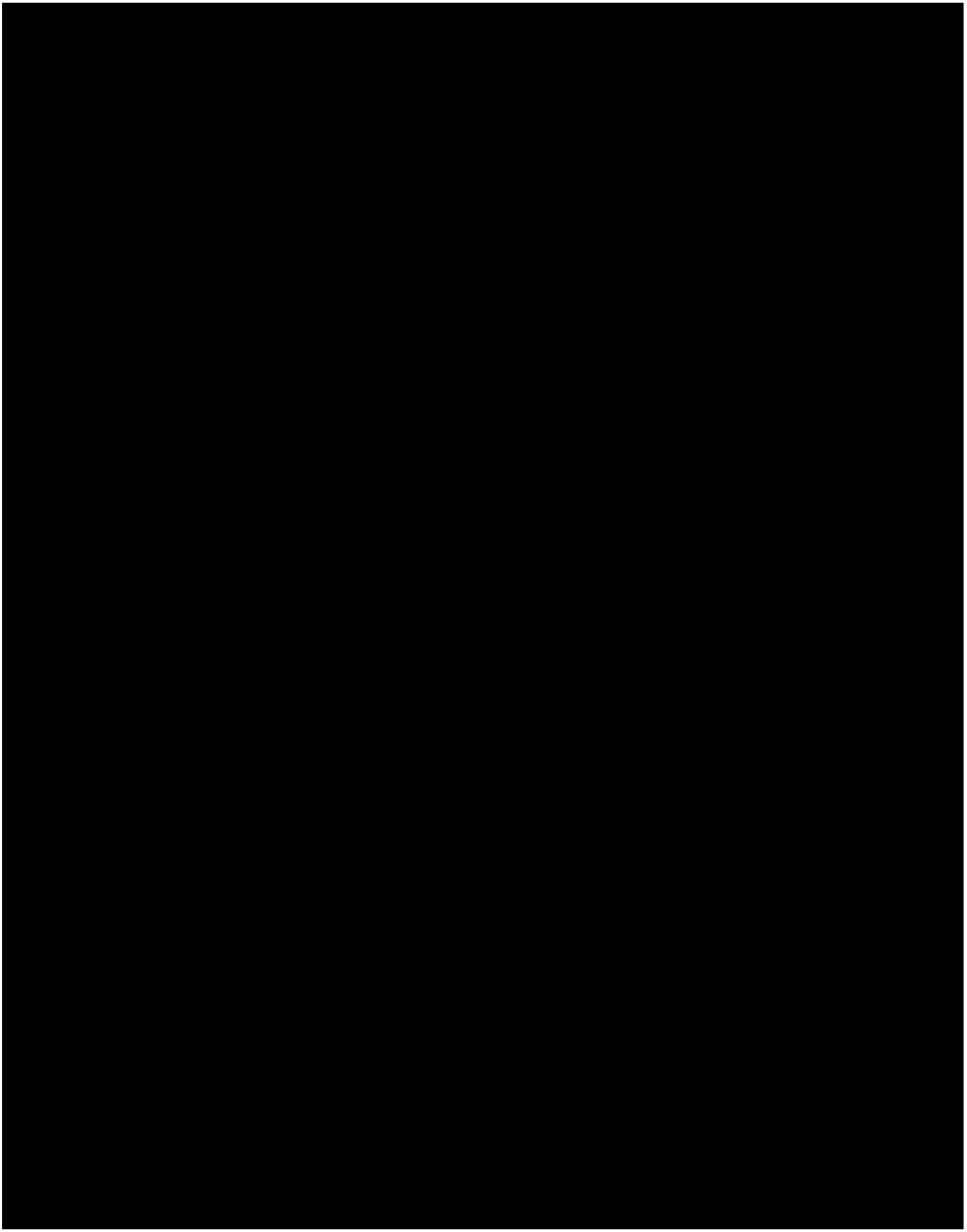


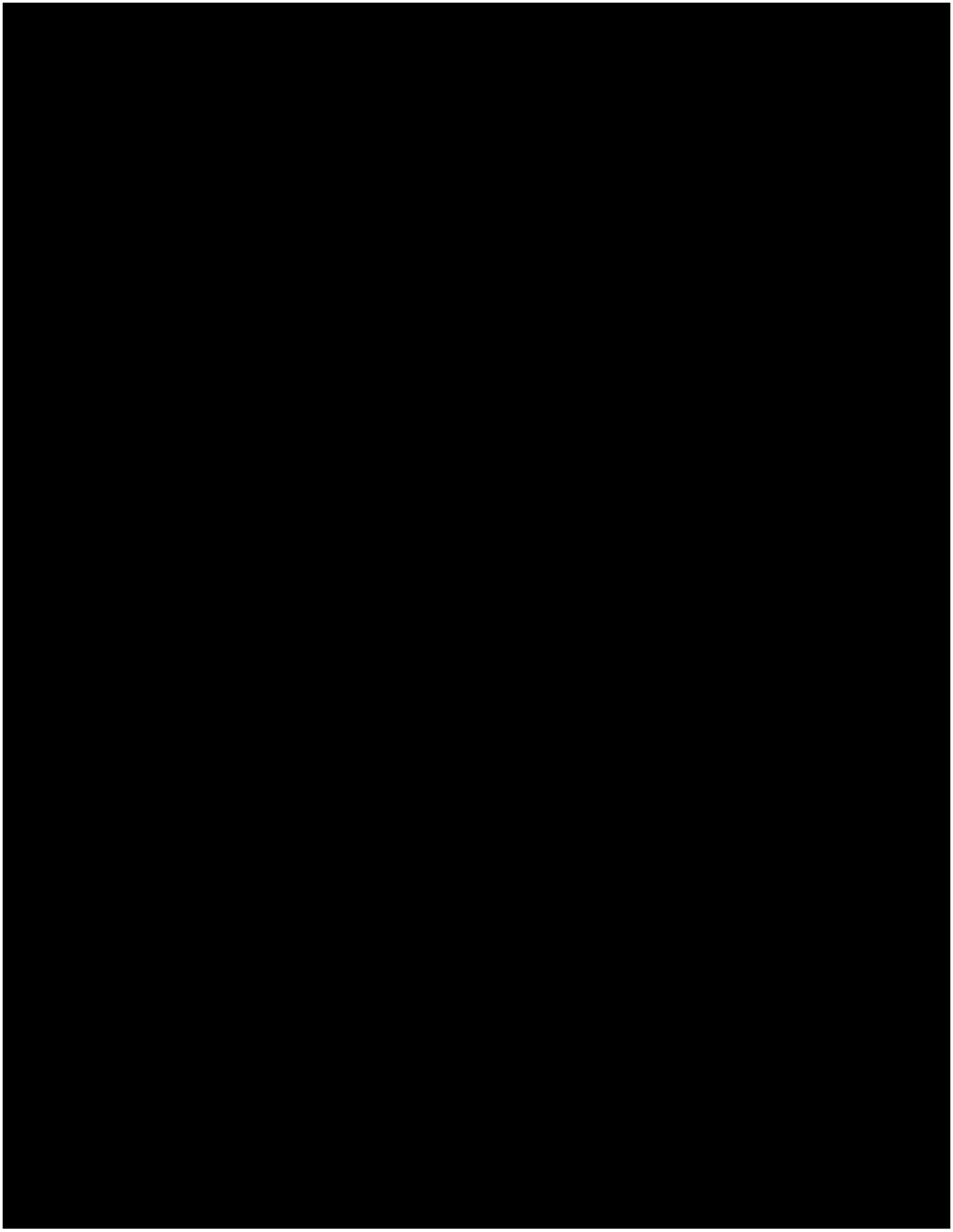


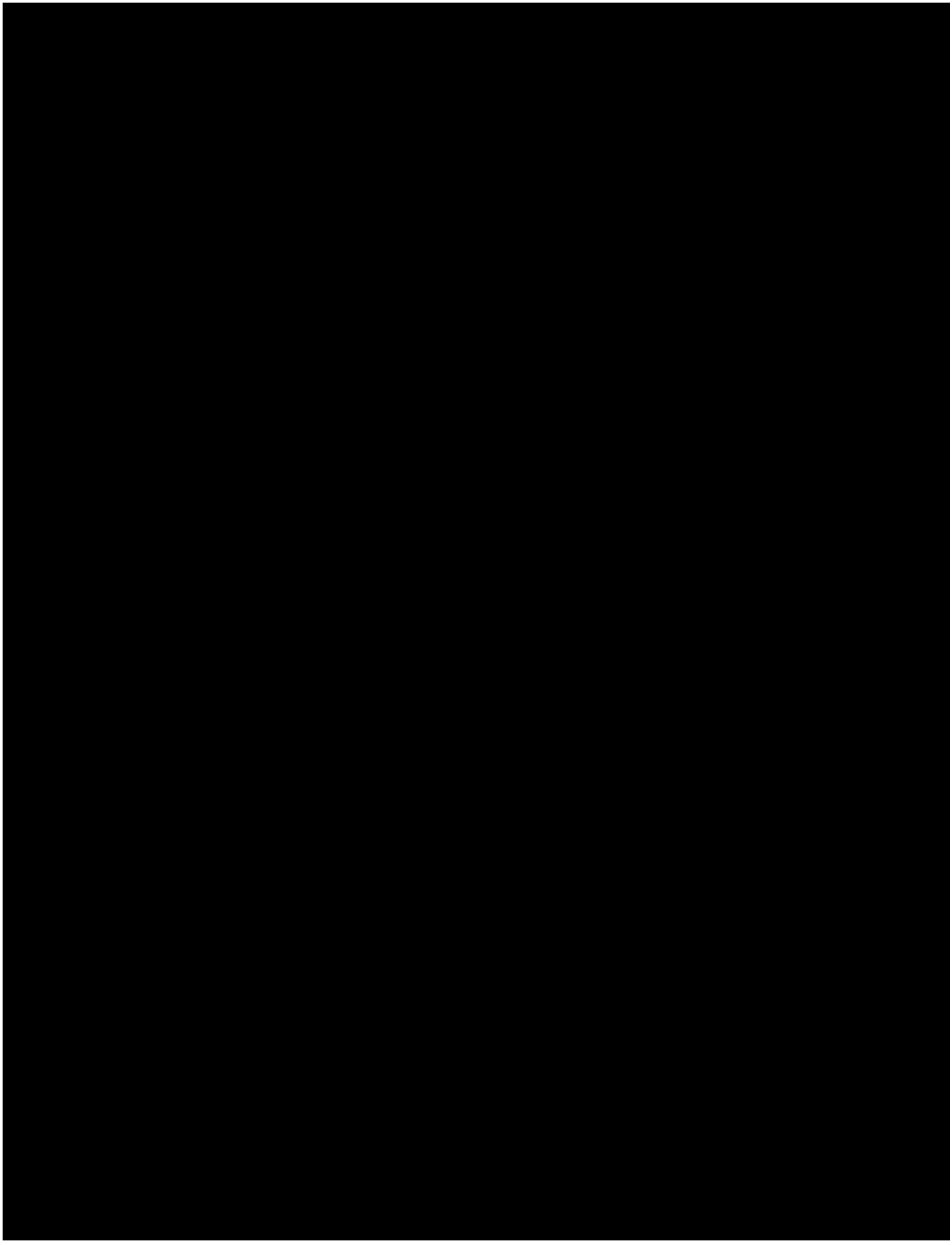


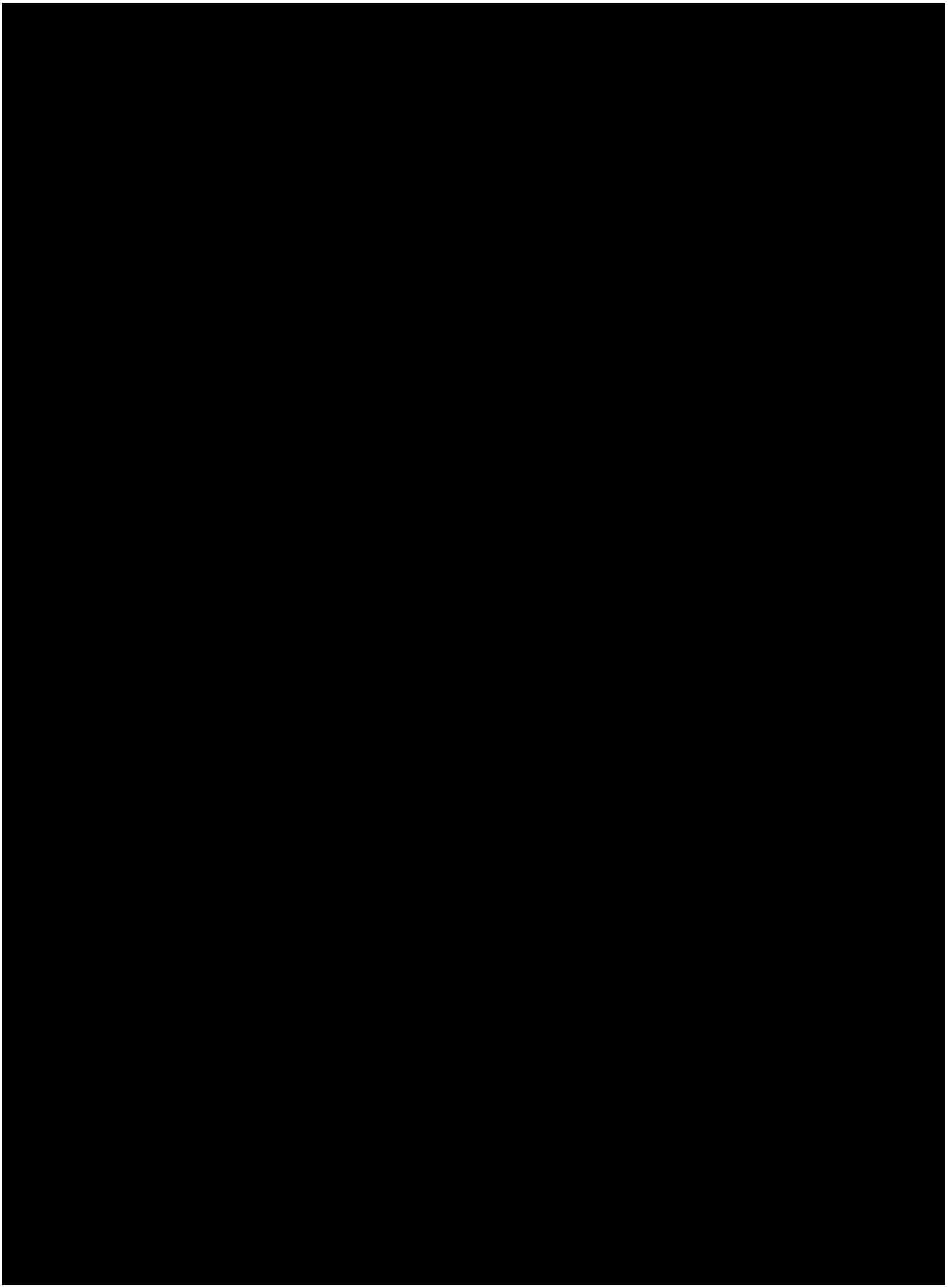












Appendix H – Literature search for HRQoL data

As part of the evidence generation strategy for glofitamab in the 3L+ setting, a series of HTA-compliant SLRs were conducted to identify the following published evidence in DLBCL:

