Bilag til Medicinrådets vurdering af blinatumomab som monoterapi som en del af konsolideringsbehandlingen af voksne patienter med akut lymfoblastisk leukæmi (ALL)

Voksne patienter med nydiagnosticeret Philadelphia-kromosom-negativ CD19-positiv B-celle-prækursor ALL

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. blinatumomab
2. Amgros' forhandlingsnotat vedr. blinatumomab
3. Ansøgning vedr. blinatumomab

18-Dec-2025
Mikkel Rasmussen
Associate Director, Value, Access &
DocuSigned by:
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Date 18. december 2025

Vedr. Medicinrådets udkast til vurdering af blinatumomab som monoterapi som en del af konsolideringsbehandling af patienter med akut lymfoblastisk leukæmi (ALL)

Tak for udkastet til vurderingsrapporten og for muligheden for at kommentere på den. Vi ønsker at anerkende det grundige arbejde, der tydeligt er afspejlet i udkastet til vurderingsrapporten samt den konstruktive dialog vi har haft med sekretariatet igennem forløbet.

Vurdering af relapsfri overlevelse (RFS) i E1910-studiet

I udkastet til vurderingsrapporten skriver Medicinrådet, at antallet af relaps i E1910-studiet muligvis er underestimeret som følge af lang tid imellem de systematiske undersøgelser efter de to første år. Det er dog Amgens vurdering, at patientpopulationen med akut lymfoblastisk leukæmi (ALL) generelt ikke vil kunne gå med uopdaget relaps i flere måneder. Sygdomsforløbet medfører, at tid fra symptomdebut til diagnose er meget kort. Det er vores opfattelse pba. Inputs fra det kliniske fagmiljø, at hvis en patient har relaps, vil det oftest blive opdaget hurtigt på baggrund af patientens symptomer og ikke ved de rutinemæssige blodprøver. På baggrund heraf virker det usandsynligt, at patienterne i E1910-studiet har gået i flere måneder med uopdaget relaps, og dermed usandsynligt, at det har medført, at den relapsfri overlevelse (RFS) er betydeligt overestimeret.

Helbredsrelateret livskvalitet

Vi anerkender Medicinrådets forbehold i forhold til det anvendte data for helbredsrelateret livskvalitet samt for de udledte nytteværdier. Samtidig ønsker vi at henlede opmærksomheden på, at Medicinrådet selv bemærker, at det ikke er muligt at identificere andet brugbart data for helbredsrelateret livskvalitet samt at understrege, at resultatet af den sundhedsøkonomiske analyse er robust overfor ændringer i nytteværdierne.

Vi ser frem til, at Rådet skal vurdere blinatumomab til behandling af patienter med ALL den 21. januar 2026, og vi står naturligvis til rådighed for eventuelt yderligere spørgsmål.

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17.12.2025

LSC/KLE

Forhandlingsnotat

Dato for behandling i Medicinrådet	21.01.2026
Leverandør	Amgen
Lægemiddel	Blincyto (blinatumomab)
Ansøgt indikation	Monoterapi i konsolideringsfasen til behandling af voksne patienter med nydiagnosticeret Philadelphia-kromosom-negativ CD19-positiv B-cellepræcursor ALL
Nyt lægemiddel / indikationsudvidelse	Ny indikation.

Prisinformation

Amgros har følgende pris på Blincyto (blinatumomab):

Tabel 1: Aftalepris

Lægemiddel	Styrke (Pakningsstørrelse)	AIP (DKK)	SAIP, (DKK)	Rabat ift. AIP
Periode: Indtil 31.01.2026				
Blincyto	38,5 µg (1 sæt pul.t.kon+op.t.inf.)	15.833,31	[redacted]	[redacted]
Periode: Fra 01.02.2026				
Blincyto	38,5 µg (1 sæt pul.t.kon+op.t.inf.)	15.500,81	[redacted]	[redacted]

Aftaleforhold

[redacted]

[redacted]

Information fra forhandlingen

[redacted]

Konkurrencesituationen

Blincyto gives i tillæg til den eksisterende behandling i konsolideringsfasen, der består af behandling med flere typer af kemoterapi.

Tabel 2 viser lægemiddeludgifter for Blincyto. Lægemiddeludgifterne til kemoterapi er ikke inkluderet i udregningen, da Blincyto gives i tillæg til nuværende behandling.

Tabel 1: Lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)*	Lægemiddeludgift pr. behandling (SAIP, DKK)
Blincyto	38,5 µg (1 sæt pul.t.kon+op.t.inf.)	28 µg i.v. infusion dagligt i 4 cyklusser**	[redacted]	[redacted]

[redacted]

**Der antages en patient som vejer 45 kg eller mere. En cyklus er 28 dages infusion efterfulgt af 14 dages pause og konsolideringsbehandlingen består af op til 4 cyklusser jævnfør Medicinrådets vurderingsrapport.

Status fra andre lande

Tabel 2: Status fra andre lande

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

Opsummering

[redacted]

Medicinrådet

Instructions for companies

This is the template for submitting evidence to the Danish Medicines Council (DMC) as part of the appraisal process for a new medicinal product or a new indication for an existing medicine. The template is not exhaustive.

Please note the following requirements:

- When preparing their application, companies must adhere to the current version of the DMC's methods guide.
- Always use the current (latest updated) version of this template downloadet from the DMC's website.
- Headings, subheadings and appendices must not be removed. Tables must not be deleted or edited, unless it is explicitly stated in the text.
- Text in grey and [in brackets] is only for example purposes and must be deleted.
- All sections in the template must be filled in. If a section or an appendix is not applicable, state "not applicable" (N/A) and explain why.
- The main body of the application must not be longer than 100 pages (including the title page, contact information and references – excluding appendices).
- The formatting is not to be altered and all cross-references must work.
- All applications must comply with the general data protection regulations, find more information on DMC's data policy here.
- Submissions in either Danish or English are accepted.

The assessment process cannot be initiated before all the requirements are met.

Documentation to be submitted

The following documentation must be sent to the DMC's email ansogning@medicinraadet.dk:

- Application in word format*
- Application in PDF format*
- Health economic model including budget impact model in one Excel file, with full access to the programming code. The model must include relevant sheets from the DMC Excel template 'Key figures including general mortality' available on the DMC's website.
- The European Public Assessment Report (EPAR) should be submitted. Send a draft version if the final one is not published at the time of submission, and send the final version as soon as possible.

Confidential information and blinding

The Danish Medicine Council publishes the application (including attachments) on the website together with the recommendation.

The applicant has the option to blind any confidential information in the application incl. appendices.

Medicinrådet

The application and paper/appendices

If there is confidential information in the application or note/appendices, the company must submit two versions of both the application and note/appendices:

- a version for the DMC's case processing, where the confidential information is marked with yellow marking.
- a version for publication on the DMC's website, where the confidential information is blinded with black marking. The DMC publishes this version.

It is the pharmaceutical companies that must ensure that the blinding is sufficient, so that the confidential information cannot be read when the document is edited.

Therefore, the applicant must ensure that the confidential information is sufficiently redacted blinded for publication on the DMC's website. This can be done, for example, by covering the text/information to be redacted with a black marker simultaneously replacing the underlying text with crosses ("XXX"), so that the text/information cannot be read when editing the document.

Read about redaction of confidential information on the DMC's website.

About macros in Excel

Due to IT security requirements, Excel files containing macros must be authorized and signed by the applicant before being submitted to the DMC. Find more information here.

Version log

Version log		
Version	**Date**	**Change**
2.6	1 April 2025	New e-mail address ansogning@medicinraadet.dk is added.
2.5	10 September 2024	Section 3.4 and 3.4.1: new information regarding ATMP (Advanced Therapy Medicinal Products). Section 6.1.1 and 8.1: Updated text regarding data-cut. Section 4, 8, 10 and 12: Clarification regarding cost-minimization analysis.
2.4	5 July 2024	Section 11: Clarification in the text regarding costs and changes in the tables 26 and 30.
2.3	1 June 2024	Clarification regarding redaction of confidential information, clarification regarding EPAR, clarification regarding literature search and changes in the text regarding costs. New information about Joint Nordic assessments has been added.
2.2	3 November 2023	'Pharmaceutical' is exchanged with 'medicine'. Tabel 26 is new.
2.1	1 September 2023	Section 4.2: Updated information about discount rate (The DMC applies a discount rate of 3.5 % for all years) Section 10.1.3: Clarification regarding EQ-5D-5L and Danish preference weights Section 11.1: Updated information about Excel sheet 'Key Figures'
2.0	15 June 2023	New application template
1.3	6 December 2022	Clarification regarding new IT security requirements concerning macros in Excel files has been added, see page 1.
1.2	20 June 2022	Clarification of the introduction, including instructions on how to complete the form.
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: Specific requirements for literature search Section 7: Stated it explicitly that statistical methods used need to be described

Version log		
		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
1.0	27 November 2020	Application form for assessment made available on the website of the Danish Medicines Council.

Application for the assessment of BLINCYTO® as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukemia

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

Contact information

Contact information	
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Title	
Phone number	
E-mail	

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Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
µg	Micrograms
AE	Adverse event
AIC	Akaike information criterion
ALD	Acute Leukemia Database
ALL	Acute lymphoblastic leukemia
Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
AMCP	Academy of Managed Care Pharmacy

ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATC	Anatomical Therapeutic Classification
ATE	Average Treatment Effect
ATMP	Advanced therapy medicinal products
ATT	Average Treatment Effect on the Treated
B-ALL	B-cell acute lymphoblastic leukemia
B-cell	B-lymphocytes
BCP	B-cell precursor
BCR::ABL1	Breakpoint cluster region-Abelson fusion gene
BIC	Bayesian information criterion
BSA	Body surface area
CAR-T	Chimeric antigen receptor cell therapy
CCA	Cost consequence analysis
CD	Cluster of differentiation
CDC	Center for Disease Control and Prevention
CEAC	Cost-effectiveness acceptability curves
CEAs	Cost-effectiveness analyses
CEM	Cost-effectiveness model
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisolone
CI	Confidence interval
CMA	Cost minimization analysis
CNS	Central nervous system
CR	Complete remission
CRi	Complete remission with incomplete blood count recovery
CRD	University of York Centre for Reviews and Dissemination
CRi	Complete remission with incomplete hematologic recovery
CRS	Cytokine release syndrome
CTCAE	Common Terminology Criteria for Adverse Events
CTEP AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
CUA	Cost-utility analysis
CVP	Cyclophosphamide, vincristine and prednisolone
D	Day
DCO	Data cut-off
Dl	Deciliter
DLBCL	Diffuse large b-cell lymphoma
DMC	Danish Medicines Council

DMCG	Danish Multidisciplinary Cancer Groups
DNA	Deoxyribonucleic acid
DK	Denmark
DKK	Danish krone
DRG	Diagnosis-related group
EBMT	European Society for Blood and Marrow Transplantation
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
ECOG-ACRIN	Eastern Cooperative Oncology Group-American College of Radiology Imaging Network
EHA	European Hematology Association
EMA	European Medicines Agency
eMIT	electronic Market Information Tool
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EPAR	European Public Assessment Report
EQ-5D-3L	EuroQol 5-Dimension 3-Level
ESMO	European Society for Medical Oncology
EU	European Union
EU CTR	European Clinical Trials Register
FAS	Full analysis set
FDA	US Food and Drug Administration
Fl	Follicular lymphoma
FLAG-IDA	Fludarabine, cytarabine, idarubicin, and filgrastim
G	Gram
GHS/QoL	Global Health Status/Quality of Life
HCC	Half Cycle Correction
HD	High dose
HR	Hazard ratio
HRQoL	Health-related quality of life
HRU	Healthcare resource utilization
HSCT	Hematopoietic stem cell transplantation
HSUV	Health-state utility value
hyper-CVAD	Alternating cycles of high-dose chemotherapy drugs, including cyclophosphamide, vincristine, doxorubicin, and dexamethasone (part a), and high-dose methotrexate and cytarabine (part b)
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICER	Incremental cost-effectiveness ratio

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive care unit
ID	Identification number
IHME	Institute for Health Metrics and Evaluation
IM	Intramuscular
IPTW	Inverse Probability of Treatment Weighting
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
IT	Intrathecal
ITC	Indirect treatment comparison
IU	International unit
IV	Intravenous
kg	Kilogram
KM	Kaplan-Meier
km	Kilometer
LoT	Lines of therapy
LY	Life year
m	Meter
MCM	Mixture Cure Model
MeSH	Medical Subject Headings
MFC	Multiparameter Flow Cytometry
Mg	Milligram
µg	Microgram
ml	Milliliter
MMRM	Mixed model for repeated measures
mOS	Median overall survival
MRD (+/-)	Minimal residual disease (positive/negative)
mRFS	Median relapse-free survival
MUGA	Multigated acquisition scan
N	Number
N/A	Not applicable/available
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCT	National Clinical Trial
NCTN	National Clinical Trials Network
NE	Not estimable
NICE	National Institute for Health and Care Excellence

NICE DSU	National Institute for Health and Care Excellence Decision Support Unit
NIH	National Institutes of Health
NOPHO	Nordic Society of Paediatric Haematology and Oncology
NR	Not registered
OS	Overall survival
OWSA	One-way sensitivity analysis
PDF	Portable document format
PEG-asparaginase	Polyethylene glycol-conjugated asparaginase
Ph (+/-)	Philadelphia chromosome (positive/negative)
PH	Proportional hazard
PICOS	Population, intervention, comparators, outcomes, and study design
PO	Per oral
POMP	Prednisone, oncovin (vincristine), methotrexate, and purinethol (mercaptopurine)
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PRO	Patient-reported outcome
PR	Post relapse
PRS	Post-relapse survival
PSA	Probabilistic sensitivity analysis
PSM	Partitioned Survival Model
PSMs	Parametric survival models
p-value	Probability value
QALY	Quality-adjusted life year
QoL	Quality of life
R&D	Research and development
RCT	Randomized controlled trial
RDI	Relative Dose Intensity
RF	Relapse-free
RFS	Relapse-free survival
RE-AIM	Reach, effectiveness, adoption, implementation, and maintenance
RKKP	Regional Clinical Quality Development Program
RoB	Cochrane Risk of Bias tool
ROBINS-I	Risk of bias in non-randomized studies of interventions
R/R	Relapsed/refractory
RWE	Real-world evidence
SAE	Serious adverse event
SATs	Single-arm trials

SC	Subcutaneous
SCT	Stem cell transplantation
SE	Standard error
SEER	Surveillance, epidemiology, and end results
SIOP Asia	Asian Society for Pediatric Oncology
SITC	Society for Immunotherapy of Cancer
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SMR	Standardized mortality ratio
SoC	Standard of care
SPSM	Standard parametric survival model
TA554	Technology Appraisal 554
TA893	Technology Appraisal 893
T-ALL	T-cell acute lymphoblastic leukemia
TAs	Technology assessments
T-cell	T-lymphocytes
TdT	Terminal deoxynucleotidyl transferase
TEAE	Treatment-emergent adverse event
TIT	Triple intrathecal therapy
TKIs	Tyrosine kinase inhibitors
TRAE	Treatment-related adverse event
TTD	Time to deterioration
UK	United Kingdom
US	United States
VP	Vincristine and prednisolone
WHO	World Health Organization
WHO ICTRP	World Health Organization International Clinical Trials Registry Platform
Yr	Year

1. Regulatory information on the medicine

Overview of the medicine	
Proprietary name	BLINCYTO®
Generic name	Blinatumomab
Therapeutic indication as defined by EMA	BLINCYTO® is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukemia (ALL) [1].
Marketing authorization holder in Denmark	Amgen
ATC code	L01FX07
Combination therapy and/or co-medication	Co-medication. BLINCYTO® is proposed to be used as monotherapy alongside the existing consolidation chemotherapy regimen.
(Expected) Date of EC approval	23 January 2025
Has the medicine received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Yes, 24 July 2009 [2].
Other therapeutic indications approved by EMA	BLINCYTO® is indicated as monotherapy for the treatment of adults with CD19 positive relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Patients with Philadelphia chromosome-positive B-cell precursor ALL should have failed treatment with at least 2 tyrosine kinase inhibitors (TKIs) and have no alternative treatment options [1]. BLINCYTO® is indicated as monotherapy for the treatment of adults with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL in first or second complete remission with minimal residual disease (MRD) greater than or equal to 0.1% [1]. BLINCYTO® is indicated as monotherapy for the treatment of pediatric patients aged 1 month or older with Philadelphia chromosome-negative CD19 positive B-cell precursor ALL which is refractory or in relapse after receiving at least two prior therapies or in relapse after receiving prior allogeneic hematopoietic stem cell transplantation [1]. BLINCYTO® is indicated as monotherapy for the treatment of pediatric patients aged 1 month or older with high-risk first relapsed Philadelphia chromosome-negative CD19 positive B-cell precursor ALL as part of the consolidation therapy [1].