- Economic evaluations for treatments of DLBCL in the 2L+ setting
- Health state utility values (HSUVs) data for relevant health states
- Cost/resource use data

The specific objective of the current SLR is to identify published HSUVs for DLBCL in the 2L+ setting to support forthcoming global HTA submissions for glofitamab in 3L+ RR DLBCL. Roche had previously commissioned a SLR to identify HSUVs in patients with RR DLBCL. The database searches for the previous SLR were conducted on 4th September 2018 and updated on 10th June 2019. For ease of reference, the four electronic database searches are referred to as follows:

- Original SLR (conducted September 2018)
- SLR update 1 (conducted June 2019)
- SLR update 2 (conducted August 2021)
- SLR update 3 (conducted September 2022)

Therefore, the methodology associated with SLR update 2 and 3 are detailed in the current report.

Health related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) in the Phase 1/2 glofitamab study (NP30179; NCT03075696) (3). As no preference-based tool was also administered, mapping of EORTC QLQ-C30 onto the EQ-5D would be required to obtain HSUVs. Although there are several published algorithms for mapping QLQ-C30 data to the EQ-5D, a targeted review was undertaken to ensure that all available relevant algorithms were identified. Methodology and findings are summarised in Table 72.

Data sources

As part of the current review, the following sources were searched to identify potentially relevant publications:

- Electronic databases
- Reference lists of eligible studies
- Conference proceedings
- Additional relevant websites

Table 72: Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion*
Embase	Embase.com	1974 to 2022	14.09.2022
Medline	Ovid	1974 to 2022	14.09.2022
American College of Physicians (ACP) Journal Club	Acponline.org	1974 to 2022	14.09.2022
Cochrane Central Registry of Controlled Trials (CENTRAL)	Cochranelibrary.com	1974 to 2022	14.09.2022
Cochrane Database of Systematic Reviews	Cochranelibrary.com	1974 to 2022	14.09.2022
Cochrane Clinical Answers	Cochranelibrary.com	1974 to 2022	14.09.2022
Cochrane Methodology Register	Cochranelibrary.com	1974 to 2022	14.09.2022
Database for Abstracts of Reviews of Effects (DARE)	Crd.ac.uk	1974 to 2022	14.09.2022
Health Technology Assessment (HTA) database	Crd.ac.uk	1974 to 2022	14.09.2022
NHS Economic Evaluation Database (EED)	Crd.ac.uk	1974 to 2022	14.09.2022

*Update 3 (conducted September 2022)
Abbreviations: NA, not applicable

Bibliographic details for NHS EED and DARE are only published in EBM Reviews up until the end of 2014, and up to the end of 2016 for the HTA database. Therefore, potentially relevant articles published post-2019 for NHS EED and DARE, and post-2019 for the HTA database were identified via the University of York Centre for Reviews and Dissemination (CRD) website

The searches for SLR update 2 were run on the 25th August 2021 and for SLR update 3 on 14th September 2022.

Supplementary sources

Reference lists

The reference lists of eligible studies (primary studies and reviews) were reviewed to identify any further relevant publications that had not been identified as part of the database searches.

Conference proceedings

The following conferences were searched (2019-2022):

- American Society of Clinical Oncology (ASCO)
- American Society of Hematology (ASH)
- European Hematology Association (EHA)
- European Society for Medical Oncology (ESMO)
- International Conference on Malignant Lymphoma (ICML)

Conference abstracts and proceedings were identified in a two-stage approach. The main Embase search strategy was employed to include conference abstracts and proceedings. For any conference proceedings that were not indexed in Embase, additional scanning of the internet conference proceedings were undertaken.

Additional sources

The following additional databases were also hand searched:

- The Cost-Effectiveness Analysis Registry: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx
- EuroQoL website: https://euroqol.org/
- Research Papers in Economics: http://repec.org/
- MAPI Institute: https://mapi-trust.org/
- National Institute for Health and Research (NIHR): https://www.nihr.ac.uk/researchers/data-publications.htm
- International Network of Agencies for Health Technology Assessment: http://www.inahta.org/
- University of Sheffield School of Health and Related Research utility database: http://www.scharrhud.org/

Search strategy

Eligibility criteria

The eligibility criteria applied throughout the SLR of HSUVs are summarised in Table 73.

Table 73: Eligibility criteria.

Criteria	Include	Exclude
Population	*Patients with 2L+ DLBCL* *(note: studies reporting results for 2L DLBCL only were excluded and are listed in the excluded studies table [Table 81]*	-
Intervention & comparators	No restriction	-
Outcomes	HSUVs (and disutilities) for relevant health states derived using the following techniques: • Generic, preference-based instruments (e.g. EQ-5D, SF-6D) • Direct methods (e.g. TTO, SG) • Mapping algorithms allowing data from disease-specific/generic measures to be mapped to preference-based HSUVs	Outcomes not listed in "include" column
Study design	Studies reporting original HSUV data	• Reviews/editorials • Budget impact models • Case reports • Pharmacokinetic studies • Animal/*in vitro* studies
Geographcy	No restriction	-
Publication date	No restriction	-
Language	English language publications or non-English language publications with an English abstract were of primary interest	-

Abbreviations: 2L+, second line and onwards; DLBCL, diffuse large B-cell lymphoma; EQ-5D, European Quality of Life – 5 Dimensions; HSUV, health state utility values; SF-6D, Short Form 6-Dimensions; SG, standard gamble; TTO, time trade-off; VAS, visual analogue scale.

Study selection and data extraction

The review and inclusion/exclusion of citations (both at the title/abstract phase and full publication review) was conducted by two independent analysts. Any disputes were referred to the project manager and resolved by consensus. Data extraction was conducted by a single analyst and quality checked for 100% of data elements by a second analyst or project lead. Disputes were referred to a third party (strategic advisor).

Search String

The search strings for update 3 for each database and resource are reported in Table 74 to Table 77.

SLR update 3 (September 2022)

Table 74: Embase (Ovid): 1974 to 2022 September 13: searched 14.9.22

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	22088
2	exp large cell lymphoma/	52500
3	(diffuse large B-cell or DLBCL or DLBL).mp.	41203
4	aggressive B-cell*.mp.	2821
5	(large B-cell adj4 lymphoma*).mp.	41291
6	(diffuse adj4 lymphoma*).mp.	42704
7	or/1-6	63118
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	29909
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	8876
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	18220
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	1796
12	(15D or 16D or 17D).mp.	4524
13	("standard gamble" or SG).mp.	19978
14	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	3293
15	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	708
16	disutilit$.mp.	1128
17	(health adj1 stat*).mp. or exp Health Status/	347101
18	(utility adj1 (value* or weight*)).mp.	4741
19	exp statistical model/	654983
20	preference$.mp.	244781
21	*patient preference/	6011
22	(utilit* or "health utility index" or "utilities index").mp.	354656
23	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	2213105
24	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	2119
25	quality of life index.mp. or exp "quality of life index"/	5340
26	quality adjusted life year.mp. or exp quality adjusted life year/	33914
27	(qaly or daly or "adjusted life").mp.	45625
28	("quality adjusted" or "disability adjusted").mp.	43150
29	disability.mp. or exp disability/	381501
30	disabled person.mp. or exp disabled person/	57204
31	life expectancy.mp. or exp life expectancy/	78761
32	(29 or 30) and 31	4393
33	(QoL or HRQoL or HRQL or "health related quality of life" or "health-related quality of life").mp.	163737

#	Searches	Results
34	quality of life.mp. or exp "quality of life"/	729000
35	or/17-28,32	3222323
36	35 and (33 or 34)	169779
37	or/8-16	81099
38	36 or 37	224917
39	7 and 38	366
40	limit 39 to yr="2021 -Current"	109

Table 75: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions: 1946 to September 13, 2022: searched 14.9.22

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	22614
2	exp Lymphoma, B-Cell/	53646
3	(diffuse large B-cell or DLBCL or DLBL).mp.	17838
4	aggressive B-cell*.mp.	1246
5	(large B-cell adj4 lymphoma*).mp.	30657
6	(diffuse adj4 lymphoma*).mp.	31830
7	1 or 2 or 3 or 4 or 5 or 6	62672
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	15297
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	4177
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	11810
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	975
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	543
13	("15D" or "16D" or "17D").mp.	3130
14	("standard gamble" or SG).mp.	13232
15	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	2199
16	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well be-ing").mp.	543
17	disutilit$.mp.	574
18	(health adj1 stat*).mp. or exp Health Status/	494015
19	(utility adj1 (value* or weight*)).mp.	2463
20	exp Models, Economic/	16144
21	preference$.mp.	197565
22	exp Patient Preference/	10408
23	(utilit* or "health utility index" or "utilities index").mp.	252563
24	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	1796377
25	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	1363
26	quality of life index.mp.	1986

#	Searches	Results
27	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	18189
28	("qaly" or "daly" or "adjusted life").mp.	27207
29	("quality adjusted" or "disability adjusted").mp.	26302
30	exp Disability Evaluation/ or disability.mp.	269922
31	disabled person.mp. or exp disabled person/	72063
32	life expectancy.mp. or exp life expectancy/	65951
33	(30 or 31) and 32	4801
34	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	98937
35	quality of life.mp. or exp "quality of life"/	421234
36	or/18-29,33	2646543
37	36 and (34 or 35)	288872
38	or/8-16	47584
39	37 or 38	317530
40	7 and 39	180
41	limit 40 to yr="2021 -Current"	35

Table 76: EBM Reviews (Ovid): Cochrane Central Register of Controlled Trials (CENTRAL): August 2022: searched 14.9.22

#	Searches	Results
1	exp Lymphoma, Large B-Cell, Diffuse/	477
2	exp Lymphoma, B-Cell/	764
3	(diffuse large B-cell or DLBCL or DLBL).mp.	1798
4	aggressive B-cell*.mp.	181
5	(large B-cell adj4 lymphoma*).mp.	1891
6	(diffuse adj4 lymphoma*).mp.	1968
7	1 or 2 or 3 or 4 or 5 or 6	2429
8	("EuroQOL 5-Dimension" or "Euroqol 5D" or "EQ-5D" or EQ5D or Euroqol or "EQ 5D" or "european quality of life").mp.	12286
9	(AQOL or "Assessment of Quality of Life" or "quality of life index" or "Australian quality of life" or "Australian qol").mp.	4150
10	("Health utilities index" or HUI or HUI$ or (health adj2 (utilities or utility))).mp.	1719
11	("short form 6D" or "short-form 6D" or SF6D or SF-6D or "SF 6D").mp.	367
12	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well being").mp.	196
13	("15D" or "16D" or "17D").mp.	344
14	("standard gamble" or SG).mp.	1651
15	("time trade off" or "time trade-off" or "time tradeoff" or TTO).mp.	312
16	("quality of wellbeing" or QWB or "quality of well-being" or "quality of well be-ing").mp.	196
17	disutilit$.mp.	98
18	(health adj1 stat*).mp. or exp Health Status/	48147
19	(utility adj1 (value* or weight*)).mp.	610

#	Searches	Results
20	exp Models, Economic/	378
21	preference$.mp.	19258
22	exp Patient Preference/	862
23	(utilit* or "health utility index" or "utilities index").mp.	19178
24	(map$ or mapping or regression or "cross walking" or "cross-walking").mp.	95666
25	("multiattribute utility" or "multi-attribute utility" or "multi attribute utility" or "mau").mp.	116
26	quality of life index.mp.	1019
27	quality adjusted life year.mp. or exp Quality-Adjusted Life Years/	5114
28	("qaly" or "daly" or "adjusted life").mp.	6934
29	("quality adjusted" or "disability adjusted").mp.	6769
30	exp Disability Evaluation/ or disability.mp.	41094
31	disabled person.mp. or exp disabled person/	1758
32	life expectancy.mp. or exp life expectancy/	7927
33	(30 or 31) and 32	249
34	("QoL" or "HRQoL" or "HRQL" or "health related quality of life" or "health-related quality of life").mp.	41903
35	quality of life.mp. or exp "quality of life"/	139047
36	or/18-29,33	176521
37	36 and (34 or 35)	47183
38	or/8-16	19644
39	37 or 38	58689
40	7 and 39	43
41	limit 40 to yr="2021 -Current"	7

Table 77: EBM Reviews (Ovid): ACP Journal Club 1991 to July 2022, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to September 7, 2022, EBM Reviews - Cochrane Clinical Answers August 2022: searched 14.9.22.

#	Searches	Results
1	[exp Lymphoma, Large B-Cell, Diffuse/]	0
2	[exp Lymphoma, B-Cell/]	0
3	(diffuse large B-cell or DLBCL or DLBL).mp.	14
4	aggressive B-cell*.mp.	6
5	(large B-cell adj4 lymphoma*).mp.	15
6	(diffuse adj4 lymphoma*).mp.	13
7	1 or 2 or 3 or 4 or 5 or 6	18
8	limit 7 to yr="2021 -Current"	1

Handsearching Methodology

The methodology used to conduct hand searching for each of the sources listed in the methods section and number of hits for each search is provided in Table 78.

Table 78: Handsearching methodology and results.

Source	Date searched	Search details	Search terms	No. hits	No. down-loaded
Conference proceedings					
ASCO 2022 annual meeting	05/09/22	ASCO Meeting Library (advanced search). URL: https://meetings.asco.org/abstracts-presentations/search?query=*&q=2022%20ASCO%20Annual%20Meeting&sortBy=Abstract-Browse&filters=%7B%22meetingTypeName%22:%5B%7B%22key%22:%22ASCO%20Annual%20Meeting%22%7D%5D,%22meetingYear%22:%5B%7B%22key%22:2022%7D%5D%7D	DLBCL	81	0
ASCO 2019, 2020, & 2021 Annual Meeting	05/11/21	ASCO Meeting Library, advanced search by meeting. ASCO annual meetings 2019, 2020, and 2021 were selected. URL: https://meetinglibrary.asco.org/results/diffuse%20large?meetingView=2021%20ASCO%20Annual%20Meeting&page=1	Diffuse large (in Title)	71	0
ESMO 2022	06/09/22	Abstract book searched using Ctrl+F URL: https://www.annalsofoncology.org/issue/S0923-7534(22)X0014-8	DLBCL	NA	0
ESMO 2021	05/11/21	ESMO virtual congress meeting resources were searched for relevant abstracts, filtered on topics (lymphomas) and format (abstracts and posters). URL: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021?event_resources_filter_form%5Bsearch%5D=diffuse%20large	Diffuse large	145	0
ESMO virtual 2020	05/11/21	ESMO virtual congress meeting resources were searched for relevant abstracts, filtered on topics (lymphomas) and format (abstracts and posters). URL: https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020?event_resources_filter_form%5Bsearch%5D=	Diffuse large	165	0
ESMO 2019	05/11/21	ESMO congress meeting resources were searched for relevant abstracts, filtered on topics (lymphomas) and format (abstracts and posters). URL: https://oncologypro.esmo.org/meeting-resources/esmo-2019-congress?event_resources_filter_form%5Bsearch%5D=	DLBCL	171	0

ASH 2022	03/11/22	ASH was searched using the search tool. URL: https://ash.confex.com/ash/2022/webprogram/start.html#srch=words%7CDLBCL%20AND%20hsuv%7Cmethod%7Cboolean%7Cpge%7C1%7CbyDayany%7Cany%7CbySymposiumany%7Cany%7CbyAudienceany%7Cany	DLBCL and HSUV	0	0
			DLBCL and utility	10	0
ASH 2021	05/09/22	ASH was searched. Filtered by date for 2021. URL: https://ashpublications.org/blood/issue/136/Supplement%201	DLBCL and utility	0	0
ASH 2020	05/11/21	Searched the ASH Annual Meeting and Exposition (no restriction on abstract category). URL: https://ash.confex.com/ash/2020/webprogram/#srch=words%7Cdiffuse%20large%7Cmethod%7Cboolean%7Cpge%7C4%7CbyDayany%7Cany%7CbySymposiumany%7Cany%7CbyAudience68812%7C68812	Diffuse large	36	0
ASH 2019	05/11/21	Searched the ASH Annual Meeting and Exposition (no restriction on abstract category). Reviewed oral abstracts in section 627 (Aggressive lymphoma [DLBCL and other aggressive B-cell non-Hodgkin lymphomas] – results from retrospective/observational studies). URL: https://ashpublications.org/search-results?q=diffuse+large&f_SemanticFilterTopics=diffuse+large+b-cell+lymphoma&fl_IssueNo=Supplement_1&fl_Volume=134&fl_SiteID=1&page=1&qb={%22q%22:%22diffuse%20large%22}	NA	473	0
EHA 2022	06/09/22	Abstract book searched using Ctrl +F URL: June 2022 - Volume 6 - Issue : HemaSphere (lww.com)	DLBCL	NA	0
EHA 2021	05/11/21	26th Congress of the EHA was searched using the advanced search. URL: https://library.ehaweb.org/eha/#!*ce_id=2035*sortby=1*search=DLBCL*browseby=8*listing=0	DLBCL	125	0
EHA 2020	05/11/21	25th congress of the EHA was searched using the advanced search. The following sections were searched: • Oral sessions ○ Aggressive lymphomas: prospective studies ○ Aggressive lymphomas: observational studies	DLBCL	165	0

		○ Aggressive lymphomas: cellular and bispecific antibody therapies • Poster session/Publication only ○ Aggressive Non-Hodgkin lymphoma - Clinical URL: https://journals.lww.com/hemasphere/Citation/2020/06001/Abstract_Book__25th_Congress_of_the_European.1.aspx			
EHA 2019	05/11/21	24th congress of the EHA was searched using the advanced search. URL: https://library.ehaweb.org/eha/#!*ce_id=1550*sortby=1*search=DLBCL*browseby=8*listing=0	DLBCL	131	0
ICML 2022	05/09/22	Unavailable at the time of the search	NA	NA	NA
ICML 2021	05/11/21	ICML 2021 was searched using Ctrl + F. URL: 16th International Conference on Malignant Lymphoma, Virtual Edition, 18–22 June, 2021: Hematological Oncology: Vol 39, No S2 (wiley.com)	DLBCL	37	0
ICML 2019	05/11/21	ICML 2019 was searched using Ctrl + F. URL: https://onlinelibrary.wiley.com/toc/10991069/2019/37/S2	DLBCL	51	0
Additional sources					
EuroQoL website	02/11/21	Search for EQ-5D in PubMed. URL: https://euroqol.org/publications/search-for-eq-5d-in-pubmed/	DLBCL	3	0
			Relapsed refractory diffuse large b cell lymphoma	4	0
			Diffuse large b cell lymphoma	5	0
EuroQoL website	05/09/22	Search for EQ-5D in PubMed. Filtered from 2021 to 2022 URL: https://euroqol.org/publications/search-for-eq-5d-in-pubmed/	DLBCL	2	0
			Relapsed refractory diffuse large b cell lymphoma	4	0
			Diffuse large b cell lymphoma	4	0
ScHARRHUD	03/11/21	Search facility, terms searched in abstract. URL: https://www.scharrhud.org/index.php?recordsN1&m=search	DLBCL	0	0
			Diffuse large b cell lymphoma	0	0
ScHARRHUD	05/09/22	Search facility, terms searched in abstract. URL: https://www.scharrhud.org/index.php?recordsN1&m=search	DLBCL	0	0
			Diffuse large b cell lymphoma	0	0
CEA Registry	03/11/21	Search the CEA Registry, basic search in methods. URL: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx	DLBCL	9	0
			Diffuse large b cell lymphoma	0	0
CEA Registry	05/09/22	Search the CEA Registry, basic search in methods.	DLBCL	0	0
			Diffuse large b cell lymphoma	0	0

		URL: http://healtheconomics.tuftsmedicalcenter.org/cear2n/search/search.aspx			
MAPI institute	03/11/21	Publications in the "hematology" category were searched. URL: https://mapi-trust.org/resources/publications/book-of-publications/hematology/	NA	3	0
MAPI institute	05/09/22	Publications in the "hematology" category were searched. URL: https://mapi-trust.org/resources/publications/book-of-publications/hematology/	NA	0	0
RePEc website (EconPapers)	03/11/21	Advanced search, limited to journal articles. URL: https://econpapers.repec.org/scripts/search.pf	"DLBCL" and "utility"	0	0
			"DLBCL" and "HSUV"	0	0
			"Diffuse large b cell lymphoma" and "utility"	2	0
			"Diffuse large b cell lymphoma" and "HSUV"	0	0
RePEc website (EconPapers)	05/09/22	Advanced search, limited to journal articles. URL: https://econpapers.repec.org/scripts/search.pf	"DLBCL" and "utility"	0	0
			"DLBCL" and "HSUV"	0	0
			"Diffuse large b cell lymphoma" and "utility"	3	0
			"Diffuse large b cell lymphoma" and "HSUV"	0	0
INAHTA	03/11/21	Searched the International HTA database, filtered by "Full HTA". URL: https://database.inahta.org/	DLBCL	7	0
			Diffuse large b cell lymphoma (title)	1	0
INAHTA	03/11/21	Searched the International HTA database, filtered by "mini HTA". URL: https://database.inahta.org/	DLBCL	0	0
			Diffuse large b cell lymphoma (title)	0	0
INAHTA	05/09/22	Searched the International HTA database, filtered by "Full HTA". URL: https://database.inahta.org/	DLBCL	8	0
			Diffuse large b cell lymphoma (title)	3	0
NIHR	03/11/21	Searched in data and publications. URL: https://www.nihr.ac.uk/researchers/data-publications.htm	DLBCL	0	0
			Diffuse large b cell lymphoma	0	0
NIHR	05/09/22	Searched in data and publications. URL: https://www.nihr.ac.uk/researchers/data-publications.htm	DLBCL	0	0
Ad hoc	03/11/21	Google Scholar: searched the first page of google scholar using keywords.	NA	NA	0
Ad hoc	05/09/22	Google Scholar: searched the first page of google scholar using keywords.	NA	NA	1
Reference checking	03/11/21	Reference checking: check references of relevant SLRs to identify additional publications.	NA	NA	1
Reference checking	05/09/22	Reference checking: check references of relevant SLRs to identify additional publications.	NA	NA	0

Other databases	03/11/21	Cross-checking with other non-clinical databases	NA	NA	0
Other databases	05/09/22	Cross-checking with other non-clinical databases	NA	NA	0
Total number of studies identified by handsearching: N=2					

Abbreviations: ASCO, American Society for Clinical Oncology; ASH, American Society for Hematology; CADTH, Canadian Agency for Drugs and Technologies in Health; CEA, cost-effectiveness analysis; DLBCL, diffuse large b cell lymphoma; EHA, European Hematology Association; ESMO, European Society for Medical Oncology; EQ-5D, European Quality of Life – 5 Dimensions; HTA, health technology assessment; ICML, International Conference for Malignant Lymphoma; NA, not applicable; NICE, National Institute of Clinical Excellence; NIHR, National Institute for Health Research; PBAC, Pharmaceutical Benefits Advisory Committee; pCODR, pan-Canadian Oncology Drug Review; SLR, Systematic literature review; SMC, Scottish Medicines Consortium.

Literature search results

SLR update 3 (September 2022)

The electronic databases identified 159 citations. Following removal of 39 duplicates and 24 duplicates from the previous search, 89 citations were screened on the basis of title and abstract. A total of 19 citations were considered to be potentially relevant and were obtained for full text review. Of these, 18 citations were excluded. One citation was identified by handsearching; however, this reported non-utility QoL results and was therefore excluded and listed separately. Therefore, one conference abstract reporting HSUVs for patients with DLBCL in the 2L+ setting was identified for inclusion in the review (9).

Summary

Across SLR update 2 (August 2021) and update 3 (September 2022), a total of six relevant HSUV studies were identified for inclusion (full publications, N=2; conference abstracts, N=4) (5-10). One additional study from SLR update 1 (June 2019) has also been summarised for ease of reference (11).

The flow of studies through the review is summarised in the PRISMA flow diagram in Figure 1. A list of studies excluded on the basis of full publication review is provided in Table 81, along with the rationale for exclusion. A list of studies excluded under the "general QoL" tag has been listed in Table 82.