Overview of the medicine	
Other indications that have been evaluated by the DMC (yes/no)	No
Joint Nordic assessment (JNHB)	No. BLINCYTO® is currently used differently between the Nordic countries.
Dispensing group	BEGR [3].
Packaging – types, sizes/number of units and concentrations	BLINCYTO® 38.5 micrograms powder for concentrate and solution for solution for infusion [1].

2. Summary table

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

Summary	
Indication relevant for the assessment	BLINCYTO® is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Philadelphia chromosome negative (Ph-) cluster of differentiation 19 positive (CD19+) B-cell precursor (BCP) acute lymphoblastic leukemia (ALL) [1]. Note: the indication has slightly changed compared to the indication provided in the request for assessment document, which was submitted on 4th of November 2024, thus before the final EC approval.
Dosage regiment and administration	As described per the SmPC, a single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-week) treatment-free interval. Patients may receive up to 4 cycles of BLINCYTO consolidation treatment [1]. Patients ≥ 45 kg should receive a fixed daily dose of 28 µg. For patients < 45 kg the daily dose is calculated using the patient's body surface area (BSA) to receive 15 µg per m^2 per day (not exceeding 28 µg/day). BLINCYTO® is administered as a continuous intravenous infusion using an infusion pump [1]. The dosing in the E1910 trial consists of two cycles of blinatumomab with a two-week interval between the two cycles, followed by three cycles of chemotherapy, one additional cycle of blinatumomab, one cycle chemotherapy and finally one cycle of blinatumomab [4].
Choice of comparator	The current frontline standard of care (SoC) in Denmark is other multiagent chemotherapy regimens. Several different regimens are available based on age, risk-stratification and biomarkers, however as there is no evidence of superiority of one regimen over another the comparator chosen is the chemotherapy regimen based on the head-to-head data available from the E1910 trial [4,5].
Prognosis with current treatment (comparator)	Even though the treatment of adults with Ph- BCP-ALL has improved significantly over the past decades, overall survival (OS) and health-related quality of life (HRQoL) for these patients remains low [6–11]. In Denmark with currently

Summary	
	available treatment, the chance of long-term survival for younger adults with acute leukemia is, on average, about 45% [12]. The poor outcomes of adults with Ph- BCP-ALL are mainly due to the limited durability of remission after receiving frontline treatment with multiagent chemotherapy [6–9]. While a high proportion of patients (79% to 95%) can achieve a complete remission (CR) after induction chemotherapy, about 40% eventually have a relapse within five years [13–21]. The risk of relapse of acute leukemia is greatest within the first two years after completing treatment [12].
Type of evidence for the clinical evaluation	ECOG-ACRIN E1910 trial (NCT02003222): an ongoing phase 3, randomized, controlled, open-label, investigator-sponsored study investigating efficacy and safety of blinatumomab in conjunction with chemotherapy vs chemotherapy alone as a consolidation regimen in Ph- BCP-ALL patients who had previously achieved CR or complete remission with incomplete hematologic recovery (CRi) with induction chemotherapy [4,22].
Most important efficacy endpoints (Difference/gain compared to comparator)	**Step 3 analysis (consolidation phase):** Median overall survival (mOS) of MRD- patients (primary endpoint): 82.4% in the blinatumomab + chemotherapy and 62.5% in the chemotherapy arm (HR: 0.44 [95% CI: 0.25–0.76]) [1]. mOS of MRD-agnostic randomized patients only (post hoc analysis): 81.4% in the blinatumomab + chemotherapy and 58.3% in the chemotherapy arm (HR: 0.42 [95% CI: 0.26–0.68]) [90]. Median relapse-free survival (mRFS) of MRD- patients (secondary endpoint): 77.0% in the blinatumomab + chemotherapy and 60.5% in the chemotherapy arm (HR: 0.53 [95% CI: 0.32–0.88]) [1]. mRFS of MRD-agnostic randomized patients only (post hoc analysis): 76.9% in the blinatumomab + chemotherapy and 57.2% in the chemotherapy arm (HR: 0.49 [95% CI: 0.31–0.76]) [90].
Most important serious adverse events for the intervention and comparator	**Step 3 analysis (consolidation phase):** In the MRD-agnostic patients: blinatumomab + chemotherapy arm, 55.8% of patients experienced expedited adverse events (AEs) (defined as serious AEs (SAEs) requiring expedited reporting via the Cancer Therapy Evaluation Program Adverse Event Reporting System), with the most frequently reported being febrile neutropenia (12.2%), pyrexia (9.5%), sepsis (8.8%), device-related infection and neutrophil count decreased (8.2% each), alanine aminotransferase increased (6.1%), and aphasia (5.4%) [22]. In the chemotherapy arm, 28.1% of patients experienced expedited AEs, with the most frequently reported being febrile neutropenia (11.7%) and sepsis (7.0%) [22].

Summary	
Impact on health-related quality of life	**Clinical documentation: EQ-5D-3L** Utility in relapse-free state (1-5 years): 0.865 for blinatumomab + chemotherapy (off-treatment), 0.836 for blinatumomab + chemotherapy (on-treatment), and 0.865 for chemotherapy. Utility in relapse-free state (year 5+): DK age-matched general population utility. Utility in post-relapse state: 0.692 Utility for death within ≤ 6 months: - 0.075
Type of economic analysis that is submitted	CUA based on a PSM with a MCM approach including efficacy and safety data from the E1910 trial.
Data sources used to model the clinical effects	The E1910 trial [4].
Data sources used to model the health-related quality of life	The BLAST and TOWER trials [23,24].
Life years gained	5.30 years
QALYs gained	4.26 QALY
Incremental costs	DKK 1,255,838
ICER (DKK/QALY)	DKK 294,820
Uncertainty associated with the ICER estimate	Proportion of patients receiving HSCT. The scenario analysis of the BLINCYTO® dose by the observed dose per treatment cycle from E1910 trial impacted the base case ICER the most.
Number of eligible patients in Denmark	15 newly diagnosed patients yearly
Budget impact (in year 5)	DKK 15,343,490

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

3.1 The medical condition

3.1.1 Disease description and classification

Acute lymphoblastic leukemia (ALL) is a malignancy of the B- or T-lymphoblasts characterized by uncontrolled proliferation of abnormal, immature lymphoid cells (blasts). This ultimately leads to the replacement of normal hematopoietic cells by abnormal white cells in the bone marrow and circulation, resulting in hematological deficiency (specifically anemia), immune system impairment, and platelet count deficiency [25,26].

ALL is broadly classified according to the lymphocytic lineage (i.e., B-lymphocyte (B-cell) or T-lymphocyte (T-cell) ALL) and the maturity of cancer cells (i.e., precursor vs mature ALL). Approximately 78% of adult ALL cases are of B-cell lineage, and approximately 93% of adult B-cell ALL cases are classified as immature or “B-cell precursor” (BCP) ALL [27–33]. BCP-ALL is further classified by cytogenetic subtype and the presence of the most common genetic abnormality in ALL, the Philadelphia chromosome (Ph) translocation between chromosomes 9 and 22, which results in a breakpoint cluster region-Abelson fusion gene (BCR::ABL1). Approximately 23% of adults with BCP-ALL have this abnormality, termed as Ph-positive (Ph+) BCP-ALL, the remaining 77% have Ph-negative (Ph-) disease [34–37]. The terminology for this genetic abnormality has been refined in recent years, leading to the term “Ph+ B-ALL” being used less frequently and increasingly replaced by "B-ALL with BCR::ABL1 fusion" which is more precise as it directly refers to the genetic fusion responsible for the disease. This definition is also specified in the latest Danish treatment guidelines. However, the change in terminology does not affect the clinical approach to patient classification and treatment [5,33]. Throughout the remainder of this application, the term Ph+/- will be applied to minimize confusion. The ALL-subtype classification is illustrated in Figure 1. Acute Lymphoblastic Leukemia (ALL) Subtypes

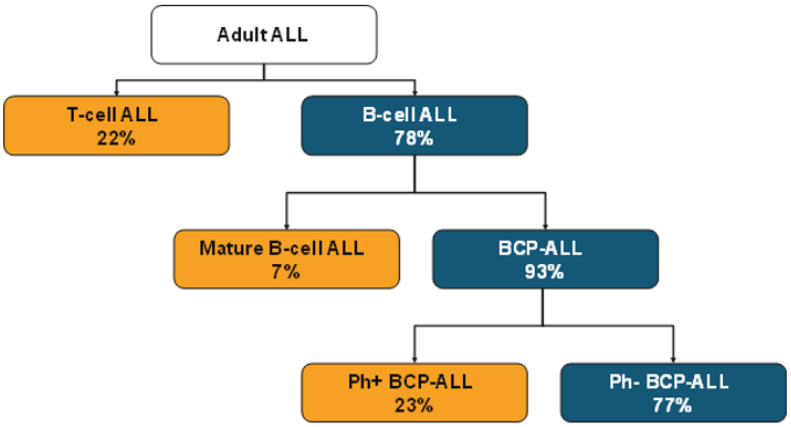

Figure 1. Acute Lymphoblastic Leukemia (ALL) Subtypes

Abbreviations: ALL, acute lymphoblastic leukemia; B-cell, B-lymphocyte; BCP, B-cell precursor; T-cell, T-lymphocyte; Ph(-/+), Philadelphia chromosome negative/positive.
Source: [27–37].

3.1.2 Clinical presentation and diagnosis

Common symptoms of ALL include fatigue, bruising, bleeding, enlarged lymph nodes, fever, and infections. Patients with ALL may also experience symptoms associated with central nervous system (CNS) involvement, including headache, weakness, seizures, and vomiting [35,38]. The severity of the symptoms causes most patients with ALL to seek urgent medical attention, and the disease is subsequently diagnosed within a few weeks of symptom onset. Diagnosis invariably leads to immediate hospital admission [39].

ALL is usually suspected when patients have an abnormal complete blood count and leukemic cells (blasts) appear in the blood. Confirmation of diagnosis generally requires demonstration of ≥ 25% bone marrow lymphoblasts on hematopathology review of bone marrow aspirate and biopsy materials [40,41]. All patients with suspected ALL should undergo a bone marrow examination supplemented with immunohistochemical and flow cytometric analyses for diagnosis and further classification of lymphatic phenotype, i.e. B-cell acute lymphoblastic (B-ALL) (terminal deoxynucleotidyl transferase (TdT), cluster of differentiation (CD)34+/-, cytoplasmic CD22, CD10, CD19+, CD79a) and T-cell acute lymphoblastic leukemia (T-ALL) (cytoplasmic CD3, CD7, TdT). Additionally, the presence of the Ph and/or BCR/ABL1 fusion protein should be investigated by cytogenetic examination and molecular biological examination, respectively [5,40,42].

Initial characterization of the disease (by type of cell involved, cell maturity, and presence/absence of Ph) must be done expeditiously and before any treatment is administered [40,42]. The confirmation of the type of ALL guides treatment decisions. Cytogenetic tests to determine further risk-group classification (including new genetics tests, if performed) are conducted after diagnosis and should not be awaited to initiate treatment [40].

3.1.3 Prognosis and HRQoL

Overall survival (OS) for ALL patients in Denmark is described within the 2021 yearly report by the Danish Acute Leukemia Database (ALD), indicating a five-year OS of 59% for

patients aged > 45 years and 92% for patients aged ≤ 45 years [43]. For the subgroup of newly diagnosed Ph- BCP-ALL patients, a three-year OS with currently available chemotherapy treatment regimens ranges between 49% and 65%, [19,21,44], while five-year OS has been reported as 47% [14], based on patient populations aged 18 to 65 and derived from studies conducted in Spain, the United Kingdom and Italy [14,19,21,44].

These low OS rates in clinical trials are confirmed by real-world studies. A Swedish registry reported a five-year OS of 46.6% in 202 adult patients diagnosed with Ph- B-ALL between 2007 and 2015 [45]. Another study that included 2,864 adult patients with Ph-B-ALL registered in the Surveillance, Epidemiology, and End Results (SEER) database in the United States (US) between 2010 and 2017 reported a five-year OS of 40% [6].

The poor outcomes of adults with Ph- BCP-ALL are mainly due to the limited durability of remission after receiving frontline treatment with multiagent chemotherapy [6,9,46,47]. While a high proportion of patients (79% to 95%) can achieve a complete remission (CR) after induction chemotherapy [13–21], about 40% eventually have a relapse within five years [14,21].

Heavy symptom burden, poor prognosis, treatment toxicity, and prolonged hospitalization for disease or adverse reaction management collectively have a profound impact on patients' physical, social, and emotional health-related quality of life (HRQL) and severely curtail their activities of daily living [10,11].

3.2 Patient population

In Denmark, 28 adults were diagnosed with ALL in 2022, and from 2018 to 2021 the median age of newly diagnosed ALL patients was 56 years with a variation of 38 to 72 years [43,48]. At the end of 2022, the Danish prevalence of adult ALL patients was 1.230 with a gender distribution of 58% men and 42% women, respectively [49].

The Global Burden of Disease Study estimated 64,190 new cases of ALL in 2017 across the globe (including adult and pediatric cases), with an estimated global age standardized incidence ratio of 0.85 per 100,000 individuals. This incidence rate has remained stable since 1990 [50]. In Europe, ALL is estimated to affect 1.8 in 10,000 people meeting the European orphan disease designation (a prevalence of ≤ 5 in 10,000 people in the EU) [2].

Due to the absence of published Danish incidence or prevalence rates for the subgroup of Ph- BCP-ALL, these specific numbers were estimated using percentages obtained through calculating weighted averages of the proportion of adult ALL cases who are of B-cell lineage (78%). Additionally, weighted averages were used to determine the proportion of adult B-lineage ALL patients who are classified as BCP-ALL (93%), together with using the midpoint from studies reporting the proportions of adult BCP-ALL patients who are Ph- (77%) [27–32,34–37]. See Figure 1 in section 3.1 for an overview of the percentage distribution for the different ALL subtypes used to estimate the expected incidence of Ph− BCP ALL.

Stated and estimated incidence and prevalence rates are presented in Table 1 below.