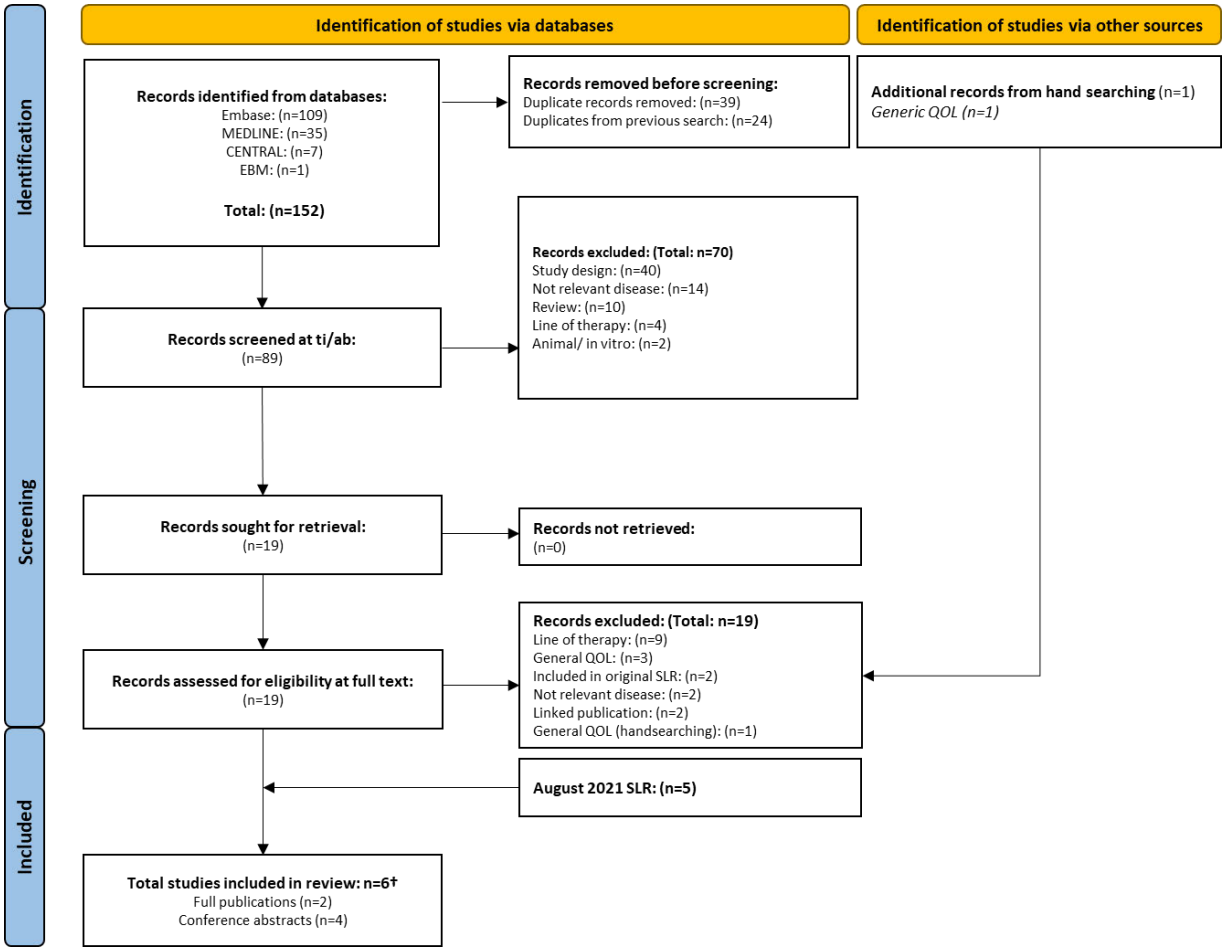


Figure 81: PRISMA flow diagram for SLR of HSUVs.
Abbreviations: HSUV, health state utility value; QOL, quality of life; SLR, systematic literature review.
† Six studies were included in the current SLR. One reference reporting primary utility values which was identified in SLR update 1 was additionally summarised in the current report for ease of reference (Patrick et al (2019) (113)).

Summary of reported HSUVs

Studies reporting results for 2L+ DLBCL

A total of seven publications (reporting on six unique studies) were identified that reported results for patients with DLBCL in the 2L+ settings (113-119) (including Patrick et al (2019) (113), a conference abstract identified in the previously conducted SLR update 1); of these, five were presented as abstracts only, and two were presented as a full publications. Patrick et al (2019) and Patrick et al (2021) are linked publications and both report unique utility data from the TRANSCEND NHL 001 trial (113, 119).

Countries from which utility data were taken included the UK (N=2) (114, 117) and the US (N=2) (116, 119). One covered multiple countries over Europe, North America, Asia, and Oceania (115) and one did not report the country (118).

Study designs of the included studies included: Phase 1 randomised multi-centre cohort studies (N=1) (119)r, health state elicitation studies (N=2) (114, 117), a single arm open label Phase 2b study (N=1) (115), a Phase 2 single arm trial (N=1) (118), and an ad hoc analysis of a safety and management study (N=1) (116).

The following populations were considered across the six included studies:

- Patients with RR DLBCL in the 3L+ settings (N=2) (115, 119)
- Patients with RR DLBCL (specific line of treatment not specified) (N=2) (116, 118)

- The UK general public from London and Edinburgh (N=1) (114)
- Patients with DLBCL in the 1L, 2L, or 3L+ settings (N=1) (117)

A number of the identified studies reported intervention-specific utilities. Treatments considered included CAR T-cell therapy (N=1) (114), axicabtagene ciloleucel (N=1) (116), lisocabtagene maraleucel (N=1) (119), naratuximab emtansine + rituximab (N=1) (118), and selinexor (N=1) (115).

Studies reported results for 3L+ DLBCL

Of the six studies reporting utility values for patients with DLBCL in the 2L+ setting, three studies (reported in four publications) specifically reported results for the 3L+ setting (115, 117, 119).

- A full publication and a conference abstract reporting utility values for patients with DLBCL in the 3L+ settings from the TRANSCEND NHL 001 trial who received prior lisocabtagene maraleucel in the US (113, 119)
- A full publication reporting utility values for multi-national patients with DLBCL who had received at least 2 and no more than 5 previous systemic regimens for enrolment in the SADAL trial (115)
- A conference abstract reporting non-treatment specific utilities for patients with DLBCL in the 1L, 2L, and 3L+ settings in the UK (117)

A summary of the included studies and reported utility values is provided in Table 79.

Table 79: Summary of identified studies reporting HSUVs associated with RR DLBCL (N=7).

Study, country, design	Population (sample size)	Treatment	Method used to derive utilities	Health states	HSUV (SD) [SE]	Summary of reported limitations and conclusions
Howell, 2020 (114) **UK** **Health state elicitation study** ***Abstract only***	The UK general public in London and Edinburgh. (N=218)	CAR T-cell therapy	**Instrument:** TTO **Tariff:** NA	UK general public, CAR T-cell therapy without AEs health state, mean score (N=NR)	0.73 (0.30)	**Limitations:** NR **Conclusions:** More serious AEs were associated with greater disutilities. As AEs were added to health states valued in a 1-year time horizon, these disutilities could be applied as QALY decrements in cost-utility analyses.
				UK general public, disutilities associated with CRS grade 1, mean score (N=NR)	–0.01 (0.04)	
				UK general public, disutilities associated with UK general public, CRS grade 2, mean score (N=NR)	–0.05 (0.09)	
				UK general public, disutilities associated with CRS grade 3/4, mean score (N=NR)	–0.23 (0.24)	
				UK general public, disutilities associated with NEs grade 1/2, mean score (N=NR)	–0.04 (0.07)	
				UK general public, disutilities associated with NEs grade 3/4, mean score (N=NR)	–0.18 (0.22)	
Lin, 2019 (116) **US** **Ad hoc analysis of a safety and management study** ***Abstract only***	Patients with RR DLBCL. (N=33[†])	Axi-cel	**Instrument:** EQ-5D-5L **Tariff:** US tariff (Shaw, 2005 (120)) [after mapping of EQ-5D-5L onto EQ-5D-3L]	Patients with RR DLBCL, screening, mean score (N=33)	0.8 (0.17)	**Limitations:** NR **Conclusions:** Health utility values appeared to transiently decrease slightly at 1 month post CAR T infusion, possibly due to CAR T-related AEs. Health utility values were numerically higher in patients with a progression-free health state compared with those with progressive disease.
				Patients with RR DLBCL, at Week 4 (N=27)	0.74 (0.15)	
				Patients with RR DLBCL, at Month 3 (N=20)	0.8 (0.13)	
				Patients with RR DLBCL, at Month 6 (N=7)	0.82 (0.21)	
				Patients with RR DLBCL, progression free health state (N=NR)	0.80 (0.14)	
				Patients with RR DLBCL, progressed disease	0.72 (0.17)	

				Patients with RR DLBCL, disutility at Week 4	0.05 (0.04)	
Orfanos, 2022 (118) **NR** **Phase 2 single arm trial** ***Abstract only***	Patients with RR DLBCL. (N=NR)	Naratuximab emtansine + rituximab	**Instrument:** FACT-L mapped to EQ-5D (version not specified) **Tariff:** NR	Patients with RR DLBCL, responders at baseline (N=NR)	0.78	**Limitations:** NR **Conclusions:** Responders were more likely to improve and less likely to decline in their HRQoL. At the same time, the difficulty of experiencing side effects was not increased for naratuximab emtansine + rituximab responders. These values were strong signals of naratuximab emtansine + rituximab efficacy and favourable tolerability.
				Patients with RR DLBCL, non-responders at baseline (N=NR)	0.73	
				Patients with RR DLBCL, responders at EOT (N=NR)	0.77	
				Patients with RR DLBCL, non-responders at EOT (N=NR)	0.67	
Studies reporting results for patients with DLBCL in the 3L+ setting (N=3)						
Patrick, 2019 and Patrick, 2021 (113, 119) **[TRANSCEND NHL 001]** **Phase 1, non-randomised, open-label, multi-centre, multi-cohort study** ***2019: abstract only; 2021: full publication***	Patients with RR DLBCL in the 3L+ setting‡. (available EQ-5D at baseline assessment, N=198; no available assessment at baseline, N=1)	Liso-cel	**Instrument:** EQ-5D-5L **Tariff:** US tariff (van Hout, 2012 (121))	Patients with LBCL, baseline, mean score (N=NR) (119)	0.82 (0.12)	**Limitations:** • Managing missing data. Missing data were assumed to be random and were not – this was not confirmed. If data were not missing at random, the missing data may be a source of bias. Loss of patients because of death or study discontinuation may have exacerbated bias • Some of the patients had not been in the TRANSCEND study long enough to reach some of the time points. Treatment responders with improved HRQoL may choose to remain in the study, whereas non-responders and patients who relapse with poor
				Patients with RR DLBCL, utility change from baseline to Month 1, mean score (N=NR) (113)	–0.016 (0.144)	
				Patients with RR DLBCL, utility change from baseline to Month 2, mean score (N=NR) (113)	0.010 (0.149)	
				Patients with RR DLBCL, utility change from Month 2 to Month 6, mean score (N=NR) (113) *Change from baseline data were also reported in Figure 5A of the full publication (see **Figure 82** below)*	0.019 (0.133)	

HRQoL due to progressive disease may discontinue

- The PRO analysis based on response to treatment was limited by the small number of non-responders who completed assessments at later time points. Due to these biases, PRO analyses by treatment response status, particularly those at later time points, should be interpreted with caution
- P-values were not calculated with multiplicity adjustment
- Patients who progressed and subsequently received another anti-cancer therapy were asked to complete PRO assessments. Including these patients in the analysis may have confounded the findings by making it impossible to distinguish between the effects of anti-cancer therapies and those of liso-cel
- A fixed threshold of 10 was used to define all clinically meaningful treatment effects for the EORTC QLQ-C30. Guidelines for the questionnaire suggest that a fixed threshold may be too simplistic for failing to differentiate between different scales. Additionally, it may not have been appropriate to use the same threshold for group level and individual-level analyses

						Conclusions: Overall, a notable proportion of patients experienced meaningful improvements in HRQoL and symptoms at various times points across pre-specified scales.
Shah, 2021 (115) **Multi-national (in multiple countries across Europe, North America, Asia, and Oceania)** **[SADAL]** **Single arm, open-label, Phase 2b study** ***Full publication***	Patients with RR DLBCL who received at least 2 but no more than 5 prior systemic regimens. (responders, N=31; non-responders, N=44[††])	Selinexor	**Instrument:** EQ-5D-5L **Tariff:** US tariff (van Hout, 2012 (121))	Patients with RR DLBCL, progressive disease, baseline, mean score (N=NR)	0.731 (95% CI: 0.668; 0.793)	**Limitations:** • As SADAL was a single arm study, treatment-associated changes in HRQoL or health utility could not be directly tested from the clinical trial data • The number of patients with post-baseline HRQoL data, particularly those with an evaluable response, was relatively small and decreased in later cycles • In the responder analysis, the mixed-effects model assumed a linear relationship between time and responder status, and that patient trajectories would remain similar following discontinuation from the study • As patients were not randomised according to responder and non-responder status, comparison of HRQoL change by responder status could be confounded by differences in unmeasured clinical characteristics which could result in residual confounding • Due to the exploratory nature of the analysis and small patient numbers, the analysis was not
				Patients with RR DLBCL, stable disease, baseline, mean score (N=NR)	0.783 (95% CI: 0.756; 0.809)	
				Patients with RR DLBCL, response, baseline, mean score (N=NR)	0.801 (95% CI: 0.741; 0.861)	
				Patients with RR DLBCL, progressive disease, EOT, mean score (N=NR)	0.669 (95% CI: 0.619; 0.719)	
				Patients with RR DLBCL, stable disease, EOT, mean score (N=NR)	0.721 (95% CI: 0.658; 0.784)	
				Patients with RR DLBCL, response, EOT, mean score (N=NR)	0.739 (95% CI: 0.689; 0.790)	
				Patients with RR DLBCL, pairwise comparison, baseline, progressive disease, mean score (N=NR)	–0.052 (95% CI: 0.0004; –0.109) (p=0.073)	
				Patients with RR DLBCL, pairwise comparison, baseline, stable disease, mean score (N=NR)	0.07 (95% CI: 0.029; 0.111) (p=0.001)	
				Patients with RR DLBCL, pairwise comparison, response, mean score (N=NR)	0.018 (95% CI: –0.035; 0.072) (p=0.507)	
				Patients with RR DLBCL, responders at baseline, mean score (N=31)	0.789 (95% CI: 0.767; 0.811)	
				Patients with RR DLBCL, responders at cycle 2, mean score (N=31)	0.787 (95% CI: 0.763; 0.811)	
				Patients with RR DLBCL, responders at cycle 3, mean score (N=31)	0.785 (95% CI: 0.747; 0.822)	