Table 1 Incidence and prevalence in the past 5 years in adults

Year	2019	2020	2021	2022	2023
Incidence of ALL in Denmark* [43,48]	36	33	40	28	N/A
Estimated incidence of Ph- BCP-ALL in Denmark**	20	18	22	16	N/A
Prevalence of ALL in Denmark [49]	1,099	1,137	1,188	1,230	N/A
Estimated prevalence of Ph- BCP-ALL in Denmark**	614	635	664	687	N/A

*Incidence of 2019-2021 are retrieved from the 2021 yearly report by the Danish Acute Leukemia Database, whereas the incidence of 2022 is retrieved from NORDCAN.
** Estimated based on percentages derived by calculating weighted averages of the proportion of adult ALL that is of B-cell lineage (78%), percentages derived by calculating weighted averages of the proportion of adult B-lineage ALL that is BCP-ALL (93%), and percentages derived using the midpoint from studies reporting the proportions of adult BCP-ALL that is Ph- (77%) [27–32,34–37].
Abbreviations: ALL, acute lymphoblastic leukemia; BCP-ALL, B-cell precursor ALL; N/A, not available; Ph-, Philadelphia chromosome-negative.

It is expected that all adult patients newly diagnosed with Ph- CD19+ BCP-ALL currently treated with the multiagent chemotherapy backbone as consolidation therapy will be eligible candidates for treatment with blinatumomab as monotherapy as part of multiagent chemotherapy in the consolidation setting, if recommended by the Danish Medicines Council (DMC). The Danish clinical expert projects that there are 15 eligible patients for treatment in Denmark annually, aligning closely with the estimated incidence rates for Ph- BCP-ALL in Denmark presented in Table 1. Therefore, it is assumed that approximately 15 patients annually will be eligible for treatment in Denmark.

Table 2 Estimated number of patients eligible for treatment

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of patients in Denmark eligible for treatment in the coming years*	~15	~15	~15	~15	~15

*Projected from Danish clinical expert.

3.3 Current treatment options

In accordance with the version 3.0 Danish clinical guidelines for ALL by the Danish Multidisciplinary Cancer Groups (DMCG) and the Regional Clinical Quality Development Program (RKKP), published in January 2025, the current frontline standard of care (SoC) in Denmark is multiagent chemotherapy regimens. Several different regimens are available based on age, risk-stratification and biomarkers confirmed at diagnosis before treatment initiation [5].

For the subgroup of newly diagnosed Ph- ALL in younger adults aged 18-45 years, the recommended treatment in Denmark is the treatment regimens of the ALLTogether protocol (participation in the ALLTogether Study), designated for children and young adults with ALL. The protocol was developed by ALL experts in 14 EU countries, including Denmark, and approved by the Scientific Ethics Committee in November 2018 [5,51].

The ALLTogether protocol has replaced the Nordic Society of Paediatric Haematology and Oncology (NOPHO) 2008 protocol, which was previously used as the standard treatment program for adult ALL patients <46 years. Modified versions of the NOPHO 2008 protocol are still used in Denmark as standard treatment for the subgroup of Ph- ALL in adults aged 46-65 years with adaptions depending on age and comorbidities [5,51,52]. Specifically, an approximately full or reduced NOPHO 2008 dose is offered to patients without significant comorbidities at the age 46-55 years and 56-65 years, respectively. Additionally, patients aged >55 years (and adults aged 40-55 years with specified comorbidities) are eligible to participate in the Golden Gate trial [5].

Alternative treatments for the subgroup of Ph- ALL in adults aged 46-65 years include the MD Anderson regimen, which is used for patients who are candidates for intensive chemotherapy. This includes 8 cycles of therapy courses consisting of cyclophosphamide, vincristine, doxorubicin and dexamethasone (hyper-CVAD) alternating with high dose (HD) cytarabine + HD methotrexate. For BCP-ALL, rituximab is added in the first cycles if there are more than 20% CD20 positive lymphoblasts in the bone marrow, which is administered together with chemotherapy treatments. For Ph- ALL patients with significant comorbidities, a reduced Hyper-CVAD treatment is an option [5].

For patients aged >65 years without significant comorbidities, the MD Anderson regimen is the recommended standard treatment in either full or reduced doses. Later, the treatment can be changed to cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) treatment. For patients aged >65 years with significant comorbidities, the standard treatment is palliative chemotherapy with cyclophosphamide, vincristine and prednisolone (CVP) or vincristine and prednisolone (VP). The addition of rituximab can also be considered for patients with more than 20% CD20 positivity [5]. An overview of current treatment options for the different subgroups of Ph- ALL in Denmark is presented in Figure 38 in Appendix K.1.

The different ALL regiments mainly vary by chemotherapy backbones. Thus, the ALLTogether and NOPHO 2008 protocols follow a similar treatment strategy with a four-phase main course being: Induction, Consolidation, Intensification, and Maintenance (with the sequence of phases varying slightly between the different regimes), resulting in a total treatment duration of approximately 2.5 years. During these different phases of treatment, risk stratifications are performed based on clinical and generic factors as well as minimal residual disease (MRD) response, with MRD positivity (MRD+) indicating a less favorable prognosis, and MRD-negativity (MRD-) indicating a more favorable prognosis [5,51,52].

In that regard, the protocols are largely MRD-driven as patients are assigned to specific risk groups during the treatment course based on their response after each treatment phase combined with clinical and generic factors. For patients at higher risk, hematopoietic stem cell transplantation (HSCT), or chimeric antigen receptor cell therapy (CAR-T) treatment for patients <26 years of age, may be offered as an option [5,51,52].

In cases of relapse second line (2L) treatment should be considered. Therapies mentioned in the guidelines include blinatumomab, inotuzumab ozogamicin, salvage chemotherapy

(i.e. FLAG-IDA consisting of fludarabine, cytarabine, idarubicin, and filgrastim), or CAR-T. Patients may receive HSCT in addition to the 2L therapies, under such circumstances, the 2L therapies should lead to new remission and serve as bridging therapies until the receipt of HSCT [5].

3.4 The intervention

Blinatumomab, BLINCYTO® is a bispecific T-cell engager (BiTE®) antibody construct for the treatment of ALL that harnesses the body's own immune system to fight cancer. It specifically binds to CD19 expressed on the surface of B-lineage cells and to CD3 expressed on the surface of T-cells [1,53–56]. Blinatumomab activates endogenous T-cells by connecting CD3 expressed on the T-cell receptor (TCR) complex with CD19 expressed on the benign and malignant B-cells. Blinatumomab mediates the formation of a cytolytic immunologic synapse between the T-cell and the malignant B-cell, triggering the release of proteolytic enzymes that kill the target cells. Blinatumomab is associated with the transient upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which together result in the elimination of CD19-expressing cells [1,57].

See Table 3.Overview of intervention for an overview of key information on the intervention.

Table 3.Overview of intervention

Overview of intervention	
Indication relevant for the assessment	BLINCYTO® is indicated as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL [1].
ATMP	N/A
Method of administration	BLINCYTO® is administered as a continuous intravenous infusion delivered at a constant flow rate using an infusion pump [1].
Dosing	As described per the SmPC, a single cycle of treatment is 28 days (4 weeks) of continuous infusion followed by a 14-day (2-week) treatment-free interval. Patients may receive up to 4 cycles of BLINCYTO® consolidation treatment. Recommended daily dose is by body weight. Patients ≥45 kg should receive a fixed daily dose of 28 µg. For patients <45 kg the daily dose is calculated using the patient's body surface area (BSA) to receive 15 µg per m^2 per day (not exceeding 28 µg/day) [1]. The dosing as per the E1910 trial consists of two cycles of blinatumomab with a two-week interval between the two cycles, followed by three cycles of chemotherapy, one

Overview of intervention	
	additional cycle of blinatumomab, one cycle of chemotherapy and finally one cycle of blinatumomab [4].
Dosing in the health economic model (including relative dose intensity)	In the base case, RDI is assumed to be 100%, since blinatumomab is assumed to be dosed at 28 µg per day in accordance with the SmPC [1]. RDI for the chemotherapies has very minor impact on the ICER and is therefore also assumed to be a 100 %
Should the medicine be administered with other medicines?	No, blinatumomab is an add-on therapy and is proposed to be used as monotherapy alongside the already existing consolidation chemotherapy regimen, thus it is not to be considered a combination treatment [1]. According to the protocol for the E1910 trial, patients should be pre-medicated within one hour prior to start of treatment in each treatment cycle for the prevention of acute reactions to blinatumomab. The pre-medication consists of an administration of dexamethasone (20 mg IV) [76].
Treatment duration / criteria for end of treatment	As described in the SmPC, patients may receive up to 4 cycles of BLINCYTO® for consolidation treatment. Each cycle has a duration of 28 days (4 weeks) with continuous infusion followed by a 14-day treatment-free interval [1]. As per the E1910 trial, the first two cycles of blinatumomab were administrated with a two-week treatment-free interval between the two cycles, followed by three cycles of chemotherapy (for 4, 4 and 6 weeks respectively), one additional cycle of blinatumomab, one cycle chemotherapy (4 weeks) and finally one cycle of blinatumomab [4]. End of blinatumomab treatment temporarily or permanently should be considered in cases of the following severe (grade 3) or life-threatening (grade 4) toxicities: cytokine release syndrome, tumor lysis syndrome, neurological toxicity, elevated liver enzymes, and any other clinically relevant toxicities [1]. For grade 1 immune effector cell-associated neurotoxicity syndrome (ICANS) (ICE score 7-9, CAPD score 1-8 or depressed level of consciousness: awakens spontaneously): interrupt BLINCYTO® until ICANS resolves. For grade 2 ICANS (ICE score 3-6, CAPD score 1-8 or depressed level of consciousness: awakens to voice): Interrupt BLINCYTO®. For grade 3 ICANS (ICE score 0-2, CAPD ≥ 9 or depressed level of consciousness or seizures or raised intracranial pressure): interrupt BLINCYTO®. For grade 4 ICANS (ICE score 0, unable to perform CAPD* or depressed level of consciousness or seizures or motor findings or raised intracranial

Overview of intervention	
	pressure/cerebral oedema): Permanently discontinue BLINCYTO® [1].
Necessary monitoring, both during administration and during the treatment period	Yes. Patients should be clinically monitored for signs and symptoms of neurologic events prior to treatment initiation. Additionally, during treatment patients should be clinically monitored for signs and symptoms of infections, serious adverse events and of neurologic events including ICANS [1].
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	Initial characterization of the disease (by type of cell involved, cell maturity, and presence/absence of Ph) must be done expeditiously and before any treatment is administered, including bone marrow examination supplemented with immunohistochemical and flow cytometric analyses [40,42]. During treatment, patients are assigned to specific risk groups based on MRD response after each treatment phase combined with clinical and generic factors. All these tests are already applied in the Danish clinical practice before any treatment is initiated [5]. It is assumed that no differences appear for the two treatment arms regarding the above-mentioned tests, which was validated by the Danish clinical expert. Therefore, these tests were not included in the CEM.
Package size(s)	Blinatumomab is formulated as a powder for concentrate and solution for solution for infusion. One vial of powder contains 38.5 µg blinatumomab, and reconstitution with water for injections results in a final blinatumomab concentration of 12.5 µg/mL [1].

Abbreviations: CEM, cost-effectiveness model; MRD, minimal residual response; N/A, not applicable; Ph- CD19+ BCP-ALL, Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukemia; µg, Micrograms.
Source: [1,4,5,22,40,42].

3.4.1 Description of ATMP

3.4.2 The intervention in relation to Danish clinical practice

Blinatumomab is proposed as being placed in the first line (1L) consolidation pathway for adult patients with newly diagnosed Ph- CD19+ BCP-ALL in the Danish clinical practice. This involves utilizing blinatumomab as a monotherapy, adding cycles of blinatumomab alongside the existing cycles of multi-agent chemotherapy regimens as part of the consolidation therapy. The introduction of blinatumomab will therefore not replace the chemotherapy regimens already in use as SoC in the Danish Clinical practice.

3.4.2.1 Comparison of treatment sequences in current vs proposed clinical practice

The introduction of blinatumomab as part of the 1L consolidation pathway will result in smaller alterations of the current course of treatment, however, solely in terms of the timing of dosage during the consolidation treatment. This is because the introduction of blinatumomab will necessitate longer intervals between chemotherapy regimen doses compared to current clinical practice.

As described per the Summary of Product Characteristics (SmPC), a single cycle of treatment is followed by a two-week treatment-free interval, whereas as per the E1910 trial only a two-week treatment-free interval is present between the initial two cycles of blinatumomab consolidation [1,4]. Going forward, the duration reported in the E1910 trial (up to 36 weeks) will be referenced and applied consistently in both the dossier and the model. However, a scenario analysis using the SmPC specified duration of up to 42 weeks is included in the model. But it doesn't have a substantial impact on the final result, as patients are not receiving any costs during the treatment-free interval and maintenance costs are very minimal. It is important to highlight that in the E1910 trial, the overall planned duration of treatment in the blinatumomab + chemotherapy arm and the chemotherapy only arm, was the same. In the blinatumomab + chemotherapy arm, the extended consolidation phase did not extend the duration of treatment, since the maintenance therapy continued for 2.5 years from the start of the intensification phase [4,5]. For a comparison of treatment sequences between the blinatumomab + chemotherapy and chemotherapy as per the E1910 trial, see Figure 2.

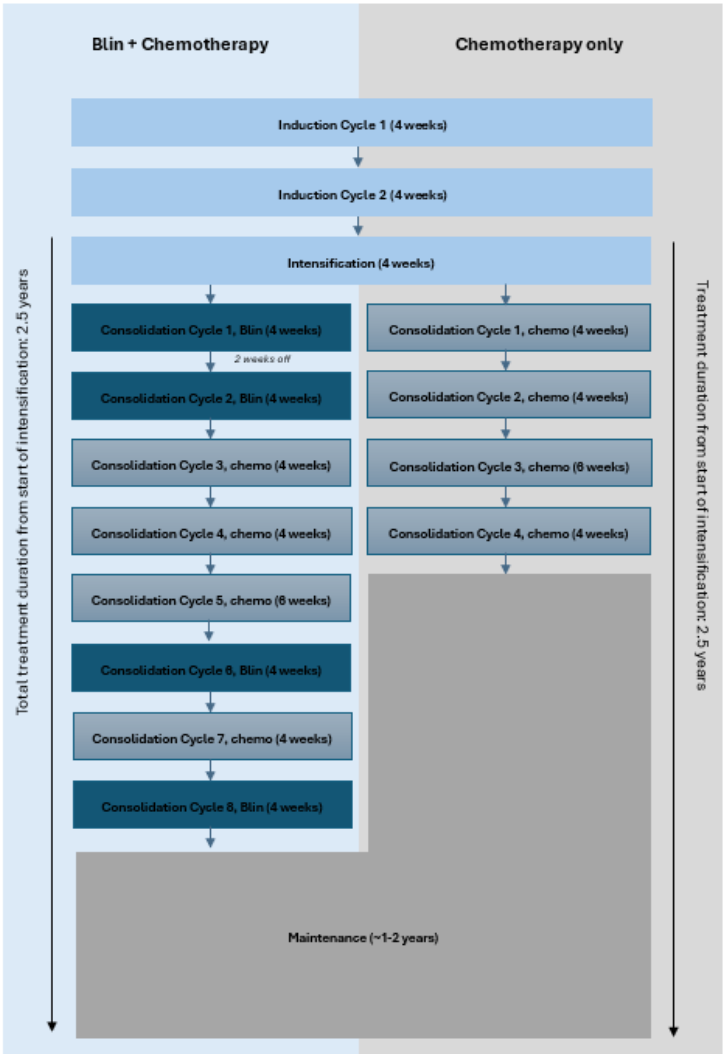

Figure 2. Comparison of treatment sequences between the blinatumomab + chemotherapy and chemotherapy as per the E1910 trial

Abbreviation: Blin, Blinatumomab; chemo, chemotherapy. Source: E1910 trial [4]

3.5 Choice of comparator(s)

From a Danish treatment perspective, the relevant comparator for BLINCYTO® as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL is the current frontline SoC being multiagent chemotherapy regimens. As outlined in section 3.3, various chemotherapy regimens are used depending on age, risk stratification, and biomarkers. However, despite minor variations among chemotherapeutic regimens, they all adhere to the same fundamental treatment principles and have demonstrated substantial similarities, with no single regimen showing clear superiority [5,58]. This is likely because the combinations of agents, doses, and frequencies are similar across the different protocols. Furthermore, the efficacy and safety outcomes of these chemotherapy regimens have shown to be largely comparable, indicating no distinct advantage of one regimen over another. Consequently, incorporating blinatumomab into these different protocols will likely yield effects similar to those observed in the E1910 trial [58]. The above was validated by the Danish clinical expert, who also noted, however, that the effect size may be difficult to extrapolate. For a comparison of consolidation therapies of different treatment protocols, see Table 4. Thus, the comparator chosen is the chemotherapy regimen based on the head-to-head data available from the E1910 trial, which uses a Berlin-Frankfurt-Münster-like regimen adapted from the UKALL XII/ECOG E2993 clinical trial [4,59]. The UKALL XII/ECOG E2993regimen was recognized as the SoC for the specific patient group when the E1910 trial was initiated in 2014 [4,60]. See Table 5 for an overview of the comparator.

Table 4. Comparison of consolidation therapies of different treatment protocols

	ALLTogether [51,61]	**NOPHO-2008** [52]	**E1910 trial (UKALL)** [4]
Chemotherapies*	1. Cytarabine	1. Cytarabine	1. Cytarabine
	2. Methotrexate	2. Methotrexate	2. Etoposide
	3. Asparaginase	3. Asparaginase	3. Methotrexate
	4. Vincristine	4. Vincristine	4. Pegaspargase
	5. Dexamethasone	5. Dexamethasone	5. Daunorubicin
	6. Cyclophosphamide	6. Cyclophosphamide	6. Vincristine
	7. Mercaptopurine	7. Mercaptopurine	7. Dexamethasone
		8. 6-Thioguanine	8. Cyclophosphamide
		9. Daunorubicin	9. Mercaptopurine

* In the ALLTogether and NOPHO-2008 protocols, risk group classifications specify which of the above chemotherapeutic agents are given to patients. Source: [4,51,52,61].

Table 5. Overview of comparator

Overview of comparator [22,62–68]	
Generic name	*Chemotherapy 1:* Cytarabine [63]
	Chemotherapy 2: Etoposide [62]
	Chemotherapy 3: Methotrexate [65]
	Chemotherapy 4: Pegaspargase [67]
	Chemotherapy 5: Daunorubicin [63]
	Chemotherapy 6: Vincristine [69]

	Chemotherapy 7: Dexamethasone [66] *Chemotherapy 8:* Cyclophosphamide [70] *Chemotherapy 9:* Mercaptopurine [64]
ATC code	*Chemotherapy 1 (Cytarabine):* L01BC01 [63] *Chemotherapy 2 (Etoposide):* L01CB01 [62] *Chemotherapy 3 (Methotrexate):* L01BA01 (IT), L04AX03 (PO) [65] *Chemotherapy 4 (Pegaspargase):* L01XX24 [67] *Chemotherapy 5 (Daunorubicin):* L01DB02 [67] *Chemotherapy 6 (Vincristine):* L01CA02 [69] *Chemotherapy 7 (Dexamethasone):* H02AB02 [66] *Chemotherapy 8 (Cyclophosphamide):* L01AA01 [70] *Chemotherapy 9 (Mercaptopurine):* L01BB02 [64]
Mechanism of action	*Chemotherapy 1 (Cytarabine):* pyrimidine analog (antimetabolite) [63] *Chemotherapy 2 (Etoposide):* topoisomerase inhibitor (podophyllotoxin derivative) [62] *Chemotherapy 3 (Methotrexate):* human dihydrofolate reductase inhibitor (antimetabolite) [65] *Chemotherapy 4 (Pegaspargase):* hydrolyzes serum asparagine to nonfunctional aspartic acid and ammonia, depriving tumor cells of a required amino acid (other antineoplastic agent) [67] *Chemotherapy 5 (Daunorubicin):* DNA replication and transcription inhibitor (anthracycline antibiotic and antineoplastic agent) [63] *Chemotherapy 6 (Vincristine):* mitosis inhibitor (antimicrotubule agent) [69] *Chemotherapy 7 (Dexamethasone):* suppressing the migration of neutrophils and decreasing lymphocyte colony proliferation (corticosteroid) *Chemotherapy 8 (Cyclophosphamide):* inhibiting humoral1, 2 and cell-mediated immune responses (immunosuppressive agent) [70] *Chemotherapy 9 (Mercaptopurine):* inhibits de novo purine synthesis and acts as an antiproliferative agent (purine antagonists) [64]
Method of administration	*Chemotherapy 1 (Cytarabine):* IV or SC [63] *Chemotherapy 2 (Etoposide):* IV [62] *Chemotherapy 3 (Methotrexate):* IT or PO [65] *Chemotherapy 4 (Pegaspargase):* IV or IM [67] *Chemotherapy 5 (Daunorubicin):* IV [63] *Chemotherapy 6 (Vincristine):* IV [69] *Chemotherapy 7 (Dexamethasone):* PO [66] *Chemotherapy 8 (Cyclophosphamide):* IV [70] *Chemotherapy 9 (Mercaptopurine):* PO [64]
Dosing	*Chemotherapy 1 (Cytarabine):* 75 mg/m2 on days 1-5 (cycle 1), 75 mg/m2 on days 1-5 (cycle 2), 75 mg/m2 on days 30-33 and 37-40 (cycle 3), 75 mg/m2 on days 1-5 (cycle 4) [63] *Chemotherapy 2 (Etoposide):* 100 mg/m2 on days 1-5 (cycle 1), 100 mg/m2 on days 1-5 (cycle 2), 100 mg/m2 on days 1-5 (cycle 4) [62] *Chemotherapy 3 (Methotrexate):* 12.5 mg on day 1 (cycle 1), 12.5 mg on day 1 (cycle 2), 12.5 mg on day 2 (cycle 3), 12.5 mg on day 1 (cycle 4) [65]

	Chemotherapy 4 (Pegaspargase): 2000 IU/m2 (1000 IU/m2 if ≥55 years) on day 5 (cycle 1). [67] *Chemotherapy 5 (Daunorubicin):* 25 mg/m2 on days 1, 8, 15 and 22 (cycle 3) [63] *Chemotherapy 6 (Vincristine):* 1.4 mg/m2 on days 1, 8, 15 and 22 (cycle 3) [69] *Chemotherapy 7 (Dexamethasone):* 10 mg/m2 on days 1-7 and 15-21 (days 15-21 only if ≥55 years) (cycle 3) [66] *Chemotherapy 8 (Cyclophosphamide):* 650 mg/m2 on day 29 (cycle 3) [70] *Chemotherapy 9 (Mercaptopurine):* 60 mg/m2 on days 29-42 (cycle 3) [64]
Dosing in the health economic model (including relative dose intensity)	*Chemotherapy 1 (Cytarabine):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 2 (Etoposide):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 3 (Methotrexate):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 4 (Pegaspargase):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 5 (Daunorubicin):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 6 (Vincristine):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 7 (Dexamethasone):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 8 (Cyclophosphamide):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% *Chemotherapy 9 (Mercaptopurine):* - Blinatumomab+chemotherapy: 100% - Chemotherapy: 100% Regimen-specific relative dose intensity is calculated as (actual dose intensity/planned dose intensity) [22].
Should the medicine be administered with other medicines?	No

Treatment duration/ criteria for end of treatment	A treatment course consists of up to 4 cycles of chemotherapy regimens for consolidation, each cycle with a duration of 28 days, except for cycle 3 which has a duration of 42 days. Criteria for end of treatment is as follows: *Chemotherapy 1 (Cytarabine):* severe/life-threatening hypersensitivity symptoms, cardiomyopathy / impaired cardiac function / acute copper toxicity. [63] *Chemotherapy 2 (Etoposide):* N/A *Chemotherapy 3 (Methotrexate):* Any serious decrease in leucocyte or platelet counts, significant hepatic or respiratory tract impacts, malignant lymphomas [65] *Chemotherapy 4 (Pegaspargase):* Serious hypersensitivity reactions, pancreatitis, serious thrombotic events [67] *Chemotherapy 5 (Daunorubicin):* severe/life-threatening hypersensitivity symptoms, cardiomyopathy / impaired cardiac function / acute copper toxicity [63]. *Chemotherapy 6 (Vincristine):* N/A *Chemotherapy 7 (Dexamethasone):* hemoglobin 10> 12 g/dl, thromboembolic events [66] *Chemotherapy 8 (Cyclophosphamide):* N/A *Chemotherapy 9 (Mercaptopurine):* Jaundice, Macrophage activation syndrome. [64]
Need for diagnostics or other tests (i.e. companion diagnostics)	Initial characterization of the disease (by type of cell involved, cell maturity, and presence/absence of Ph) must be done expeditiously and before any treatment is administered, including bone marrow examination supplemented with immunohistochemical and flow cytometric analyses [40,42]. During treatment, patients are assigned to specific risk groups based on MRD response after each treatment phase combined with clinical and generic factors. All these tests are already applied in the Danish clinical practice [5,40,42]. It is assumed that no differences appear for the two treatment arms regarding the above-mentioned tests, which was validated by the Danish clinical expert. Therefore, these tests were not included in the CEM.
Package size(s)	Numerous package size(s) are available for each medication; these are listed within the sheet “Medicine” of the health economic model.

Abbreviations: Blin, blinatumomab; CEM, cost-effectiveness model; IT, intrathecal; IV, intravenous; MRD, minimal residual disease; N/A, not applicable; Ph, Philadelphia chromosome; PM, per muscle; PO, per oral; SoC, standard of care.
Source: [1,22,62–67,70,71].

3.6 Cost-effectiveness of the comparator(s)

The DMC has previously evaluated treatments for B-cell ALL, including an assessment of Inotuzumab ozogamicin (Besponsa) in 2018 and an assessment of Tisagenlecleucel (Kymriah) in 2019. In both evaluations, the comparator is multiagent chemotherapy regimens, comparable to the comparator chosen in the present application [72,73]. In

the assessment of Besponsa, the comparator was deemed most cost-effective, for which reason Besponsa did not receive a recommendation by the DMC [72].

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

To assess the efficacy of blinatumomab as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL compared to multiagent chemotherapy regimens alone as consolidation therapy are overall survival (OS), relapse-free survival (RFS), and treatment-related adverse events (TRAEs) [1,4].

The definitions of the respective outcomes are presented in Table 6 below. Additionally, health-related quality of life (HRQoL) is an outcome of relevance, however these data have not been included in this section [1,4]. Instead, HRQoL data are presented in section 10.

Table 6 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
Overall survival (OS) [90]	DCO: 23 June 2023. Median follow-up time: 4.5 years in blinatumomab + chemotherapy and 4.6 years in the chemotherapy alone arm.	Defined as the time between randomization and death from any cause.	Measures were calculated by means of the Kaplan–Meier method. Comparison of OS between the treatment groups was conducted using the two-sided stratified log-rank test with the stratification factors of age, CD20 status, rituximab use, and intention to receive a transplant. Stratified Cox proportional-hazards models using the above-mentioned stratification factors were used to assess the treatment effect on OS and RSF with adjustment for possible clinical and biologic risk factors.
Relapse-free survival (RFS) [90]	DCO: 23 June 2023. Median follow-up time: 4.5 years in blinatumomab + chemotherapy and 4.6 years in the chemotherapy alone arm.	Defined as the time between randomization and relapse or death (whichever occurred first).	
TRAEs of grade ≥3 [4,22,90]	During consolidation therapy only.	Safety was assessed according to the Common Terminology Criteria for Adverse	TRAEs of grade 3-5 that occurred during consolidation therapy in at least 3% of the patients were reported.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
		Events, version 4, of the National Cancer Institute.	

* Time point for data collection used in analysis (follow up time for time-to-event measures).
Abbreviations: DCO, data cut-off; OS, overall survival; RFS, relapse-free survival; TRAE, treatment-related adverse event.
Source: [1,22].

3.7.1.1 Validity of outcomes

OS is a universally accepted direct measure of clinical benefit in oncology studies and is the primary endpoint of the E1910 trial [4,74]. Additionally, OS has previously been accepted as a clinically plausible efficacy outcome measure for the assessment of other treatments for ALL by the DMC [72,73]. Therefore, OS is assessed highly relevant for the assessment of blinatumomab as part of consolidation therapy compared to chemotherapy regimens alone.

RFS is also a relevant efficacy outcome measure for assessing the benefit of blinatumomab in terms of durable CR. RFS is a composite endpoint that accounts for survival and the durability of CR. Additionally, RFS can be assessed before a survival benefit can be demonstrated and is based on objective and quantitative assessments. Including RFS as a secondary endpoint is in line with anticancer guidelines, such as the Committee for Medicinal Products for Human guidance on Evaluation of Anticancer Medicinal Products in Man and the FDA (Food and Drug Administration) Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [74,75].

Lastly, TRAEs is also a relevant efficacy outcome measure. Previously, the DMC has included TRAEs in assessments of other ALL treatments, aiming at elucidating the safety of the treatment and including side effects that may significantly impact the quality of life (QoL) of individual patients [72,73].

4. Health economic analysis

To evaluate the cost-effectiveness of blinatumomab as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph-CD19+ BCP-ALL compared to SoC, a cost-utility analysis (CUA) was performed.

4.1 Model structure

The CUA is designed as a three-state partitioned survival model (PSM), comprising three mutually exclusive health states: Relapse free (RF), Post relapse (PR), and death, see Figure 3.

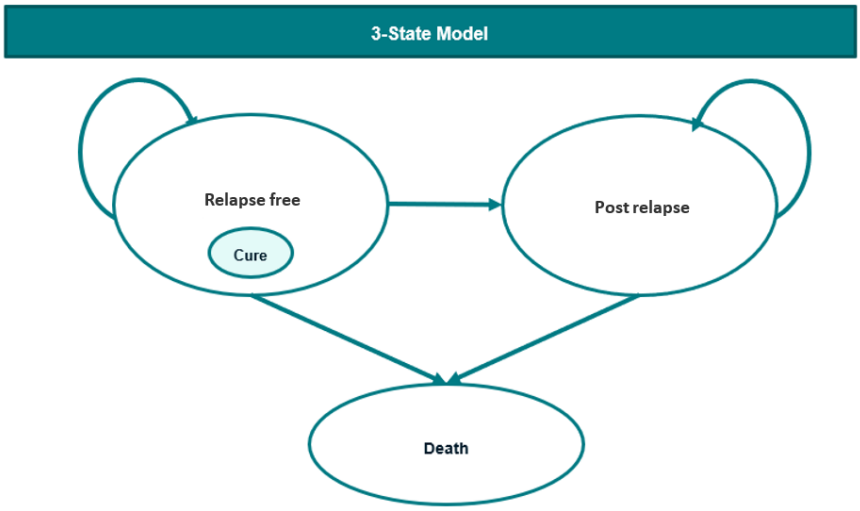

Figure 3. Model structure

All patients enter the model in the RF state, where it is assumed that a patient's disease is either in a stable state or does not actively progress. Patients can thereafter either remain in the relapse free state or transition to the PR state or to the death state. In line with the E1910 trial, relapse is defined as reappearance or persistence of blasts in the blood or the presence of > 5% blasts that are not attributable to another cause (e.g. bone marrow regeneration) [76]. As patients in the PR state have relapsed, they move on to relapse (2L/subsequent) treatment. Patients in the PR state can either stay within the PR state, or transition to the death state. Patients who remain in remission for around 3 to 5 years are generally perceived to be cured [77]. The Danish clinical expert validated that patients who remain in remission for 3 years is normally considered cured in Danish clinical practice. This is aligned with the plateau observed in the blinatumomab + chemotherapy arm Kaplan-Meier (KM) RFS curve, where no relapse or death events are observed after 4 years, suggesting that these patients are cured. Therefore, in order to probably capture this plateau in survival, survival is modelled using Mixture Cure Models (MCM), which among other is recommended by NICE in situations where a proportion of patients is effectively "cured" and should be subjected to background mortality [78]. The applied MCMs include a cured fraction of patients that follows a survival function that is closely in line with the general population, just whit a slightly higher mortality risk compared to the general population. That is applied using a standardized mortality ratio (SMR) of 1.09 to account for potential lingering complications from ALL or HSCT, which was validated by the clinical expert. For the non-cured population, the overall additional risk of excess mortality will continue to be applied. Additionally, it is assumed that patients remaining relapse-free for 4 years are no longer at risk of ALL-related disutilities (i.e. they switch to general population utilities) and costs (i.e. they no longer receive subsequent therapy and terminal care costs). For further details regarding the cured fractions, see Section 8 and

Appendix D.