Patients with RR DLBCL, responders at cycle 4, mean score (N=31)	0.782 (95% CI: 0.728; 0.837)
Patients with RR DLBCL, responders at cycle 5, mean score (N=31)	0.780 (95% CI: 0.708; 0.852)
Patients with RR DLBCL, responders at cycle 6, mean score (N=31)	0.778 (95% CI: 0.688; 0.868)
Patients with RR DLBCL, responders at cycle 7, mean score (N=31)	0.776 (95% CI: 0.668; 0.884)
Patients with RR DLBCL, non-responders at baseline, mean score (N=44)	0.801 (95% CI: 0.781; 0.822)
Patients with RR DLBCL, non-responders at cycle 2, mean score (N=44)	0.756 (95% CI: 0.735; 0.776)
Patients with RR DLBCL, non-responders at cycle 3, mean score (N=44)	0.710 (95% CI: 0.676; 0.745)
Patients with RR DLBCL, non-responders at cycle 4, mean score (N=44)	0.664 (95% CI: 0.612; 0.716)
Patients with RR DLBCL, non-responders at cycle 5, mean score (N=44)	0.619 (95% CI: 0.548; 0.689)
Patients with RR DLBCL, non-responders at cycle 6, mean score (N=44)	0.573 (95% CI: 0.484; 0.662)
Patients with RR DLBCL, non-responders at cycle 7, mean score (N=44)	0.527 (95% CI: 0.419; 0.636)

powered to explore the relationship between HRQoL and disease-specific characteristics such as de novo or transformed DLBCL, genetic subtypes or prior number of therapies. Notably in SADAL, response to Selinexor was maintained across patients with de novo or transformed DLBCL, GCB or non-GCB subtype, >2 prior systemic anti-DLBCL regimens and those who had previously received ASCT, with overall response rates ranging from 20.6 to 38.7% (Kalakonda, 2020 (122))

Conclusions: The analyses showed that patients with RR DLBCL who responded to treatment with single-agent Selinexor in the SADAL trial maintained higher HRQoL and health utilities whereas non-responders experienced deterioration, which was clinically meaningful. Treatment responders had higher mean health state utility compared with patients with progressive disease and stable disease. This evidence complements the clinical benefits and manageable AE profile of oral single-agent Selinexor, which provided durable and consistent responses in heavily pre-treated patients with RR DLBCL.

Wang, 2018 (117) **UK** **Health state elicitation study** ***Abstract only*** ***Not identified by previous SLRs. Identified in the SLR update 2 during handsearching.***	Patients with DLBCL in the 1L and 2L+ settings. (N=319)	NA	**Instrument:** EQ-5D-5L **Tariff:** The population from which valuation was taken was NR. Two societal tariffs were used: 1) An EQ-5D-5L value set that directly converts EQ-5D-5L to EQ-5D-3L 2) An EQ-5D-5L crosswalk index value set	Patients with DLBCL, using the EQ-5D-5L value set directly, 2L treatment, mean score (N=NR)	0.66 [0.025]	**Limitations:** NR **Conclusions:** Different value sets generated different utility values; making comparison work challenging and highlighting the need for method standardisation.
				Patients with DLBCL, using the EQ-5D-5L value set directly, 3L+ treatment, mean score (N=NR)	0.59 [0.093]	
				Patients with DLBCL, using the EQ-5D-5L value set directly, 2nd remission, mean score (N=NR)	0.81 [0.057]	
				Patients with DLBCL, using the EQ-5D-5L value set directly, 3rd+ remission, mean score (N=NR)	0.70 [0.059]	
				Patients with DLBCL, using the crosswalk value set, 2L treatment, mean score (N=NR)	0.53 [0.065]	
				Patients with DLBCL, using the crosswalk value set, 3L+ treatment, mean score (N=NR)	0.53 [0.105]	
				Patients with DLBCL, using the crosswalk value set, 2nd remission, mean score (N=NR)	0.69 [0.081]	
				Patients with DLBCL, using the crosswalk value set, 3rd+ remission, mean score (N=NR)	0.58 [0.116]	

Abbreviations: 1L/2L/3L+, first-line/second-line/third-line and onwards; AE, adverse event; ASCT, autologous stem cell transplant; CI, confidence interval; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; EQ-5D-5L, European Quality of Life Questionnaire – 5 Dimensions – 5 Levels; FL, follicular lymphoma; HRQoL, health related quality of life; HSUV, health state utility value; RR, relapsed/refractory; NA, not applicable; NE, neurological event; NHL, non-Hodgkin lymphoma; NR, not reported; PMBCL, primary mediastinal B-cell lymphoma; PRO, patient reported outcomes; QALY, quality adjusted life year; SD, standard deviation; SE, standard error; TTO, time trade off; UK, United Kingdom; US, United States.
†Patients with EQ-5D assessment available at screening.
††Responders and non-responders with complete EQ-5D data.
‡The population enrolled in the TRANSCEND NHL 001 trial was classified as DLBCL cohort if they had the following diagnoses: DLBCL not otherwise specified, high grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements with DLBCL histology, PMBCL, and FL grade 3B.

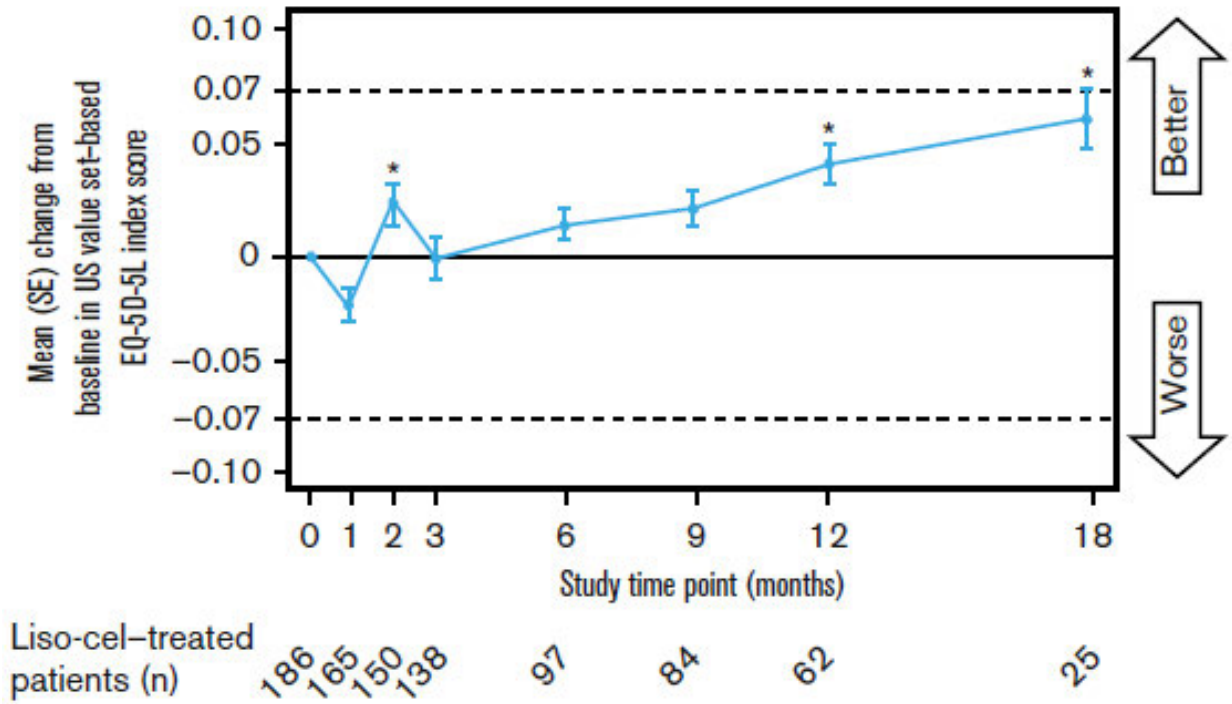


Figure 82: Change in EQ-5D-5L index score for patients enrolled in in the TRANSCEND NHL 001 trial over time
Abbreviations: EQ-5D-5L, European Quality of Life Questionnaire – 5 Dimensions – 5 Levels; SE, standard error; US, United States.
Figure taken from Patrick et al (2021) (119).

Quality assessment and generalizability of estimates

During data extraction, the relevance of utilities and the quality of the studies generating them were assessed and recorded, and the quality of any mapping algorithms examined. This process is as recommended in the NICE technical support documents 8–10 and enables justification of the use/non-use of different utility values or mapping algorithms in an economic model (12). In particular, the following issues were addressed:

- Whether response rates, loss to follow-up, or missing data level are likely to threaten the validity of the utility estimate
- Whether the selection criteria yield a population similar to that being modelled
- Whether utility incorporated decrement for QoL loss from adverse events
- Whether the utility meets the NICE reference case (i.e. health states should be described by the patient and valued according to societal preferences using UK/English societal preferences) (13)

Quality assessment of the included studies highlighted a number of limitations associated with the utility values reported. In particular, although response rates to instruments were generally well reported, only three out of the six studies reported details of missing data (6, 8, 10), of which one did not clearly present these details (8). Furthermore, three out of six publications reported details of the loss to follow up (6, 7, 10). Additionally, four publications were abstracts only and therefore, reporting of methods and results were limited. It should be noted that caveats of the individual studies were only reported in the full publications (N=2) (6, 10). Limitations across both of these studies were unique; however, it should be noted that both reported that patients may not have reached later timepoints in the studies. For example, Patrick et al (2021) reported that some patients were not in the study for long enough to reach later time points, which could lead to bias as patients who responded to lisocabtagene maraleucel would remain in the study, but non-responders and patients who relapse would drop out (10). Similarly, Shah et al (2021) stated that the number of patients with post-baseline HRQoL data decreased in later cycles of treatment with Selinexor (6).

Results of the quality assessment of the included studies are presented in Table 80

Table 80: Quality assessment of included HSUV studies

Study	Sample size	Response rates to instruments?	Loss to follow up?	Missing data?	Comparable to population of patients with DLBCL in the 2L or 3L+ setting?	Other considerations
Howell, 2020 (114)	N=218	Yes - interviews were completed with 218 participants.	No	No	No - the UK general public	Abstract only; limited information reported
Lin, 2019 (116)	Patients with available screening stage EQ-5D assessment: N=33	Yes - EQ-5D-5L data were collected for 33, 27, 20, and 7 patients at screening, week 4, month 3, and month 6, respectively.	Yes - the number of evaluable patients at each time point was reported (screening: N=33; week 4: N=27; month 3: N=20; month 7: N=7).	No	Yes - patients with RR DLBCL	Abstract only; limited information reported
Orfanos, 2022 (118)	NR	No	No	No	Yes – patients with RR DLBCL	Abstract only; limited information reported
Patrick, 2019 (113)	N=90	Yes - ninety patients were evaluable.	No	No	Yes - patients with RR DLBCL	Abstract only; limited information reported
Patrick, 2021 (119)	1) Patients with available EQ-5D baseline assessment: N=198 2) Patients with no available baseline assessment: N=1	Yes - the EQ-5D evaluable population consisted of 186 (93%) of the 199 patients in the liso-cel treated LBCL arm enrolled in the study. The number of patients who responded to the EQ-5D questionnaire at each follow up point was also reported in Figure 5 of the publication (baseline: N=186; month 1: N=165; month 2: N=150; month 3: N=138; month 6:	Yes - the number of evaluable patients at each time point was reported in Figure 5 of the publication (baseline: N=186; month 1: N=165; month 2: N=150; month 3: N=138; month 6: N=97; month 9: N=84; month 12: N=62; month 18: N=25).	Yes - missing data were assumed to be missing at random and were not imputed.	Yes - patients with RR LBCL	None

		N=97; month 9: N=84; month 12: N=62; month 18: N=25).				
Shah, 2021 (115)	Patients with complete EQ-5D data: 1) Responders: N=31 2) Non-responders: N=44	Yes - the number of patients with complete EQ-5D data were analysed (responders: N=31; non-responders: N=44).	Yes - there were 19 patients excluded as they had no follow up data.	Yes - eleven patients were excluded as they had no baseline data.	Yes - patients with RR DLBCL	None
Wang, 2018 (117)	N=319	No	No	Unclear - patients had at least one EQ-5D-5L questionnaire completed. Details of missing data were NR quantitatively.	Yes - patients with newly diagnosed DLBCL	Abstract only; limited information reported

Abbreviations: 2L/3L+, second-line/third-line and onwards; ABC, activated B cell; DLBCL, diffuse large B-cell lymphoma; EQ-5D (-5L), European Quality of Life – 5 Dimensions (-5 Levels); FL, follicular lymphoma; HSUV, health state utility value; NR, not reported

Four of the studies included EQ-5D-5L, and the last one included EQ-5D (version not specified). However, to most accurately reflect the patient population of interest, the health state utility values used in the model were estimated using the EORTC-QLQ-C30 and mapped to EQ-5D-3L from clinical trial NP30179 (Indirect mapping). Hence, the above studies were not used in the current health economic model. As per the Danish guidelines, it is recommended to map health state utilities to Danish utility tariffs. However, due to the unavailability of a mapping algorithm from EORCT to EQ-5D-3L/5L Danish tariff as per the guidelines provided by the DMC, it was not possible to follow the recommended method for Danish utility values (75). Consequently, the model employs utilities based on UK tariffs. The EQ-5D-3L and EQ-5D-5L versions have been found to have high levels of agreement, with the 5L version showing moderately better distribution parameters and significantly improved informativeness compared to the 3L version. Moreover, both measures are effective in assessing health-related quality of life (123).