4.2 Model features

The analysis was conducted from a limited societal perspective applying a lifetime horizon, corresponding to a 50-year time horizon. A weekly model cycle length was considered to accommodate chemotherapy regimens with varying cycle durations. Given the short cycle length in the model, half-cycle correction (HCC) is not applied in the base case. However, it is possible to apply HCC in the sheet "Controls" within the CEM in Excel. Both costs and effects were discounted at 3.5% annually after the first year. All costs are stated as or adjusted to 2024/2025 values. A summary of the key features of the health economic model is provided in Table 7. Please ensure Excel formatting is set to English for proper functioning of model inputs and formulas.

Table 7 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with newly diagnosed Ph- CD19+ BCP ALL (regardless of MRD-status) and who are in CR/CRi.	The population of the model is in line with the EMA indication as well as the population investigated in the E1910 trial [1,4].
Perspective	Limited societal perspective	According to DMC guidelines [79].
Time horizon	Lifetime (50 years)	Sufficiently long to track differences in costs and effects between BLINCYTO® chemotherapy and chemotherapy alone and to capture health implications from a cured population, thus being in line with DMC guidelines [79].
Cycle length	1 week	Allows for granularity to capture all necessary events and allows for the flexibility to model the dosing schedules of the intervention and comparator.
Half-cycle correction	No	Given the short cycle length, HCC is deemed not relevant, however, the model allows for the possibility to apply HCC in the sheet "Controls".
Discount rate	3.5 %	In accordance with DMC practice applying a discount

Model features	Description	Justification
		rate of 3.5 % annually after the first year [81].
Intervention	Blinatumomab alternating with consolidation chemotherapy.	Intervention: following the E1910 trial [4].
Comparator(s)	Multiagent chemotherapy regimen alone as consolidation therapy. At any time after the commencement of consolidation chemotherapy, eligible patients may receive HSCT.	According to national treatment guidelines and comparable to the comparators of previously DMC evaluations of other treatments for B-cell ALL [5,72,73].
Outcomes	OS, RFS, LYs, QALY	Relevant outcomes for patient population and in accordance with DMCs guidelines.

Abbreviations: CR/CRi, complete remission/complete remission with incomplete hematologic recovery; DMC, Danish Medicines Council; EMA, European Medicines Agency; HSCT, hematopoietic stem cell transplantation; LYs, life years; OS, overall survival; Ph- B-cell ALL, Philadelphia chromosome negative B-cell acute lymphoblastic leukemia; QALY, quality-adjusted life year; RFS, relapse-free survival.
Source: [1,4,5,72,73,79].

5. Overview of literature

5.1 Literature used for the clinical assessment

Efficacy and safety differences between blinatumomab + chemotherapy and chemotherapy alone have been directly compared in a head-to-head study with a sufficient follow-up period. Therefore, literature used for the clinical assessment in this application is the published head-to-head E1910 trial together with additional internal, unpublished data on file hereof, see Table 8 below.

Table 8 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper, data on file and conference abstract]

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Litzow, Mark R., et al. "Blinatumomab for MRD-negative acute lymphoblastic leukemia in adults." *New England Journal of Medicine* 391.4 (2024): 320-333 [4,80].	E1910 trial	NCT02003222	Start (as per ClinicalTrial.gov): 19/05/2014 Primary Completion (as per ClinicalTrial.gov): 23/06/2023 Estimated Study Completion (as per ClinicalTrial.gov): 25/03/2026 Future data cut-offs: Not reported	Blinatumomab as monotherapy as part of chemotherapy consolidation therapy vs. chemotherapy consolidation therapy alone for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL

* If there are several publications connected to a trial, include all publications used.
Abbreviations: Ph- CD19+ BCP-ALL, Philadelphia chromosome negative CD19 positive B-cell precursor acute lymphoblastic leukemia
Source: [4,80].

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

The head-to-head E1910 trial did not collect HRQoL data. For this reason, a systematic literature review (SLR) was conducted to obtain HRQoL data for the assessment of blinatumomab as monotherapy as part of consolidation therapy for the treatment of patients newly diagnosed with Ph- CD19+ BCP-ALL. However, the SLR did not identify any completed clinical trials evaluating HRQoL or other patient-reported outcomes (PRO) solely for newly diagnosed patients with Ph- CD19+ BCP-ALL using blinatumomab as part of consolidation therapy, see Appendix I.

Instead, HRQoL associated with blinatumomab has been evaluated in a wealth of other blinatumomab studies including the BLAST and TOWER trials [23,24]. Therefore, HRQoL data from the BLAST and TOWER studies was leveraged for generating health-state utility values (HSUVs) for the core CEM, see Table 9.

Table 9 Relevant literature included for (documentation of) health-related quality of life (See section 10)

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Bargou, Ralf C., et al. "Health-related quality of life in adults with B-cell precursor acute lymphoblastic leukemia and minimal residual disease treated with Blinatumomab". Blood, 2018, 132: 1377. BLAST study [24]	Utilities for the relapse-free health state and disutility for the death within ≤ 6 months health state, both for blinatumomab and chemotherapy and chemotherapy alone.	Section 10
Topp, Max S., et al. "Health-related quality of life in adults with relapsed/refractory acute lymphoblastic leukemia treated with blinatumomab." Blood, The Journal of the American Society of Hematology 131.26 (2018): 2906-2914. TOWER study [23]	Utilities for the PR health state for both blinatumomab and chemotherapy and chemotherapy alone.	Section 10

Abbreviations: SoC, standard of care.
Source: [23,24].

5.3 Literature used for inputs for the health economic model

A SLR was conducted for obtaining inputs for the health economic model, however, the SLR identified only sparse evidence with several limitations, including that outcomes were reported inconsistently across studies; discrepancies were found in the reported data and insufficient details on methodology meant that it was difficult to interpret the outcomes. Thus, the SLR highlighted the considerable lack of evidence on economic outcomes relating to Ph- B-cell ALL, see Appendix J. No evidence relating to indirect medical costs could be identified for the target population. Therefore, data from grey literature of relevance for a Danish setting was used in the health economic model, including utility values, cost data and additional information on assumptions, see section 4.2 and section 11 for further details. A table presenting sources found through a targeted literature search for health economic inputs, see section J.1.6 in appendix.

Table 10 Relevant literature used for input to the health economic model

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Authors. Article title. Journal. Year; volume (issue): pp [reference number]	Overall survival	Targeted literature review	Section 9.2. Table X

5.4 Ongoing trials

In accordance with the DMC method guidelines, a search for active and unpublished phase ≥2 studies that include blinatumomab as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL compared to SoC alone has been carried out on Clinicaltrials.gov and the EU Clinical Trials Register on 27 May 2025 [81,82]. Four active trials were located, listed in Table 11 below.

Table 11. Ongoing trials

Sponsor	Trial title	NCT identifier	Dates of study	Source
Stichting Hemato-Oncologie voor Volwassenen Nederland	Blinatumomab Added to Prephase and Consolidation Therapy in Precursor B-acute Lymphoblastic Leukemia in Adults. (HOVON146ALL)	NCT03541083	Start: 04/06/2018 Completion (estimated): 15/12/2026	[83]
National Cancer Institute (NCI)	A Study to Investigate Blinatumomab in Combination With Chemotherapy in Patients With Newly Diagnosed B-Lymphoblastic Leukemia	NCT03914625	Start: 03/07/2019 Completion (estimated): 30/09/2027	[84]
National Cancer Institute (NCI)	Blinatumomab and Combination Chemotherapy or Dasatinib, Prednisone, and Blinatumomab in Treating Older Patients With Acute Lymphoblastic Leukemia	NCT02143414	Start: 30/06/2015 Completion (estimated): 23/10/2025	[85]
Amgen	Study Comparing Blinatumomab Alternating With Low-intensity Chemotherapy Versus Standard of Care Chemotherapy for Older Adults With Newly Diagnosed Philadelphia-negative B-cell Precursor Acute Lymphoblastic Leukemia	NCT04994717	Start: 02/11/2021 Completion (estimated): 30/09/2031	[86]

Source: [83–86]

6. Efficacy

6.1 Efficacy of blinatumomab in conjunction with chemotherapy vs chemotherapy alone as a consolidation regimen in patients with Ph- BCP-ALL

6.1.1 Relevant studies

The efficacy and safety of blinatumomab in adults aged ≥ 30 years and ≤ 70 years and newly diagnosed with Ph- BCP-ALL was evaluated in the E1910 trial, which is an ongoing phase 3, randomized, controlled, open-label, investigator-sponsored study, conducted in 77 centers in the US, Canada, and Israel [4,22,76]. The E1910 trial investigated the addition of blinatumomab to consolidation chemotherapy vs consolidation chemotherapy alone in patients who had previously achieved CR or complete remission with incomplete blood count recovery (CRi) with induction chemotherapy. The protocol-specified consolidation chemotherapy backbone was based on the modified UKALL XII/ECOG E2993 regimen [59,76].

The age range of patients being ≥ 30 years and ≤ 70 years was chosen to avoid competition for enrollment in a National Clinical Trials Network (NCTN) trial involving adolescents and young adult patients led by the Alliance for Clinical Trials in Oncology group [4]. The Study Initiation Date was 19 May 2014 (first randomization), while primary analysis data cutoff date (DCO) was 23 June 2023. The median follow-up time was 4.5 years in the primary and secondary endpoint analyses [80].

The study was conducted in a 4-step process with additional inclusion and exclusion criteria applied to steps prior to randomization, and with blinatumomab added as a part of the consolidation phase (Step 3) [76]:

- **Induction phase (Step 1), Arm A:** All eligible patients (Ph- BCP-ALL aged 30 -70 years with an Eastern Cooperative Oncology Group (ECOG) performance-status of 0 to 3) received 2 cycles of induction chemotherapy with the addition of pegasparaginase for patients aged < 55 years and the addition of rituximab for CD20+ patients [76].
- **Intensification phase (Step 2), Arm B:** Patients in hematologic CR/CRi after the induction phase with an ECOG performance-status of 0 to 2 continued within the study and received 1 cycle of intensification chemotherapy of high-dose methotrexate with pegasparaginase for central nervous system (CNS) prophylaxis [76].
- **Consolidation phase (Step 3):** Patients who had maintained CR or CRi, with an ECOG performance-status of 0 to 2, were randomized to receive either Arm C: blinatumomab + chemotherapy or Arm D: chemotherapy alone [76].
- **Maintenance phase (Step 4), Arm E:** After consolidation therapy, patients proceeded to maintenance therapy with the planned duration of treatment being the same in the two trial arms. Maintenance therapy consisted of POMP (Purinethol

(6-mercaptopurine), oncovin (vincristine), methotrexate, and prednisone) treatment [76]. In the blinatumomab + chemotherapy and in the chemotherapy-arm alone 73 and 71 MRD-agnostic randomized patients only initiated maintenance therapy after consolidation therapy, respectively.

Randomization was risk stratified based on patient age (<55 years vs ≥ 55 years), CD20 status (positive vs negative), rituximab use (yes vs no), and whether HSCT was intended (yes vs no)[1] [4].

Initially, in the E1910 trial MRD+ and MRD- patients were intended to be equally randomized to blinatumomab + chemotherapy or chemotherapy alone, with MRD+ defined as MRD > $1x10^{-4}$ [1,4,76]. However, in March 2018, the Food and Drug Administration (FDA) granted accelerated approval of blinatumomab to treat adults and children with BCP ALL who were in remission but still MRD+ [87]. This resulted in an amendment of the E1910 trial protocol leading to a discontinuation of the randomization of MRD+ patients. Consequently, all subsequent MRD+ patients were assigned at the consolidation phase (step 3) to receive blinatumomab + chemotherapy (Arm C). MRD- patients assigned to the consolidation phase were continuously randomized to receive either blinatumomab + chemotherapy (Arm C) or chemotherapy alone (Arm D).

Due to the E1910 protocol amendment, three efficacy analysis sets are available including MRD+ patients only, MRD- patients only, and MRD+ and MRD- patients combined (i.e. MRD-agnostic patients) [1,4]. Furthermore, the efficacy analysis sets for both the MRD+ and the MRD-agnostic patients can either include or exclude the non-randomized patients. To mitigate bias, the randomized MRD-agnostic patients build the foundation in the health economic model.

Following the protocol amendments, the primary endpoint was limited to OS for MRD- patients only and selected secondary endpoint was RFS for MRD- patients [1,4,76]. For an overview of the E1910 trial design, see Table 12.

As noted, efficacy results of the three analysis sets of the E1910 trial are available. Firstly, results from the full analysis set (FAS) are available, providing data on all Step 3 (consolidation phase) subjects who are assessed as MRD- centrally after induction and intensification chemotherapy. This includes the published data of the third efficacy interim analysis of September 2022 (the E1910 publication [4]), together with data of the primary analysis DCO date of 23 June 2023 retrieved from the published data of the SmPC ([1]) combined with unpublished data from the CSR (CSR, Amgen data on file [22]). Secondly, results from the Step 3 Analysis Set, including MRD-agnostic patients are available, providing evidence supporting the totality of benefits of blinatumomab use in the frontline setting irrespective of MRD status retrieved from the SmPC and CSR only

[1] Due to amendments of the E1910 trial protocol (as a result of the FDA accelerated approval in March 2018 of blinatumomab to treat MRD+ patients with BCP-ALL who were in remission), risk stratification throughout the dossier may vary in regard to the inclusion of MRD-status as a stratification factor. Accordingly, MRD-status (MRD+/-) is either or not included as a stratification factor in the E1910 trial protocol and the E1910 trial publication (of MRD- patients), respectively [4,76,87].

[1,22]. This analysis set provides data corresponding to the EMA label, and the intended population of the E1910 study before the FDA amendment. Thirdly, results from the Step 3 Analysis Set including MRD+ patients are available, retrieved partly from the published data of the SmPC ([1]) combined with unpublished data of the CSR (CSR, Amgen data on file [22]).

Importantly, the approved EMA indication for consolidation is independent of MRD status, which is also the indication in scope for this application. Therefore, only the MRD-agnostic randomized patients only efficacy analysis set is presented in section 6 and used as the health economic base case. However, for some of the parameters in the health economic analysis, data for the MRD-agnostic randomized patients only has not been accessible, why data for the MRD-agnostic patients including the 18 nonrandomized patients are applied instead. The efficacy analysis set of the MRD- patients only, all MRD-agnostic patients and MRD+ patients only are presented in Appendix B.