Excluded studies

Full publication exclusions

A list of studies excluded on the basis of full text review is provided in Table 81, along with the rationale for exclusion.

Table 81: List of studies excluded on full text review

#	Reference	Rationale
SLR update 2 (N=6)		
1	Casasnovas, RO. PCN325 Health Utility in Relapsed/Refractory Diffuse Large B-Cell Lymphoma (RR-DLBCL) Patients - Results of a Phase II Trial with ORAL Selinexor. Value in Health. 2020;23(Supplement 2):S479-S480.	Superseded by Shah 2021 full publication
2	Chiappella, A. Quality of Life Was Not Negatively Impacted By the Addition of Lenalidomide to R-CHOP Chemotherapy (R2-CHOP) Compared with Placebo Plus R-CHOP Chemotherapy in Patients with Previously Untreated Activated B-Cell (ABC)-Type Diffuse Large B-Cell Lymphoma (DLBCL): Health-Related Quality of Life (HRQoL) Analysis of the International Robust Study. Blood. 2019; 134 (Supplement 1):3475.	Population – 1L DLBCL
3	Garcia-Munoz, R. Safety of switching from intravenous to subcutaneous rituximab during first-line treatment of patients with non-Hodgkin lymphoma: the Spanish population of the MabRella study. British Journal of Haematology. 2020; 188(5):661-673.	Population – 1L DLBCL
4	Lemieux, C. Evaluation of the Impact of Autologous Hematopoietic Stem Cell Transplantation on the Quality of Life of Older Patients with Lymphoma. Biology of Blood and Marrow Transplantation. 2020; 26(1):157-161.	Population
5	Patrick, D. Impact of lisocabtagene maraleucel (liso-cel) treatment on health-related quality of life and health utility in patients with relapsed/ refractory aggressive B-cell non-Hodgkin lymphoma: TRANSCEND NHL 001 (NCT02631044). British Journal of Haematology. 2020; 189 (Supplement 1):220-221.	Superseded by Patrick 2021
6	Patrick, D. Pcn262 Preference-Weighted Health Status in Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma (R/R Dlbcl) Treated with Lisocabtagene Maraleucel (Liso-Cel; Jcar017) in the Ongoing, Multicenter, Phase 1 Transcend Nhl 001 Trial. Value in Health. 2019;22(Supplement 2):S106.	Included in SLR update 1
SLR update 3 (N=18)		
1	Abramson, JS. Improved quality of life (QoI) with lisocabtagene maraleucel (Liso-cel), a CD19-directed chimeric antigen receptor (CAR) T cell therapy, compared with standard of care (SOC) as second-line (2l) treatment in patients (pts) with relapsed or refractory (R/R) large B-cell lymphoma (LBCL): Results from the phase 3 transform study. Blood. 2021;138(SUPPL 1):3845.	Line of therapy (2L only)
2	Cwynarski, K. Patient-Reported Outcomes in ZUMA -7, a Phase 3, Randomised, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel (Axi-Cel) Vs. Standard-of-Care Therapy in Relapsed/ Refractory Large B-Cell Lymphoma. British Journal of Haematology. British Journal of Haematology. 2022; 197(SUPPL 1):154-156.	Linked publication
3	Elsawy, M. Patient-reported outcomes in ZUMA-7, a phase 3 study of axicabtagene ciloleucel in second-line large B-cell lymphoma. Blood. 2022;15.	Line of therapy (2L only)
4	Elsawy, M. Patient-Reported Outcomes in a Phase 3, Randomized, Open-Label Study Evaluating the Efficacy of Axicabtagene Ciloleucel (Axi-Cel) Vs. Standard of Care Therapy in Patients with Relapsed/Refractory Large B-Cell Lymphoma (ZUMA-7). Blood. 2021;138(Supplement 1):430.	Line of therapy (2L only)

#	Reference	Rationale
5	Gordon, LI. Lisocabtagene Maraleucel (Liso-Cel) as Second-Line Treatment for R/R Large B-Cell Lymphoma (Lbcl) in Patients Not Intended for Hsct: Patient-Reported Outcomes (Pro) from the Phase 2 Pilot Study. HemaSphere. 2022; 6(Supplement 3):2999-3000.	Line of therapy (2L only)
6	Howell, TA. Health State Utilities for Adverse Events Associated with Chimeric Antigen Receptor T-Cell Therapy in Large B-Cell Lymphoma. 2022;6(3):367-376.	Included in the original SLR
7	Hu, Y. Quality of life and related demographic factors in long-term survivors of childhood non-Hodgkin's lymphoma. Chinese Journal of Contemporary Pediatrics. 2021;23(9):882-888.	Not relevant disease
8	Kersten, MJ. Quality-adjusted time without symptoms or toxicities (Q-TWiST) analysis of ZUMA-7, a randomized controlled trial of axicabtagene ciloleucel vs. standard of care for second-line large B-cell lymphoma. Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2022;40(16 Supplement 1).	Line of therapy (2L only)
9	Launonen, A. Exploring the Impact of Diffuse Large B-Cell Lymphoma (International Prognostic Index [IPI] 2-5) on Clinical and Patient-Relevant Outcomes in the Context of a Clinical Trial. Blood. 2021; 138(Supplement 1):3577.	Line of therapy (1L and first relapse)
10	Ma, Q. Real-world health-related quality of life in patients with diffuse large B-cell lymphoma: Comparisons with reference populations and by line of therapy. Blood. 2021;138(SUPPL1):4111.	General QoL
11	Marte, C. Unmet mental health needs in patients with advanced B-cell lymphomas. Palliative & Supportive Care. 2022;20(3):328-333.	General QoL
12	Paunescu, AC. Quality of life of survivors 1 year after the diagnosis of diffuse large B-cell lymphoma: a LYSA study. Annals of Hematology. 2022;101(2):317-332.	Line of therapy
13	Shah, J. Health-related quality of life and utility outcomes with selinexor in relapsed/refractory diffuse large B-cell lymphoma. Future Oncology. 2021; 17(11):1295-1310.	Included in original SLR
14	Spira, A. Health-Related Quality of Life, Symptoms, and Tolerability of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma and Leukemia. 2022;22(3):158-168.	General QoL
15	Spira, A. Health-Related Quality of Life and Tolerability of Loncastuximab Tesirine in High-Risk Patients with Relapsed/Refractory Diffuse Large B-Cell Lymphoma Treated in a Phase 2 Clinical Trial (Lotis 2). HemaSphere. 2022; 6(Supplement 3):3011-3013.	Linked publication
16	Sureda, A. Clinical and Patient-Reported Outcomes in a Phase 3 Study of Axicabtagene Ciloleucel (Axi-Cel) Vs Standard-of-Care in Elderly Patients with Relapsed/Refractory Large B-Cell Lymphoma (Zuma-7). HemaSphere. 2022; 6(Supplement 3):231-232.	Line of therapy (2L only)
17	Wang, XS. Patient-Reported Symptom and Functioning Status during the First 12 Months after Chimeric Antigen Receptor T Cell Therapy for Hematologic Malignancies. Transplantation and Cellular Therapy. 2021; 27(11):930.e1-930.e10.	Not relevant disease
18	Westin, J. Clinical and patient (pt)-reported outcomes (PROs) in a phase 3, randomized, openlabel study evaluating axicabtagene ciloleucel (axi-cel) vs. standard-of-care (SOC) therapy in elderly pts with relapsed/refractory (R/R) large B-cell lymphoma (LBCL; ZUMA-7). Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO. 2022;40(Supplement 1).	Line of therapy (2L only)

Abbreviations: 1L/2L/3L+, first-line/second-line/third-line and onwards; DLBCL, diffuse large B-cell lymphoma; HSUV, health state utility value; QoL, quality of life.

A list of studies excluded as they report results of non-utility QOL measures is presented in Table 82.

Table 82: Excluded studies tagged as "general QOL"

#	Reference	Publication type	Instrument	Treatment line
1	Hoogland, AI. Acute patient-reported outcomes in B-cell malignancies treated with axicabtagene ciloleucel. Cancer Medicine. 2021;10(6):1936-1943.	Full	SF-36, PROMIS-29	RR
2	Maziarz, RT. Patient-reported long-term quality of life after tisagenlecleucel in relapsed/refractory diffuse large B-cell lymphoma. Blood Advances. 2020; 4(4):629-637.	Full	FACT-Lym, SF-36	RR
3	Spira, AI. Symptoms, health-related quality of life, and tolerability of loncastuximab tesirine in patients with relapsed or refractory diffuse large B cell lymphoma. Blood. 2020;136 (SUPPL 1):3-4.	Abstract	FACT-Lym, EQ-5D-5L VAS	RR
4	Patrick, DL. TRANSCEND NHL 001: Health-related quality of life (HRQL) and symptom (Sx) impact in patients (pts) with relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL) receiving lisocabtagene maraleucel (Liso-cel; JCAR017). Journal of Clinical Oncology. Conference. 2019;37(Supplement 15).	Abstract	EORTC QLQ-C30	RR
5	Ma, Q. Real-world health-related quality of life in patients with diffuse large B-cell lymphoma: Comparisons with reference populations and by line of therapy. Blood. 2021;138(SUPPL 1):4111.	Abstract	EORTC QLQ-C30, EQ-5D-5L VAS	1L, 2L, 3L+
6	Marte, C. Unmet mental health needs in patients with advanced B-cell lymphomas. Palliative & Supportive Care. 2022; 20(3):328-333.	Full	HADS, SF-12	2L+
7	Spira, A. Health-Related Quality of Life, Symptoms, and Tolerability of Loncastuximab Tesirine in Patients With Relapsed or Refractory Diffuse Large B-Cell Lymphoma. Clinical Lymphoma, Myeloma and Leukemia. 2022; 22(3):158-168.	Full	FACT-Lym, EQ-5D VAS	2L+
8	Thuresson P-O. Quality of Life (QoL) in Patients With Relapsed/Refractory Non-Hodgkin Lymphoma (NHL) Treated with Polatuzumab Vedotin Plus Rituximab in the ROMULUS Study. Blood. 2019; 134 (Supplement 1): 4767.	Abstract	MDASI questionnaire	RR

Abbreviations: 1L/2L/3L+, first-line/second-line/third-line and onwards; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D (-5L), European Quality of Life Questionnaire - 5 Dimensions (-5 Levels); FACT-Lym, Functional Assessment of Cancer Therapy – Lymphoma; MDASI, MD Anderson Symptom Inventory; PROMIS-29, Patient Reported Outcome Measurement Information System – 29; RR, relapsed refractory; HADS, Hospital Anxiety and Depression Scale; SF-12, Short Form – 12; SF-36, Short Form – 36; VAS, visual analogue scale.

Unpublished data

No unpublished data was used.

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Appendix I Mapping of HRQoL data

Number of patients answering EORT QLQ-C30 in NP30179 study.

Table 83:Summary table for EORT QLQ–C30 outcomes in Glofit 3L+ patients

Intent–to–Treat patients; Clinical Cut Off Date: JUN2022	
Time point	**Number of patients**
Baseline	143
Cycle 1 Day 1	2
Cycle 2 Day 1	114
Cycle 3 Day 1	94
Cycle 5 Day 1	74
Cycle 7 Day 1	54
Cycle 9 Day 1	21
Cycle 12 Day 1	23

Table 84: Summary table for EORT QLQ–C30 outcomes change from baseline in Glofit 3L+ patients

Intent–to–Treat patients; Clinical Cut Off Date: JUN2022	
Time point	**Number of patients**
Baseline	143
Cycle 1 Day 1	1
Cycle 2 Day 1	108
Cycle 3 Day 1	88
Cycle 5 Day 1	73
Cycle 7 Day 1	53
Cycle 9 Day 1	20
Cycle 12 Day 1	23

Mapping

Given the absence of lymphoma specific algorithms estimating values from Western country tariffs, a target literature search of HSUV evidence associated with DLBCL to identify the best candidates for use in the mapping. Please refer to Appendix H for more details on the search. The algorithm used in this submission to map utilities is derived from EORTC-QLQ to EQ-5D-3L, using the direct mapping algorithm published by Proskorovsky et al, 2014 (100) (full model) and indirect mapping algorithm published in Longworth et al, 2014 (80).

Both of the preferred mapping algorithms were estimated in patients with multiple myeloma (or where multiple myeloma was the predominant cancer type). The direct and indirect mapping algorithms were preferred over other potentially options for the following reasons:

- Good predictive ability (based on model performance statistics and accuracy of predicted values)
- Relevance and size of the patient sample used to estimate the algorithm
- Sufficient amount of detail on how the regression was estimated and on the baseline characteristics of the sample
- External validation
- Use in previous NICE submissions

Both Proskorovsky et al, 2014 (100) and Longworth et al, 2014 (80) algorithms were accepted in previous NICE TAs for hematological malignancies (TA695, TA657, TA450 and TA399), with the former being the one most frequently used. However, the model base case uses the algorithm from Longworth et al, 2014 (63) as, unlike Proskorovsky et al, 2014, (100) this has recently been externally validated (124).

Mapping from EORTC to EQ-5D was performed using the same population of patients as described in section 7.2.6, which is patients from the part III dose-expansion cohorts (pivotal cohort and mandatory dexamethasone cohort) who have had a baseline assessment and at least one post-baseline assessment before the date of progression.

The mapped EQ-5D-3L index values based on UK tariffs were used to estimate utilities for three health states: PFS on-treatment, PFS off-treatment and PPS. A distinction between PFS on- and off-treatment was made to account for the potential impact of treatment related factors (such as toxicities, burden of administration, etc.) on utility. This allows to more granularly characterize the utility experienced by patients in PFS over time and to better distinguish between the utility for patients receiving treatment until progression and e.g., that of patients off-treatment but in remission, compared to an average PFS utility. This approach is also likely able to better capture the impact of treatment related toxicities on utility compared to estimating individual AEs disutilities, as utility measurements are typically rarely available for the same visits at which AEs take place.

Utility measurements were assigned to PFS or PPS health states by comparing the date of progression with the corresponding date of measurement for the predicted utility. If the date of measurement was larger than the date of progression, the patient was set as PPS. If it was not possible to assign a utility measurement to either PFS or PPS due to censoring, then that measurement was classified as unknown, as the patient could have progressed between the date of censoring and the date of measurement. These visits were then excluded from the sample. A similar approach was used for on- and off-treatment states but using the date of treatment discontinuation as reference.

Results of the HSUV derived from EORTIC-QLQ-C30 to EQ-5D-3L using direct and indirect mapping and HSUV informed in previous NICE submissions are reported in Table 85.

Table 85: Summary of health state utility values mapped from EORTC-QLQ-C30.

Health state	Utility value	SE	PSA	Justification
EORTC-QLQ-C30 to EQ-5D 3L Mapped Utility Values, direct Mapping (UK tariff) (100)				
On PFS - on treatment	0.772	0.010	0.76	EORTC-QLQ-C30 to EQ-5D-3L has been used in previous NICE submissions
On PFS - off treatment	0.836	0.017	0.79	
On PPS	0.673	0.016	0.66	
EORTC-QLQ-C30 to EQ-5D 3L Mapped Utility Values, indirect Mapping (UK tariff) (80)				
On PFS - on treatment	0.729	0.011	0.72	EORTC-QLQ-C30 to EQ-5D-3L has been used in previous NICE submissions
On PFS - off treatment	0.774	0.020	0.80	
On PPS	0.629	0.019	0.64	

Note: a beta distribution has been used to sample all these utilities in the probabilistic sensitivity analysis. To ensure accurate ordered sampling of health state utilities, the method described in Ren et al 2018 was used (125).
Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-3L, European Quality of Life 5 Dimensions 3 Level version; NICE, National Institute for Health and Care Excellence; PFS, progression-free survival; PPS, post-progression survival; PSA, probabilistic sensitivity analysis; SE, standard error.
Source: *CEM Glofit_3L+_DLBCL_NP30179_1.1.*

All utilities were estimated through a mixed regression model on post-baseline utilities only while controlling for centralized baseline utilities and using random intercepts for each patient. This technique is relatively robust to distribution violation. The analysis takes the basic assumptions of the lme4 package lmer() function (126), i.e. a complete-case perspective. Although this is a less "powered" approach, there are limitations with respect to how missing values can be predicted. Bootstrapping (2000 resamples) was used to estimate confidence intervals around point estimates. Descriptive statistics and plots of the mapped EQ-5D-3L utilities and predicted health state utility values are provided in the relevant appendix file (*mapped_utilities_NP30179_2022-08*).

AE disutilities based on literature/clinical opinion are by default set to off (utility values tab; E38 *ae_disutil*) when using mapped utilities. If one wants to assess the impact of the toxicity profiles of individual treatments, then it is recommended to use the PFS/PPS health state utilities based on literature/previous NICE TAs. AE disutilities are applied in the model for the time patients are on-treatment. The only exception to this is for CAR-T cell therapies, whose main AEs tend to occur in the first 2-3 weeks after injection, and thus these were all assumed to occur within the first model cycle, as a modeling simplification.

The model also allows to test scenarios where proximity to death utilities (on-/off-treatment) are applied (80), Table 86. These were estimated only using the indirect mapping algorithm from Longworth et al, 2014. (80)

Table 86: Proximity to death utilities (based on EORTC-QLQ-C30 to EQ-5D 3L indirect mapping).

	Time intervals	Arm	Estimate	SE	Distribution	PSA
On Treatment	≤ 10 weeks before death	Glofitamab	0.684	0.025	Normal	0.69
	> 10 & ≤ 30 weeks before death	Glofitamab	0.733	0.015	Normal	0.76

	> 30 & ≤ 60 weeks before death	Glofitamab	0.729	0.015	Normal	0.71
	> 60 weeks before death	Glofitamab	0.728	0.017	Normal	0.75
Off Treatment	≤ 10 weeks before death	Glofitamab	0.565	0.030	Normal	0.55
	> 10 & ≤ 30 weeks before death	Glofitamab	0.720	0.023	Normal	0.73
	> 30 & ≤ 60 weeks before death	Glofitamab	0.724	0.025	Normal	0.67
	> 60 weeks before death	Glofitamab	0.796	0.045	Normal	0.75

Abbreviations: EORTC-QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; PSA, probabilistic sensitivity analysis; SE, standard error.

Source: *CEM Glofit_3L+_DLBCL_NP30179_1.1.*

Appendix J Probabilistic sensitivity analyses

Table 87: Probabilistic sensitivity analyses

Input sheet	Parameter	Mean	Lower 95% CI	Upper 95% CI	α	β	Distribution	SE
Results								
Efficacy Inputs								
OS HR	Glofitamab vs. R-chemother-apy	0.42	0.25	0.79	NA	NA	NA	NA
PFS HR OS	R-chemother-apy PFS vs. R-chemotherapy OS	0.65	0.52	0.78	NA	NA	NA	NA
PFS HR	Glofitamab vs. R-chemother-apy	0.62	0.46	0.81	NA	NA	NA	NA
Post-progres-sion therapies	Total post dis-continuation cost for Glofitamab	21,073.46	NA	NA	NA	NA	Gamma	1,063.74
	Total post dis-continuation cost for R-chemotherapy	22,802.10	NA	NA	NA	NA	Gamma	1,063.74
Cost Inputs								
Adverse event cost (weekly cost)	AE - Glofitamab	1,246.19	1,050.00	1,511.00	NA	NA	Gamma	NA
	AE - R-chemo-therapy	74.34	67.00	83.00	NA	NA	Gamma	NA
	Incremental Adverse Events	1,171.85	979.00	1,432.00	NA	NA	Gamma	NA
Administration costs	IV administra-tion	1,872.45	1,604.00	2,406.00	NA	NA	Gamma	594.96
	Oral admin-istration	0.00	0.00	0.00	NA	NA	Gamma	0.00
Supportive care costs	PFS on treat-ment	1,447.31	1,209.36	1,814.03	NA	NA	Gamma	151.17
	PFS off treat-ment	66.56	48.03	72.04	NA	NA	Gamma	6.00
	PS	686.08	634.77	952.15	NA	NA	Gamma	79.35
	One off pro-gression cost	9,789.55	8,419.72	12,629.58	NA	NA	Gamma	1,052.47
Diagnostic cost	Cost of diag-nostic test	0.00	0.00	0.00	NA	NA	Gamma	0.00
Patient cost	patient time cost per hour	184.13	144.80	217.20	NA	NA	Gamma	18.10
	PFS - patient cost per model cycle	13.58	11.10	16.65	NA	NA	Gamma	1.39

	PPS - patient cost per model cycle	112.62	105.45	158.18	NA	NA	Gamma	13.18
	One off progression time cost	822.73	622.54	933.82	NA	NA	Gamma	77.82
	PFS On Tx - Glofitamab - patient cost per treatment cycle 1st admin	3,171.45	2,389.20	3,583.80	NA	NA	Gamma	298.65
	PFS On Tx - Glofitamab - patient cost per treatment cycle 2nd-3rd admin	1,092.27	941.20	1,411.80	NA	NA	Gamma	117.65
	PFS On Tx - Glofitamab - patient cost per treatment cycle 4th-12th admin	855.32	651.60	977.40	NA	NA	Gamma	81.45
	PFS On Tx - R-chemotherapy - patient cost per treatment cycle R-DHAP	6,979.43	7,022.80	10,534.20	NA	NA	Gamma	877.85
	PFS On Tx - R-chemotherapy - patient cost per treatment cycle R-ICE	6,765.16	7,022.80	10,534.20	NA	NA	Gamma	877.85
Travel cost	Travel cost	127.19	112.32	168.48	NA	NA	Gamma	14.04
Utility Inputs								
Direct	On PFS - On treatment	0.77	NA	NA	NA	NA	Beta	0.010
Direct	On PFS - Off treatment	0.85	NA	NA	NA	NA	Beta	0.017
Direct	On PPS	0.69	NA	NA	NA	NA	Beta	0.016
Indirect	On PFS - On treatment	0.73	NA	NA	NA	NA	Beta	0.011
Indirect	On PFS - Off treatment	0.79	NA	NA	NA	NA	Beta	0.020
Indirect	On PPS	0.61	NA	NA	NA	NA	Beta	0.019
Proximity to death utilities	≤ 10 weeks before death (On Tx)	0.71	NA	NA	NA	NA	Normal	0.025
	> 10 & ≤ 30 weeks before death (On Tx)	0.74	NA	NA	NA	NA	Normal	0.015
	> 30 & ≤ 60 weeks before death (On Tx)	0.74	NA	NA	NA	NA	Normal	0.015

> 60 weeks before death (On Tx)	0.73	NA	NA	NA	NA	Normal	0.017
≤ 10 weeks before death (Off Tx)	0.60	NA	NA	NA	NA	Normal	0.030
> 10 & ≤ 30 weeks before death (Off Tx)	0.73	NA	NA	NA	NA	Normal	0.023
> 30 & ≤ 60 weeks before death (Off Tx)	0.79	NA	NA	NA	NA	Normal	0.025
> 60 weeks before death (Off Tx)	0.75	NA	NA	NA	NA	Normal	0.045

Abbreviations: CI, confidence interval; SE, standard error; OS, overall survival; HR, hazard ratio; PFS, progression-free survival; AE, adverse events; IV, intravenous; Tx, treatment; R-chemotherapy , rituximab + cyclophosphamide + doxorubicin hydrochloride (hydroxydaunorubicin) + vincristine sulfate (Oncovin) + prednisone; R-ICE, rituximab, ifosfamide, carboplatin, etoposide; R-DHAP, rituximab, dexamethasone, cytarabine, cisplatin; GDP - gemcitabine, dexamethasone, cisplatin; NA, not applicable

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Appendix K Dosing Scheme ICE, DHAP and GDP

Dosing scheme for ICE

HÆMATOLOGISK AFDELING X, OUH:

Label med adresse	**ICE** Malignt lymfom BWHA2 + BOHE20A Højde: Vægt: Overflade: GFR:

DOSIS **Dobbelt lumen CVK er obligatorisk**

Etoposid	100 mg/m^2 i.v. dag 1-3
Carboplatin	5 x (GFR + 25) mg i.v. dag 2 **- max 600 mg**
Ifosfamid	5000 mg/m^2 i.v. dag 2
Mesna	5000 mg/m^2 i.v. (dag 2 = 2/3 af samlet dosis, dag 3 = 1/3 af samlet dosis)

Gives hver 3 uge. OBS opmærksomhed på plan for stamcellemobilisering/høst

Kur nr.												
Dato + år												
Dag nr	1	2	3	4	5	6	1	2	3	4	5	6
Vægt												
Etoposid i.v. mg												
Carboplatin i.v. mg												
Ifosfamid i.v. mg												
Mesna i.v. (2/3) mg												
Mesna i.v. (1/3) mg												
	SUPPLERENDE BEHANDLING											
Inj. Pegfilgastrim 6 mg s.c.												
Tbl. Aprepitant 125 mg x1												
Tbl. Aprepitant 80 mg x 1												
Tbl. Ondansetron 8 mg x 2												
Tbl. Metoclopramid 10 mg p.n.max x 3												
Tbl. Allopurinol 300 mg x 1 i 5 dage												
Tbl. Furosemid 20 mg p.n												
Læge												
Sygeplejerske												

Ordinationer i lyseblå felter ordineres og administreres i FMK/EPJ
Ordinationer i hvide felter administreres via kurskema

Administration

- Etoposid gives dag 1-3 i NaCl over 1 time. På dag 2 gives Etoposid før Carboplatin.
- Carboplatin gives dag 2 i Glucose over 1 time.
- Ifosfamid gives dag 2 i NaCl over 22 timer. Blandes med 2/3 af samlet Mesnadosis i ét infusionssæt.
- Mesna 2/3 gives dag 2 sammen med Ifosfamid over 22 timer. 1/3 gives dag 3 over 12 timer.
- Cytostatikaproduktionen blander Mesna begge dage. Dag 2 leveres Ifosfamid tilsat Mesna i ét infusionssæt og Carboplatin og Etoposid i to infusionssæt. Dag 3 leveres Mesna i ét infusionssæt og Etoposid i ét infusionssæt.
- Selv om patienten har dobbeltløbet CVK, må kun gives et cytostatika ad gangen.

Forholdsregler

GFR: Beregnes ud fra Cockcroft-Gault formel, som tager hensyn til køn, alder, vægt og kreatinin

CVK: Der anlægges dobbeltløbet CVK. På førstedagen kan kur gives i venflon.

Hydrering: Ind- og udgift registreres og patienten vejes x 1 dagligt.