Furthermore, it should be noted that the overall population of the E1910 trial includes 31 (14%) patients who are Ph-like (also referred to as BCR::ABL1-like genotype). The E1910 publication reports results for this subpopulation and although the result for OS is not significant (HR:0.28 (0.06-1.36)) it indicates a beneficial effect of blinatumomab for the Ph-like population [4]

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

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up time
E1910, NCT: 02003222 [1,4, 80]	Phase 3, randomized, controlled, open-label, investigator-sponsored study, investigating the addition of blinatumomab to consolidation chemotherapy vs consolidation chemotherapy alone.	19 May 2014 (first randomization). After the receipt of consolidation therapy, patients proceeded to maintenance therapy for 2.5 years from the start of the intensification phase. The primary analysis DCO date was 23 June 2023.	Subjects aged 30-70 years with newly diagnosed Ph- BCP-ALL who had previously achieved CR/CRi with induction chemotherapy.	Blinatumomab + chemotherapy consolidation therapy.	Chemotherapy consolidation therapy.	**Primary endpoints:** • OS for MRD- patients (E1910 publication): Median follow-up: 43 months • OS for MRD- patients (SmPC data): Median follow-up: 4.5 years. **Selected secondary endpoints:** • RFS for MRD- patients (E1910 publication): Median follow-up: 43 months • RFS for MRD- patients (SmPC data): Median follow-up: 4.5 years **Selected post hoc analysis** (SmPC data and data on file)**:** • OS for MRD-agnostic randomized patients only: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm)RFS for MRD-agnostic randomized patients only: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm)OS for MRD+ patients: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm) RFS for MRD+ patients: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm)

Abbreviations: CR/CRi, complete remission/complete remission with incomplete hematologic recovery; DCO, data cut-off; OS, overall survival; Ph- BCP-ALL, Philadelphia chromosome negative B-cell precursor acute lymphoblastic leukemia; RFS, relapse-free survival. Source: [1,4,80, 90].

6.1.2 Comparability of studies

Baseline demographics and characteristics were generally well balanced between the two treatment arms in the Step 3 Analysis Set [1,22].

In total, 62 (21.7%) out of 286 patients were MRD+ (40 patients [26.3%] in the blinatumomab + chemotherapy arm and 22 [16.4%] in the chemotherapy arm) [1]. Out of the 40 patients with MRD+ disease in the blinatumomab arm, 18 were not randomized but were assigned to this arm following the FDA's approval of blinatumomab for MRD+ ALL in March 2018 as described above [22].

6.1.2.1 Comparability of patients across studies

Baseline characteristics of patients included in each arm of the Step 3 Analysis Set from the E1910 trial are presented in Table 13 below. The baseline characteristics presented in Table 13 are for the MRD-agnostic randomized patients only.

For the blinatumomab + chemotherapy arm (N = 134) and chemotherapy arm (N = 134), 47.8% and 52.2% of subjects, respectively, were male; mean age at enrollment was 49.8 years and 50.2 years, respectively [90].

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

	E1910 trial (Step 3 Analysis Set*(consolidation phase)) [90]		
	Blinatumomab + chemotherapy (N=134)	**Chemotherapy (N=134)**	**Overall (N = 268)**
Sex, n (%)			
Male	64 (47.8)	70 (52.2)	134 (50.0)
Female	70 (52.2)	64 (47.8)	134 (50.0)
Ethnicity, n (%)			
Hispanic or Latino	17 (12.7)	15 (11.2)	32 (11.9)
Not Hispanic or Latino	112 (83.6)	111 (82.8)	223 (83.2)
Not Reported	2 (1.5)	3 (2.2)	5 (1.9)
Unknown	3 (2.2)	5 (3.7)	8 (3.0)
Race, n (%)			
American Indian or Alaska Native	2 (1.5)	1 (0.7)	3 (1.1)
Asian	3 (2.2)	2 (1.5)	5 (1.9)
Black or African American	12 (9.0)	5 (3.7)	17 (6.3)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	1 (0.7)	0 (0.0)	1 (0.4)
White	103 (76.9)	110 (82.1)	213 (79.5)
Not reported	7 (5.2)	6 (4.5)	13 (4.9)
Unknown	6 (4.5)	10 (7.5)	16 (6.0)
Age at enrollment (years)			

	E1910 trial (Step 3 Analysis Set*(consolidation phase)) [90]		
	Blinatumomab + chemotherapy (N=134)	**Chemotherapy (N=134)**	**Overall (N = 268)**
Mean (min, max)	49.8 (30, 69)	50.2 (30, 70)	50.0 (30, 70)
Age group, n (%)			
< 55 years	81 (60.4)	76 (56.7)	157 (58.6)
≥ 55 years	53 (39.6)	58 (43.3)	111 (41.4)
Country of residence, n (%)			
Canada			
Israel	7 (5.2)	7 (5.2)	14 (5.2)
United States	2 (1.5)	7 (5.2)	9 (3.4)
	125 (93.3)	120 (89.6)	245 (91.4)
ECOG performance status, n (%)			
0			
1	50 (37.3)	49 (36.6)	99 (36.9)
2	78 (58.2)	81 (60.4)	159 (59.3)
3	6 (4.5)	4 (3.0)	10 (3.7)
4	0 (0.0)	0 (0.0)	0 (0.0)
	0 (0.0)	0 (0.0)	0 (0.0)
MRD status, n (%)			
Positive	22 (16.4)	22 (16.4)	44 (16.4)
Negative	112 (83.6)	112 (83.6)	224 (83.6)
Inadequate			
Prior radiation therapy, n (%)			
Yes			
No	4 (3.0)	4 (3.0)	8 (3.0)
	130 (97.0)	130 (97.0)	260 (97.0)
Prior surgery[a] n (%)			
Yes	6 (4.5)	7 (5.2)	13 (4.9)
No	128 (95.5)	127 (94.5)	255 (95.1)
Intent to receive allo-HSCT, n (%)			
Yes	45 (33.4)	42 (31.3)	87 (32.4)
No	89 (66.4)	92 (68.7)	181 (67.5)

***** Data of all step 3 (consolidation phase) randomized or registered subjects, regardless of MRD status at step 3.
Abbreviations: allo-HSCT, allogeneic hematopoietic stem cell transplantation; ECOG, Eastern Cooperative Oncology Group; MRD, minimal residual disease; SoC, standard of care.
[a] Prior surgery refers to prior cancer treatment with therapeutic intent.
Source: [90].

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

This section presents the practice and patient population of the E1910 trial compared to the Danish clinical practice and population eligible for treatment with blinatumomab as

part of consolidation chemotherapy. These comparisons have been validated by the Danish clinical expert.

6.1.3.1 Comparability to Danish population and clinical practice

To a large extend, the Danish clinical practice of Ph- BCP-ALL is comparable to the practice used within the E1910 trial. However, differences can be highlighted between the two practices, including the smaller variations in the chemotherapy backbone used. The Danish clinical expert has commented that the intensity of the chemotherapy regimen used in the E1910 trial is expected to be close to the regimens used in the Danish clinical practice, despite some variations in design and substances. As elaborated in section 3.5, the chemotherapy backbones adhere to the same fundamental treatment principles and have demonstrated substantial similarities in efficacy and safety outcomes, indicating no distinct advantage of one regimen over another [4,5,51,52,58].

Furthermore, smaller variations in the use of MRD testing are present. Collectively, MRD testing is conducted during the different treatment phases to assess the treatment response for prognostication and management decisions [4,5,51,52]. In the Danish clinical practice patients are roughly offered the same chemotherapy regimen during the consolidation phase regardless of MRD status but with exceptions for example of the ALLTogether protocol offering standard risk MRD- patients at day 29 a slightly milder consolidation [5,51,52,61]. Offering a similar consolidation therapy regardless of MRD status was the initial intention of the E1910 trial design, however, due to the FDA accelerated approval of blinatumomab for patients with MRD+ status during the trial, a protocol amendment assigned all subsequent patients with MRD+ status to the blinatumomab group, for which reason the randomization after the FDA approval only occurred for the MRD- patients [1,24,87]. Thus, the practice of the E1910 trial varies slightly from the Danish clinical practice as MRD status determined the consolidation treatment pathway to a higher extend.

Additionally, as described in section 6.1.1 the E1910 trial enrolled patients aged 30 to 70 years. This age range was selected to avoid competition with another trial involving adolescents and young adult patients [4]. Therefore, the eligibility criteria for the E1910 trial differ from the proposed inclusion threshold of $\geq$ 18 years for blinatumomab use in the Danish clinical practice. However, various studies have examined the effect of blinatumomab in adolescents and young adults [88], including a study investigating the use of blinatumomab as 1L consolidation therapy in Ph- B-cell ALL patients [89]. The Danish clinical expert further noted that there is no reason to suggest that the treatment would be less effective in younger adults. Supporting this view, subgroup analyses from the E1910 trial indicated that blinatumomab appeared to be most effective in younger adults, although the reliability of these findings is limited by the small sample size in this subgroup [4].

When evaluating the Danish population eligible for treatment against the E1910 trial population, it becomes clear that they are comparable. In Denmark, from 2018 to 2021 the median age of newly diagnosed ALL patients was 56 years, ranging from 38 to 72 years [43,48]. The gender distribution of Danish ALL patients was 58% men and 42% women, respectively [49]. From 2018 to 2021, 96% of ALL patients in Denmark had an

ECOG performance-status score of ≤ 2 [43]. These patient characteristics are therefore comparable to the MRD-agnostic randomized patients only population, of the E1910 trial, with a median age of 51 years, ranging from 30 to 70 years, where 50% was male and 100% having a ECOG performance-status score of ≤ 2 [22].

6.1.3.2 Values used in the health economic model

The values used in the health economic model are primarily retrieved from internal analyses of the MRD-agnostic population based on data from E1910 trial [22,90]. For an overview of the comparability of the Danish patient population and the MRD-agnostic study patient population used in the health economic model, see Table 14.

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

	Value in Danish population	Value used in health economic model
Age (median)	56 years [43,48]	51 years [90]
Gender distribution	58% male [49]	50 % male [90]
Weight, mean	N/A	86.9 [90]
ECOG performance-status score	96% with a score of ≤ 2 [43]	100% with a score of ≤ 2 [90]

Abbreviations: ECOG, Eastern Cooperative Oncology Group; N/A, Not available.
Source: [43,48,49,90].

6.1.4 Efficacy – results per E1910 trial

To evaluate the clinical benefit of frontline consolidation with blinatumomab in Ph- BCP-ALL patients, the E1910 trial endpoints of OS, defined as the time between randomization and death from any cause, and RFS, defined as the time between randomization and relapse or death (whichever occurred first), were used. As elaborated earlier in this section, the primary endpoint was OS for MRD- patients only, whereas selected secondary endpoint was RFS for MRD- patients. Selected post hoc analyses were OS and RFS for MRD-agnostic randomized patients only as well as for MRD+ patients [1].

As elaborated earlier in this section, only the MRD-agnostic randomized patients only efficacy analysis set (the Step 3 Analysis Set (consolidation phase)) is presented in the following sections, whereas the efficacy analysis set of the MRD-, all the MRD-agnostic and the MRD+ patients respectively are presented in Appendix B. For an overview, relevant subpopulation analysis sets presented are listed below:

- **The Full Analysis Set (FAS)**: providing data of all step 3 randomized MRD- patients who are assessed centrally after induction and intensification chemotherapy (see appendix B.1) [1,4,22].
- **The Step 3 Analysis Set**: providing data of all step 3 randomized or registered patients, regardless of MRD status, at step 3 (subsection 6.1.4.1 and appendix B.2) [1,22].
- **The Step 3 MRD Positive Analysis Set**: providing data of all patients from the Step 3 analysis set who are MRD+ at step 3 using the protocol-specified 10^{-4} cut-off (appendix B.4) [1,22].

6.1.4.1 Efficacy results of the Step 3 Analysis Set

To evaluate OS and RFS for blinatumomab combined with chemotherapy to chemotherapy alone across all Step 3 randomized patients – regardless of MRD status – post hoc analyses were performed. The chosen Step 3 analysis included a total of 268 participants (134 subjects in the blinatumomab + chemotherapy arm and 134 subjects in the chemotherapy arm), irrespective of MRD status [90].

Post hoc analyses: OS in MRD-agnostic randomized patients only (23 June 2023 DCO, Amgen data on file):

In the post hoc analysis of the MRD-agnostics randomized patients only, death from any cause occurred in 24 subjects (17.9%) in the blinatumomab + chemotherapy arm and in 53 subjects (39.6%) in the chemotherapy arm. Median follow-up was 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm [90]. The stratified HR for OS, derived from a Cox regression model, was 0.42 (95% CI: 0.26, 0.68), indicating a 58% reduction in the hazard rate for OS in the SoC blinatumomab + chemotherapy arm. At the time of analysis, the median OS had not been reached in either treatment arm [22]. At 5-years, the Kaplan-Meier estimate for OS was 81.4% (95 CI: 73.5, 87.1) in the blinatumomab + chemotherapy arm and 58.3% (95% CI: 48.8, 66.7) in the chemotherapy arm [1,22] A KM plot illustrating the OS comparison between the two treatment arms is presented in Figure 13 in appendix B.6.5. Additional details on the KM estimates for OS can be found in Table 15.

Table 15. Overall Survival in MRD-agnostic randomized patients only at Step 3 (Step 3 Analysis Set)

	Blinatumomab + chemotherapy (N=134)	Chemotherapy (N=134)
KM estimate - % [90]		
At 0.5 years (95% CI)	97.7 (93.1, 99.3)	96.2 (91.2, 98.4)
At 1 year (95% CI)	96.2 (91.2, 98.4)	84.7 (77.3, 89.9)
At 2 years (95% CI)	88.6 (81.9, 93.0)	76.1 (67.7, 82.5)
At 3 years (95% CI)	84.0 (76.5, 89.3)	65.7 (56.7, 73.2)
At 4 years (95% CI)	81.4 (73.5, 87.1)	60.9 (51.6, 68.9)
At 5 years (95% CI)	81.4 (73.5, 87.1)	58.3 (48.8, 66.7)
At 6 years (95% CI)	81.4 (73.5, 87.1)	51.3 (38.6, 62.6)
At 7 years (95% CI)	81.4 (73.5, 87.1)	51.3 (38.6, 62.6)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [90].

Post hoc analyses: RFS in MRD-agnostic randomized patients only (23 June 2023 DCO, Amgen data on file):

In the post hoc analysis of the MRD-agnostics randomized patients only, death from any cause occurred in 11 subjects (8.2%) in the blinatumomab + chemotherapy arm and in 14

subjects (10.4%) in the chemotherapy arm. Median follow-up was 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm [90]. The stratified HR for RFS, derived from a Cox regression model, was 0.49 (95% CI: 0.31, 0.76), indicating a 51% reduction in the hazard rate for RFS in the blinatumomab + chemotherapy arm. At the time of analysis, the median RFS had not been reached in either treatment arm [90].

At 5 years, the KM estimate for RFS was 76.9% (95% CI: 68.6, 83.2) in the blinatumomab + chemotherapy arm and 57.2% (95% CI: 47.9, 65.4) in the Chemotherapy arm [90]. Additional details on the KM estimates for OS, can be found in Table 16.

A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 14 in appendix B.6.6.

Table 16. Relapse-free Survival in MRD-agnostic randomized only patients at Step 3 (Step 3 Analysis Set)

	Blinatumomab + chemotherapy (N=134)	Chemotherapy (N=134)
KM estimate - % [90]		
At 0.5 years (95% CI)	92.5 (86.4, 95.9)	86.5 (79.5, 91.3)
At 1 year (95% CI)	89.4 (82.8, 93.6)	75.8 (67.5, 82.2)
At 2 years (95% CI)	81.8 (74.1, 87.4)	66.2 (57.4, 73.7)
At 3 years (95% CI)	80.3 (72.5, 86.1)	61.4 (52.4, 69.2)
At 4 years (95% CI)	76.9 (68.6, 83.2)	58.5 (49.3, 66.5)
At 5 years (95% CI)	76.9 (68.6, 83.2)	57.2 (47.9, 65.4)
At 6 years (95% CI)	76.9 (68.6, 83.2)	51.1 (39.3, 61.8)
At 7 years (95% CI)	76.9 (68.6, 83.2)	51.1 (39.3, 61.8)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [90].