Dag 1: Totalindgift mindst 3 l indgift per os og i.v. (skift mellem NaCl og Glucose)

Dag 2: Kl. 08.00 Hydrering med isotonisk NaCl skiftevis Glucose cum KCl (obs diabes!) 167 ml/time. påbegyndes.

Dag 3: Kl. 08.00 Hydrering med isotonisk NaCl skiftevis Glucose cum KCl (obs diabetes!) 167 ml/time forsættes indtil 12 timers Mesna infusion er afsluttet.

Dosisjustering

Som hovedregel gives der fuld dosis. Er der behov for dosisjustering følges nedenstående skema.
På den planlagte behandlingsdag:

Neutrofiltal	og/eller	Trombocyttal	Behandling:
≥ 1,0 mia/l		≥ 80 mia/l	Fuld dosering (100% dosering)
< 1,0 mia/l		< 80 mia/l	Behandlingen udskydes 3-4 dage af gangen. Når leukocyttallet ≥ 1,0 mia/l og trombocyttal ≥ 80 mia/l gives behandlingen efter nedenstående skema

Dosisreduktion efter udsættelse af behandling:

Udsættelse i antal dage	Cytostatikadosis		
	Etoposid	Carboplatin	Ifosfamid
8-14 dage	75%	75%	75%
> 14 dage	50%	50%	50%

Dosing scheme for DHAP

HÆMATOLOGISK AFDELING X, OUH:

Label med adresse	**DHAP CADD pumpe** Malignt lymfom BWHA2 + BOHE20A Højde: | Vægt: | Overflade: | GFR:

DOSIS **Dobbelt lumen CVK obligatorisk**

Cisplatin	100 mg/m^2 i.v. dag 1 (24-timers kontinuerlig infusion på CADD)
Cytarabin	4000 mg/m^2 i.v. dag 2+3 (Én ordination svt. 2 doser; 3-timers infusion med 12 timers interval på CADD)
Dexametason	40 mg dgl p.o. dag 1-4

OBS: Der skal altid foreligge Tc-99m-DTPA-clearance inden ordination af Cisplatin
DHAP gives hver 3 uge .OBS opmærksomhed på plan for stamcellemobilisering/høst

Kur nr.					
År	Dato				
Vægt					
DTPA clearance					
Dag nr.		1	2	3	4
Cisplatin i.v. kl. 20	mg				
Cytarabin	mg				
Cytarabin i.v. kl. 20	mg		Pumpe 250 ml		
Cytarabin i.v. kl. 08	mg			Pumpe 250 ml	
Tbl. Dexametason	mg				
		SUPPLERENDE BEHANDLING			
Inj. Pegfilgastrim 6 mg					
Kaps. Aprepitant 125 mg x 1					
Kaps. Aprepitant 80 mg x 1					
Tbl. Ondansetron 8 mg x 2 i 5 dage					
Tbl. Metoclopramid 10 mg p.n. max x 3					
Tbl. Allopurinol 300 mg x 1 i 5 dage					
Tbl. Furosemid 20 mg p.n					
Læge					
Sygeplejerske dobbeltkontrol m. signatur					
Sygeplejerske dosiskontrol					

Ordinationer i lyseblå felter ordineres og administreres i FMK/EPJ
Ordinationer i hvide felter administreres via kurskema

Administration

- Hydrering med isoton NaCl tilsat magnesiumklorid (5 mmol magnesium/1000 ml NaCl) starter kl. 14, dvs. 6 timer før Cisplatininfusion og afsluttes efter 30 timer (CADD pumpe nr.1).
- Forceret diurese med Mannitol 150 mg/ml starter kl. 14, dvs. 6 timer før Cisplatininfusion og afsluttes efter 30 timer (CADD pumpe nr. 2). Hydrering og Mannitol må gives på samme "CVK ben" og om nødvendigt samtidigt med Rituximab på det andet "CVK ben".
- Cisplatin gives dag 1 kl. 20.00 som kontinuerlig infusion (CADD pumpe nr. 3) over 24 timer. forudgået af hydrering i 6 timer – se separat arbejdsskema. Cisplatin leveres i et samlet volumen svt. 600 ml uden tilsat volumenoverskud. Infusionsposen vil derfor være tom efter endt infusion. Sygeplejerske foretager dosiskontrol efter afsluttet infusion.
- Cytarabin indgives på CADD pumpe nr. 3 efter afsluttet Cisplatin. Posen indeholder 2 doser, og hver dosis gives over 3 timer med 12 timers interval. Blandecentralen leverer én kemopose indeholdende begge doser, med et volumenoverskud på 10% svt. i alt 550 ml. Der vil således være en rest i infusionsposen på ca. 50 ml efter endt infusion. Sygeplejerske foretager dosiskontrol efter hver afsluttet infusion.
- Tablet Dexametason 40 mg gives dagligt p.o. kl. 08.00 eller så tidligt som muligt.
- Tablet Furix 20-40 mg gives ved vægtøgning på $\geq$ 2 kg i forhold til udgangsvægt dag 1.

Forholdsregler

- Patienten skal have anlagt 2 lumen CVK
- Der skal altid foreligge DTPA-clearance inden ordination af Cisplatin. Cisplatin-dosis afhængig af DTPA-clearance – se nedenfor under dosisjustering.
- Væskebehandling og Mannitol startes 6 timer før Cisplatin indgift – se separat arbejdsskema.
- CAVE: Aminoglykosid pga. Cisplatinbehandling. Dette gælder fremover. Husk at anføre dette i CAVE feltet i EPJ.
- Blodprøver 2 gange ugentligt med "TLFÆ" mhp. transfusionsbehov.
- Forud for næste kur tages "Kemo start" blodprøver SAMT P-Magnesium.

Dosisjustering

Cisplatin dosisjusteres på basis af EDTA-clearance, således

DTPA-clearance	Cisplatin dosis %
> 75% af normal	100%
50-75 %	66%
< 50%	0

Cytarabin dosisjusteres på basis af bilirubin og kreatinin, således:

- Ved bilirubin > 34 mikromol/l, skal dosis reduceres med 50 %
- Ved S-kreatinin mellem 130-175 mikromol/l reduceres dosis til 1 g/m^2 i hver dosis
- Ved S-kreatinin > 175 mikromol/l reduceres dosis til 100 mg/m^2 pr. døgn og det gives som døgninfusion på pumpe.

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DHAP arbejdsskema

Label

DHAP (CADD) arbejdsskema

Dag nr.	Tid	Kl.		Vægt	Signatur
1	- 1 time	13.00	Patient modtages, informeres og vejes		
1	0 timer	14.00	Inf. Isotonisk NaCl tilsat magnesium (5 mmol/l) 200 ml/ time i alt 30 timer. Monitorering diurese påbegyndes. (CADD pumpe nr. 1, program: "R-DHAP hydrering")		
1	0 timer	14.00	Inf. Mannitol 150 g/l, 83 ml/time i alt 30 timer (CADD pumpe nr. 2, program: "R-DHAP Mannitol" Der påbegyndes diuresemåling.		
1	6 timer	20.00	Diurese på mindst 400 ml over de seneste 6 timer. Hvis ja, da fortsæt. Patient vejes.		
1	6 timer	20.00	Start inf. Cisplatin 100 mg/m^2 over 24 timer. (CADD pumpe nr. 3, program: "R-DHAP Cisplatin")		
2	18 timer	08.00	Patienten vejes		
2	30 timer	20.00	Afslut Cisplatin infusion, re-programmer CADD pumpe nr. 3 jf. nedenfor. Dosiskontrol og patient vejes.		
2	30 timer	20.00	Afslut infusion Mannitol og NaCl og afmonter CADD pumpe nr. 1 og 2.		
2	30 timer	20.00	Start inf. Cytarabin 4000 mg/m2, to doser over 3 timer med 12 timers interval. (CADD pumpe nr. 3, program: "R-DHAP Cytarabin")		
3	42 timer	08.00	Patient vejes.		
3	45 timer	11.00	Afslut Cytarabin infusion og afmonter CADD pumpe nr. 3. Udfør dosiskontrol		
3	48 timer	14.00	Patient vejes. Udskriv patient. Bestil blodprøver med "TLFÆ" x 2 ugentligt.		

Dosing scheme for GDP

HÆMATOLOGISK AFDELING X, OUH:

Label med adresse	**GDP** Malignt lymfom BWHA2+BOHE20 (dag 1) BWHA114 (dag 8)
	Højde: / Vægt: / Overflade: / GFR:

DOSIS **Dobbelt lumen CVK obligatorisk**

Gemcitabin	1000 mg/m^2 iv. dag 1 + 8 (dag 8 gives Gemcitabin ambulant)
Cisplatin	75 mg/m^2 iv. dag 1
Dexamethason	40 mg p.o. dag 1 – 4

Der skal altid foreligge Tc-99m-DTPA-clearance inden ordination af Cisplatin
Gives med 3 ugers interval.

Kur nr.								
Dato + år								
Dag nr.	1	2	3	4	5	6	7	8
Gemcitabin i.v. mg								
Cisplatin i.v. mg								
Tbl. Dexametason mg								
	SUPPLERENDE BEHANDLING							
Kaps. Aprepitant 125 mg								
Kaps. Aprepitant 80 mg								
Tbl. Ondansetron 8 mg x 2								
Tbl. Metoclopramid 10 mg p.n. max x 3								
Tbl. Pantoprazol 40 mg x 1								
Tbl. Furix 20 mg p.n.								
Tbl. Allopurinol 300 mg x 1								
Inj. Pegfilgastrim 6 mg								
Læge								
Sygeplejerske								

Ordinationer i lyseblå felter ordineres og administreres i FMK/EPJ
Ordinationer i hvide felter administreres via kurskema

Forholdsregler

- Patienten skal have anlagt dobbeltlumen CVK inden kuren.
- Der skal altid foreligge DTPA-clearance inden ordination af Cisplatin. Cisplatin-dosis afhængig af DTPA-clearance – se nedenfor under dosisjustering.
- Væskebehandling startes 6 timer før Cisplatin indgift – se separat arbejdsskema.
- CAVE: Aminoglykosid pga Cisplatinbehandling. Dette gælder fremover. Husk at anføre dette i CAVE feltet i EPJ
- Blodprøver 2 gange ugentligt med "TLFÆ" mhp. transfusionsbehov.
- Forud for næste kur tages "Kemo start" blodprøver SAMT P-Magnesium.

Dosisjustering

Cisplatin dosisjusteres på basis af DTPA-clearance, således

DTPA-clearance	Cisplatin dosis %
> 75% af normal	100%
50-75 %	66%
< 50%	0

Gemcitabin dosisjusteres efter nedenstående skema

Gemcitabin dosis			
Absolut granulocyttal (x 10^9/l)		**Trombocyttal (x 10^9/l)**	**Procent af normaldosis**
>1,5	og	≥ 100	100
1-1,5	eller	75-100	50
< 1	eller	<75	Seponering *

Gemcitabindosis bør reduceres til 75 % af den oprindelige startdosis i efterfølgende cyklus i tilfælde af følgende hæmatologiske toksiciteter:

- Absolut granulocyttal < 0,5 x 10^9/l i mere end 5 dage
- Absolut granulocyttal < 0,1 x 10^9/l i mere end 3 dage
- Febril neutropeni
- Trombocytter < 25 x 10^9/l
- Udsættelse af en cyklus i mere end 1 uge på grund af toksicitet

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Administration

- Gemcitabin gives over 30 min (se arbejdsskema nedenfor)
- Cisplatin gives over 2 timer (se arbejdsskema nedenfor). Cisplatin er meget nefrotoxisk og det er derfor væsentligt at overholde nedenstående hydreringsregime. Tidspunktet for de enkelte handlinger noteres indledningsvist i "Klokken"-kolonnen. Ligeledes føres vægt- og diureseresultater ind i skemaet såvel som der signeres, når de nævnte væsker er givet. Ved vægtøgning gives Furix pn.
- Dexametason gives ½ time før kurstart på dag 1.

GDP arbejdsskema

Dag nr.	Tid	Kl.		Vægt	Diurese	Signatur
1	Time 0	09.00	Patient modtages, informeres og vejes.			
1	Time 0	09.00	Tbl. Dexametaon udl. Der ophænges 1 l isotonisk NaCl, hvoraf de første 100 ml gives med hurtigt indløb.			
1	Time 0	09.00	Inf. Gemcitabin 1000 mg/m^2 gives over 30 min, når de 100 ml NaCl er løbet ind.			
1	Time 0,5	09.30	De resterende 900 ml isotonisk NaCl gives over 60 min			
1	Time 1,5	10.30	Inf. Isotonisk NaCl m. magnesium 200 ml/ time i alt 4,5 timer (1 l NaCl tilsættes 10 mmol magnesiumklorid)			
1	Time 1,5	10.30	Inf. Mannitol 150 g/l, 83 ml/time i alt 4,5 timer Der påbegyndes diuresemåling.			
1	Time 6	15.00	Diurese på mindst 450 ml over de seneste 4,5 timer inden inf. Cisplatin opstartes. Hvis ja, da fortsæt. Patient vejes.			
1	Time 6	15.00	Inf. Cisplatin 75 mg/m^2 gives over 2 timer			
1	Time 8	17.00	Inf. Isotonisk NaCl 1000 ml tilsat 5 mmol magnesiumklorid. Gives over 2 timer			
1	Time 10	19.00	Inf. Isotonisk NaCl 1000 ml tilsat 5 mmol magnesiumklorid. Gives over 2 timer			
1	Time 12	21.00	Patient vejes og der måles diurese. Der skal være diurese på over 600 ml siden seneste diuresemåling. Giv furix ved vægtøgning			

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