6.1.5 Efficacy – results per [study name 2] (N/A)

N/A since only one study is included in the efficacy analysis.

7. Comparative analyses of efficacy

As efficacy and safety differences between blinatumomab + chemotherapy and chemotherapy relevant to Danish clinical practice have been directly compared in a head-to-head study, this section is not applicable. However, as outlined in the guidelines

of the DMC application template, results from the head-to-head study are still presented in section 7.1.3.

7.1.1 Differences in definitions of outcomes between studies (N/A)

Not applicable because the E1910 trial is head-to-head.

7.1.2 Method of synthesis (N/A)

Not applicable because the E1910 trial is head-to-head.

7.1.3 Results from the comparative analysis

In Table 17 below, comparative results from the Step 3 Analysis Set (MRD-agnostic randomized patients only) of the E1910 trial are presented.

Table 17. Results from the comparative analysis of blinatumomab + chemotherapy vs. chemotherapy alone for adult patients with newly diagnosed Ph- CD19+ BCP-ALL

Step 3 Analysis Set (MRD-agnostics)			
Outcome Measure	**Blinatumomab + Chemotherapy (n = 134)**	**Chemotherapy (n = 134)**	**Result**
Overall survival (OS) [90]	81.4 (95% CI: 73.5, 87.1)	58.3 (95% CI: 48.8, 66.7)	DCO: 23 June 2023; median follow-up time: 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm alone. HR: 0.42 (95% CI: 0.26, 0.68; p < 0.001) [a,b]
Relapse-Free Survival (RFS) [90]	76.9 (95% CI: 68.6, 83.2)	57.2 (95% CI: 47.9, 65.4)	DCO: 23 June 2023; median follow-up time: 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm alone. HR: 0.49 (95% CI: 0.31, 0.76; p = 0.002) [a,b]

[a] The hazard ratio estimates are obtained from a stratified Cox regression model. A hazard ratio < 1.0 indicates a lower average death rate and a longer survival for subjects in the blinatumomab + chemotherapy arm relative to subjects in the chemotherapy arm.
[b] Stratification factors: patient age (< 55 years vs. ≥ 55 years), CD20 status (positive vs. negative vs. not collected), rituximab use (yes vs. no vs. not collected), and whether transplantation was intended (yes vs. no). Abbreviations: CI, confidence interval; DCO, data cut-off; HR, hazard ratio; OS, overall survival; RFS, relapse-free survival; SoC, standard of care.
Source: [90].

7.1.4 Efficacy – results per [outcome measure] (N/A)

Not applicable because the E1910 trial is head-to-head.

8. Modelling of efficacy in the health economic analysis

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

To model costs and effects of blinatumomab, efficacy data (OS and RFS) from the E1910 trial for the MRD-agnostic patient population was extrapolated to the time horizon of the health economic model.

To mitigate bias, the randomized patients form the basis of the health economic model. Therefore, the 18 non-randomized MRD+ patients who received blinatumomab + consolidation chemotherapy (i.e. after 2018), were excluded. In that regard, the base-case analysis based on the MRD-agnostic patient population only includes the 22 randomized MRD+ patients in the blinatumomab + chemotherapy arm and the 22 (randomized) patients in the chemotherapy arm alone combined with the 224 (112 in each arm) (randomized) MRD- patients [22]. The MRD-agnostic inputs are therefore based on internal analyses of the E1910 trial data. For both the MRD+ and MRD-agnostic patient population, OS and RFS results are reported both with and without the randomized patients in Appendix B. In the Excel model, a scenario analysis is included focusing on the MRD- patients only, based on the FAS.

However, for some of the parameters in the health economic analysis, data for the MRD-agnostic randomized patients only has not been accessible, why data for the MRD-agnostic patients including the 18 nonrandomized patients are applied instead in these cases. This is for example the case for HSCT post relapse and RDIs for the different chemotherapies.

The E1910 trial data indicates that a group of patients achieved durable treatment remission. This is indicated by the observed plateau in the KM RFS curve for the blinatumomab + chemotherapy arm of the E1910 trial, where no relapse or death events are observed after 4 years, suggesting that patients are cured, see Figure 10 in appendix B.6.2. As outlined in Section 4.1, in order to better capture this plateau in survival, MCMs were used to model survival, where long-term survival is modeled by estimating an implicit “cured fraction” (i.e. the proportion of patients “cured”). Thus, MCMs include a cured fraction of patients that follows a survival function in line with the general population compared with the non-cured population, but where the cured fraction’s additional risk of excess mortality will continue to be applied. The “flexsurvcure” R package was used to fit the MCMs.

8.1.1 Extrapolation of efficacy data

Survival of the “cured” patients is modeled assuming age- and sex-matched general population mortality. An SMR of 1.09 was applied to account for potential lingering complications from ALL or HSCT, sourced from Maurer et al. 2014 and validated by the

Danish clinical expert [91]. The survival of non-cured patients (i.e. 1 – cure fraction) is modeled using a parametric survival model. Both jointly and separately fitted MCMs were explored. For further details regarding the calculated cured fractions, see Appendix D.

To address uncertainty around the SMR, the model includes sensitivity analyses with an elevated SMR of 1.34, calculated as the weighted average of patients who received HSCT (26.12% in the blinatumomab + chemotherapy arm and 29.10% in the chemotherapy alone arm [90]) multiplied by an SMR of 2 assumed for patients post-HSCT, based on statements from the Danish clinical expert, and patients who did not receive HSCT (73.88% in the blinatumomab + chemotherapy arm and 70.9% in the chemotherapy alone arm [90]) multiplied by the base case SMR of 1.09 [91]. Finally, the modeled SMR is capped to never fall below 1 in the probabilistic sensitivity analysis (PSA), as an SMR<1 would imply cured ALL patients would have better survival than the general population, which is not plausible.

Exponential MCMs were selected for modeling both RFS and OS in both treatment arms. The selected extrapolations were based on the best statistical and visual fits together with clinical plausibility. The modeled RFS and OS curves for the base case are presented in Figure 4.

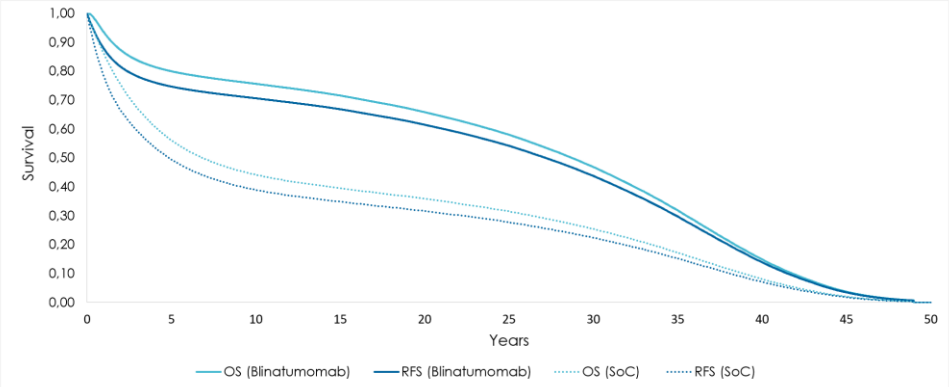

Figure 4. Extrapolated RFS (Exponential MCM for both treatment arms) and OS (Log-normal MCM for blinatumomab + chemotherapy-arm and exponential MCM for Chemotheraphy-arm) in the MRD-agnostic population

Abbreviations: MCM, Mixture cure model; MRD, Minimal residual disease; OS, Overall survival; RFS, Relapse-free survival.

The full method description and results, including the survival extrapolation models and curves together with the rationale behind the curve selection for the base case and scenarios are described in detail in Appendix D.

8.1.1.1 Extrapolation of [effect measure 1]

Assumptions associated with extrapolation of OS for the base case analysis are summarized in Table 18.

Table 18. Summary of assumptions associated with extrapolation of OS

Method/approach	Description/assumption
Data input	E1910 trial: NCT02003222 [4,22,90]
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	The analyses focused on fitting separate effect models to the data due to violation of the PH assumption.
Function with best AIC fit	Intervention: Gompertz MCM Comparator: Log-Normal MCM
Function with best BIC fit	Intervention: Gompertz MCM Comparator: Exponential MCM
Function with best visual fit	Intervention: Log-normal and exponential MCM Comparator: Exponential and Log-Normal MCM
Function with best fit according to evaluation of smoothed hazard assumptions	Most appropriate parametric distributions: generalized gamma, log-normal or log-logistic. However, the general trajectory of the hazards decreasing over time supported the use of MCMs.
Validation of selected extrapolated curves (external evidence)	The survival curves have been discussed with the Danish clinical expert, who agreed with the extrapolations chosen, however, commented on the early convergence between arms, which alternative extrapolation functions do not seem to affect markedly given their overall similarity.
Function with the best fit according to external evidence	N/A
Selected parametric function in base case analysis	Blinatumomab + SoC: Log-normal MCM SoC: Exponential MCM
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	Yes: MCMs including cure fractions were selected for modeling survival based on their clinical validity, given the potential for long-term remission and cure in newly diagnosed ALL patients, and their best visual and statistical fit to the plateaus observed in the RFS and OS

Method/approach	Description/assumption
	KM curves. For further details of calculated cured fractions, see Appendix D.

Abbreviations: ALL, acute lymphoblastic leukemia; KM, Kaplan-Meier; MCM, mixture cure model; N/A, not applicable; OS, overall survival; RFS, relapse-free survival.
Source: [4,22,90].

8.1.1.2 Extrapolation of RFS

Assumptions associated with the extrapolation of RSF for the base case analysis are summarized in Table 19.

Table 19. Summary of assumptions associated with extrapolation of RFS

Method/approach	Description/assumption
Data input	E1910 trial: NCT02003222 [4,22,90]
Model	Full parametrization
Assumption of proportional hazards between intervention and comparator	No violation of the PH assumption, however, the analyses focused on fitting separate effect models to the data.
Function with best AIC fit	Intervention: Exponential MCM Comparator: Gamma MCM
Function with best BIC fit	Intervention: Exponential MCM Comparator: Log-Normal MCM
Function with best visual fit	All models provided a good statistical and visual fit to the trial data in both arms but underestimated RFS towards the tail of the KM curve for blinatumomab + chemotherapy, while overestimating the tail of the chemotherapy KM curve.
Function with best fit according to evaluation of smoothed hazard assumptions	Most appropriate parametric distributions: generalized gamma, Weibull, Gompertz, gamma or log-logistic. However, the general trajectory of the hazards decreasing over time supported the use of MCMs.
Validation of selected extrapolated curves (external evidence)	The survival curves have been discussed with the Danish clinical expert, who agreed with the extrapolations chosen, however, commented on the early convergence between arms, which alternative extrapolation functions do not seem to affect markedly given their overall similarity.
Function with the best fit according to external evidence	N/A

Method/approach	Description/assumption
Selected parametric function in base case analysis	Blinatumomab + chemotherapy: Exponential MCM Chemotherapy: Exponential MCM
Adjustment of background mortality with data from Statistics Denmark	Yes
Adjustment for treatment switching/cross-over	N/A
Assumptions of waning effect	N/A
Assumptions of cure point	Yes: MCMs including cure fractions were selected for modeling survival in the base case based on their clinical validity, given the potential for long-term remission and cure in newly diagnosed ALL patients, and their best visual and statistical fit to the plateaus observed in the RFS and OS KM curves. For further details of calculated cured fractions, see Appendix D.

Abbreviations: KM, Kaplan-Meier; MCM, mixture cure model; N/A, not applicable; OS, overall survival; RFS, relapse-free survival; SoC, standard of care.
Source: [4,22,90].

8.1.2 Calculation of transition probabilities (N/A)

Not applicable because of MCM analysis.

Table 20. Transitions in the health economic model (N/A)

Health state (from)	Health state (to)	Description of method	Reference
Disease-free survival	Recurrence	N/A	N/A
	Death	N/A	N/A
Recurrence	Death	N/A	N/A
Health state/Transition		N/A	N/A

8.2 Presentation of efficacy data from [additional documentation] (N/A)

Not relevant.

8.3 Modelling effects of subsequent treatments

The E1910 trial includes efficacy data from potential 2L treatment. Therefore, extrapolation of the underlying OS and RFS beyond the study period already includes efficacy of subsequent treatments, including varying 2L treatment options for the two treatment arms based on differing patient population distributions. For further details of the proportion of patients receiving subsequent treatment in each treatment arm, see section 11.6.

8.4 Other assumptions regarding efficacy in the model (N/A)

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

The observed median for OS and RFS for the E1910 trial was not reached. The modeled estimates of OS and RFS for the MRD-agnostic patient population are presented in Table 21.

Table 21. Estimates in the model

	Modeled average	Modeled median	Observed median from E1910 trial
Overall survival (OS) of MRD-agnostic patients			
Blinatumomab + SoC	24.75 years	28.75 years	Not reached
SoC	15.17 years	6.86 years	Not reached
Relapse-free (RF) for MRD-agnostic patients			
Blinatumomab + SoC	23.13 years	27.18 years	Not reached
SoC	13.44 years	4.87 years	Not reached

In Table 22 an overview of the modeled average treatment length and time in the RF health state and OS are provided for the intervention and comparators.

Table 22. Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction (adjust the table according to the model)

Treatment	Treatment length, months (years)	Relapse free (RF), months (years)	Post relaps (PR), months (years)	Overall survival, months, (years)
Blinatumomab + SoC	26 (2.2)	278 (23.13)	20 (1.6)	297 (24.75)
SoC	23 (1.9)	161 (13.44)	21 (1.7)	182 (15.17)

Abbreviations: SoC, standard of care.

9. Safety

9.1 Safety data from the clinical documentation

This section presents safety data from the Step 3 safety analysis set of the E1910 trial, which includes all MRD- and MRD+ patients who received at least one dose of protocol-specified therapies. In total, the Step 3 safety analysis set included 275 randomized or registered patients (147 patients in the blinatumomab + chemotherapy, and 128 patients in the chemotherapy arm) [22]. The safety events of the Step 3 treatment period include blinatumomab cycles, consolidation cycles, allogeneic SCT or late AEs with onset within 30 days of end of step 3 treatment. The data cut-off date for the analysis was 23 June 2023 [22].

Overall, 145 (98.6%) MRD-agnostic patients in the blinatumomab + chemotherapy arm and 125 (97.7%) in the chemotherapy arm reported a step 3 treatment-emergent adverse event (TEAE, defined as any AE recorded during the step 3 treatment period including blinatumomab cycles, consolidation cycles, allogeneic SCT or late AEs with onset within 30 days of end of step 3 treatment) [22]. For an overview of the safety events of the Step 3 safety analysis set of the E1910 trial, see Table 23.

Table 23. Overview of safety events. State the time period the table covers.

	Blinatumomab + chemotherapy (n =147) [22]	**Chemotherapy (n=128)** [22]	**Difference, % (95 % CI)** [22]
Number of adverse events, n	145	125	NR
Number and proportion of patients with ≥1 adverse events, n (%)	145 (98.6%)	125 (97.7%)	0.98% (-0.0224; 0.0420)
Number of serious adverse events*, n	82	36	NR
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	82 (55.8%)	36 (28.1%)	NR
Number of CTCAE grade ≥ 3 events, n	141	125	NR
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	141 (95.9%)	125 (97.7%)	NR
Number of adverse reactions, n	NR	NR	NR
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	NR	NR	NR

	Blinatumomab + chemotherapy (n =147) [22]	Chemotherapy (n=128) [22]	Difference, % (95 % CI) [22]
Number and proportion of patients who had a dose reduction, n (%)[b]	**Blinatumomab** Cycle 1: [redacted] Cycle 2: Cycle 3: Cycle 4: **Chemo cycle 1:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: Pegaspargase: [redacted] **Chemo cycle 2:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: [redacted] **Chemo cycle 3:** Cytarabine: [redacted] Metotrexate: [redacted] Cyclophosphamide: [redacted] Daunorubicin: Dexamethasone: Vincristine: Mercaptopurine: **Chemo cycle 4:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: [redacted]	**Chemo cycle 1:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: [redacted] Pegaspargase: [redacted] **Chemo cycle 2:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: [redacted] **Chemo cycle 3:** Cytarabine: [redacted] Metotrexate: [redacted] Cyclophosphamide: [redacted] Daunorubicin: [redacted] Dexamethasone: [redacted] Vincristine: [redacted] Mercaptopurine: [redacted] **Chemo cycle 4:** Cytarabine: [redacted] Etoposide: [redacted] Metotrexate: [redacted]	NR
Number and proportion of patients who discontinue treatment regardless of reason, n (%)[c]	53 (34.9%)	58 (43.3%)	NR
Number and proportion of patients who discontinue	14 (9.2%)	19 (6.6%)	NR

	Blinatumomab + chemotherapy (n =147) [22]	Chemotherapy (n=128) [22]	Difference, % (95 % CI) [22]
treatment due to adverse events, n (%)			

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
[a] Serious adverse event (SAE) meeting requiring expedited reporting via Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP AERS, also defined as expedited adverse events).
§ CTCAE v. 5.0 must be used if available.
[b] It has not been possible to provide the total number and proportion of patients having dose reductions, but only patients who were dose reduced divided by each pharmaceutical in each cycle.
[c] The number and proportion of patients is calculated from all the Step 3 MRD-agnostic patients (n=286).
Abbreviations: CTCAE, common terminology criteria for adverse events; DCO, data cut-off; NR, not registered; SoC, standard of care.
Source: [22].

9.1.1 Serious adverse events

In the E1910 trial, serious adverse events (SAEs) are reported as TEAEs requiring expedited reporting (defined as SAEs requiring expedited reporting via Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP AERS)). Overall, adverse events requiring expedited reporting were reported for 82 (55.8%) MRD-agnostic patients in the blinatumomab + chemotherapy arm and 36 (28.1%) in the chemotherapy arm [22]. In Table 24 all SAEs with a frequency of ≥ 5% are presented. For an overview of all SAEs observed in the E1910 trial, see Appendix E.

Table 24. Serious adverse events with a frequency of ≥ 5% during the Step 3 treatment period for MRD-agnostic patients (DCO: 23 JUNE 2023)

Adverse events	Blinatumomab + chemotherapy (n =147) [22]		Chemotherapy (n=128) [22]	
	Number of patients with adverse events	Number of adverse events	Number of patients with adverse events	Number of adverse events
Aphasia, n (%)	8 (5.4%)	NR	0 (0.0%)	NR
Alanine aminotransferase increased, n (%)	9 (6.1%)	NR	0 (0.0%)	NR
Device related infection, n (%)	12 (8.2%)	NR	5 (3.9%)	NR
Febrile neutropenia, n (%)	18 (12.2%)	NR	15 (11.7%)	NR
Nausea, n (%)	6 (4.1%)	NR	0 (0.0%)	NR

Adverse events	Blinatumomab + chemotherapy (n =147) [22]		Chemotherapy (n=128) [22]	
Neutrophil count decreased, n (%)	12 (8.2%)	NR	2 (1.6%)	NR
Pyrexia	14 (9.5%)	NR	1 (0.8%)	NR
Sepsis	13 (8.8%)	NR	9 (7.0%)	NR

* A serious adverse event is an event or reaction that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect (see the ICH's complete definition).
Abbreviations: NR, not registered.
Source: [22].

9.1.2 Adverse events used in the health economic model

All Grade ≥3 treatment-emergent AEs (TEAEs) that occurred in ≥ 5% of patients in either arm of the E1910 trial for the randomized MRD-agnostic patients were included in the model. Additionally, cytokine release syndrome (CRS), while only affecting 3.6% of patients in the blinatumomab + chemotherapy arm, was also included as it is an AE specific to treatment with blinatumomab and is associated with substantial resource use. All AEs included in the CEM are presented in Table 25 below.

Table 25. Adverse events used in the health economic model for MRD-agnostic (randomized only) patients

Adverse events	Blinatumomab + chemotherapy (n = 134) n (%)	Chemotherapy (n = 134) n (%)		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Alanine aminotransferase increased, n (%)	6.72%	5.97%	[90]	≥ 5%
Anemia, n (%)	29.10%	40.30%	[90]	≥ 5%
Aphasia, n (%)	5.22%	0.00%	[90]	≥ 5%
Aspartate aminotransferase increased, n (%)	4.48%	2.24%	[90]	≥ 5%
Cytokine release syndrome, n (%)	3.73%	0.00%	[90]	AE specific to treatment with blinatumomab and is associated with

Adverse events	Blinatumomab + chemotherapy (n = 134) n (%)	Chemotherapy (n = 134) n (%)		
				substantial resource use
Device-related infection, n (%)	9.70%	5.97%	[90]	≥ 5%
Diarrhea, n (%)	5.22%	5.22%	[90]	≥ 5%
Fatigue, n (%)	4.48%	3.73%	[90]	≥ 5%
Febrile neutropenia, n (%)	22.39%	27.61%	[90]	≥ 5%
Headache, n (%)	5.97%	6.72%	[90]	≥ 5%
Hyperglycemia, n (%)	9.70%	8.96%	[90]	≥ 5%
Hypertension, n (%)	8.96%	2.99%	[90]	≥ 5%
Hypertriglyceridemia, n (%)	2.99%	4.48%	[90]	≥ 5%
Hypotension	4.48%	2.24%	[90]	≥ 5%
Lymphocyte count decreased, n (%)	29.10%	26.12%	[90]	≥ 5%
Nausea, n (%)	5.22%	1.49%	[90]	≥ 5%
Neutrophil count decreased, n (%)	84.33%	88.81%	[90]	≥ 5%
Platelet count decreased, n (%)	67.91%	75.37%	[90]	≥ 5%
Sepsis, n (%)	11.19%	9.70%	[90]	≥ 5%
White blood cell count decreased, n (%)	48.51%	60.45%	[90]	≥ 5%

Abbreviations: AE, adverse event.
Source: [90].

9.2 Safety data from external literature applied in the health economic 3model

N/A as no safety data from external literature was applied in the health economic model.

Table 26. Adverse events that appear in more than X % of patients (N/A)

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

Adverse events	Intervention (N=x)			Comparator (N=x)			Difference, % (95 % CI)	
			intervention			comparator		
Adverse event, n	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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

As the E1910 trial did not collect HRQoL data, an SLR was conducted for obtaining HRQoL data, however, no completed clinical trials evaluating HRQoL or other PROs of adult patients newly diagnosed with Ph- BCP ALL using blinatumomab solely in the 1L setting were identified. Instead, HRQoL data from the BLAST and TOWER trials were used [92,93]. More specifically, secondary analyses of the BLAST and TOWER studies were leveraged for generating HSUVs for the health economic analysis [23,94–97]. See Table 27 for an overview of the included HRQoL instruments for each of the two trials.

Unfortunately, none of the studies collected EQ-5D-5L data, which is DMCs preferred measuring instrument.

Table 27 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-3L	BLAST trial (secondary analysis) [95–97]	HSUV's for the RF and death within ≤ 6 months in the death health state
EORTC QLQ-C30	TOWER trial (secondary analysis) [23,94]	HSUV's for the PR health state

Abbreviations: EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D-3L, EuroQol 5-Dimension 3 Levels; HRQoL, health-related quality of life; HSUV, health-state utility value.
Source: [23,94–97].

As the E1910 trial did not include HRQoL data, the HRQoL data applied in this assessment is presented in section 10.3, for which reason section 10.1 and 10.2 are omitted.

10.1 Presentation of the health-related quality of life [make a subsection for each of the applied HRQoL instruments] (N/A)

Section 10.1 is N/A as the E1910 trial did not include HRQoL data. Instead, see section 10.3.

10.1.1 Study design and measuring instrument

10.1.2 Data collection

N/A as the E1910 trial did not include HRQoL data, the HRQoL data applied in this assessment is presented in section 10.3.

Table 28 Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	E.g. 100	10 (10%)	99	90 (91%)
Time point 1	100	12 (12%)	85	80 (94%)
Time point 2	100	20 (20%)	80	…
Etc.	…	…	…	…

10.1.3 HRQoL results (N/A)

N/A as the E1910 trial did not include HRQoL data, the HRQoL data applied in this assessment is presented in section 10.3.

Table 29 HRQoL [instrument 1] summary statistics (N/A)

	Intervention		Comparator		Intervention vs. comparator
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline					
Time point 1					
Time point 2					
…					
Follow-up					

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

Section 10.2 is N/A as the E1910 trial did not include HRQoL data. Instead, see section 10.3.

10.2.1 HSUV calculation

10.2.1.1 Mapping

10.2.2 Disutility calculation

10.2.3 HSUV results

N/A as the E1910 trial did not include HRQoL data, the HRQoL data applied in this assessment is presented in section 10.3.

Table 30 Overview of health state utility values [and disutilities] (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
HSUV A	0.761 [0.700-0.810]	EQ-5D-5L	DK	For example: Estimate is based on mean of both trial arms.
HSUV B	0.761 [0.700-0.810]	EQ-5D-5L	DK	For example: Estimate is based on mean of both trial arms.
…				
[Disutilities]				
…				

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

Within this section, the two studies used for obtaining HSUV's for the CEM are presented, being secondary analyses of the BLAST and TOWER trials [23,94–97]. Primarily, HRQoL data from the BLAST trial is utilized, specifically the utility for the RF health state and a disutility for death within 6 months for the death health state. Since post relapse utility assessments of HRQoL were limited and not likely representative in the BLAST trial, post-relapse utility estimates were calculated by matching TOWER (R/R)

patients to BLAST patients who were relapsed. The HRQoL data and HSUV's from each trial is presented in section 10.3.1 and 10.3.2, respectively.

10.3.1 HRQoL data and HSUVs from the BLAST trial

10.3.1.1 Study design (BLAST)

The BLAST trial (protocol MT103-203, clinicaltrials.gov identifier: NCT01207388) is an open-label, multicenter, international confirmatory, single-arm, phase 2 study which investigated the efficacy and safety of blinatumomab in adults ≥ 18 years with BCP-ALL in first or later CR with persistent or recurrent MRD-positivity ($\geq 10^{-3}$) after a minimum of 3 blocks of chemotherapy [93]. Patients received 15 µg /m^2 of blinatumomab per day by continuous IV infusion for up to 4 cycles. Each cycle comprising 4 weeks of blinatumomab infusion followed by a 2-week treatment-free period. A total of 116 patients were enrolled and received blinatumomab. Median age was 45 years (range 18–76); 15 (13%) patients were aged ≥65 years [93].

The patient population of the BLAST trial differs to some extent from the population of the E1910 trial, since the BLAST population was slightly younger and of MRD+ status only when entering the trial. The age difference between the BLAST and E1910 trial populations is assessed to be negligible for the HRQoL outcomes because blinatumomab's efficacy has also been examined in adolescents and young adults, as mentioned in section 6. The Danish clinical expert also noted that HRQoL for patients in the BLAST and E1910 trials, respectively, can be expected to be similar due to similar disease burden. Therefore, the differences between the BLAST and the E1910 trials are assumed to have minimal consequences for the transferability between the study populations.

In the BLAST trial, HRQoL was assessed for patients during and after treatment with blinatumomab through the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30) tool and the EuroQol-5 dimensions (EQ-5D) tool in Key Secondary Analyses [24,97]. Based on the guidelines from the DMC, only HRQoL based on the EQ-5D measurement is presented in this submission, see 10.3.1.2 to 10.3.1.4 below.

10.3.1.2 Data collection (BLAST)

HRQoL data was collected at baseline, at the end of each treatment cycle (i.e. on day 29 of each cycle), at End of Core Study, and at the efficacy follow-up visits 1-8 (occurring until 24 months after treatment start). The population for HRQoL analysis included [redacted] patients of the FAS with available data at relevant time points, however, only HRQoL data from pre-relapse patients was used to match the E1910 population, resulting in [redacted] patients in total for which EQ-5D-3L values were available. Patients with a non-missing 5 indicator score for at least one visit were included [95,96]. See Table 31 below for an overview of the pattern of missing data and completion.

It should be interpreted in the context that a high proportion of patients received alloSCT following treatment with blinatumomab in BLAST and that HRQoL data were not

collected after alloSCT, therefore, the sample sizes for the HRQoL assessments during later assessments were small.

Table 31. Pattern of missing data and completion

Time point	HRQoL population N	Missing N (%)	Expected to complete N	Completion N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization)	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Baseline	[redacted]	[redacted]	[redacted]	[redacted]
End of cycle 1	[redacted]	[redacted]	[redacted]	[redacted]
End of cycle 2	[redacted]	[redacted]	[redacted]	[redacted]
End of cycle 3	[redacted]	[redacted]	[redacted]	[redacted]
End of cycle 4	[redacted]	[redacted]	[redacted]	[redacted]
End of Core Study*	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 1	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 2	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 3	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 4	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 5	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 6	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 7	[redacted]	[redacted]	[redacted]	[redacted]
Efficacy follow-up 8	[redacted]	[redacted]	[redacted]	[redacted]

*30 days after end of treatment; end of the core study, a maximum of 26 weeks.
Abbreviations: HRQoL, health-related quality of life; N, number; N/A, not available.
Source: [95].

It was assumed that the missing values in the outcome were missing completely at random, i.e., the distribution of missingness in the data was independent of the outcome. Under this assumption, methods such as multilevel models were able to use the available data from incomplete observations, which was used for the analysis.

10.3.1.3 HRQoL results (BLAST)

Maximum change from baseline in EQ-5D Scales during cycle 1 to 4 were minimal across the 5 dimensions (Mobility: [redacted], Self-Care: [redacted], Usual Activities: [redacted], Pain/Discomfort: [redacted], Anxiety/Depression: [redacted]). The trend in EQ-5D scores was similar for changes from baseline at the end of the core study (Mobility: [redacted], Self-Care: [redacted], Usual Activities: [redacted], Pain/Discomfort: [redacted]), Anxiety/Depression: [redacted]) [95]. Figure 5 below displays the mean changes from baseline at the different data collection time points from the BLAST trial. In Table 32 a summary of the HRQoL results from the BLAST trial is presented.

Figure 5. Mean changes from baseline in HRQoL (EQ-5D scale) thought the different data collection time points of the BLAST trial

Abbreviations: EQ-5D, EuroQol 5-Dimension; HRQoL, health-related quality of life.
Source: [90].

Table 32 HRQoL EQ-5D scale summary statistics from the BLAST study

	Intervention		Comparator		Change in mean from baseline
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value
Baseline	[redacted]	[redacted]	N/A	N/A	[redacted]
End of cycle 1	[redacted]	[redacted]	N/A	N/A	[redacted]
End of cycle 2	[redacted]	[redacted]	N/A	N/A	[redacted]
End of cycle 3	[redacted]	[redacted]	N/A	N/A	[redacted]

	Intervention		Comparator		Change in mean from baseline
End of cycle 4	[redacted]	[redacted]	N/A	N/A	[redacted]
End of Core Study*	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 1	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 2	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 3	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 4	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 5	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 6	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 7	[redacted]	[redacted]	N/A	N/A	[redacted]
Efficacy follow-up 8	[redacted]	[redacted]	N/A	N/A	[redacted]

*30 days after end of treatment; end of the core study, a maximum of 26 weeks.

Abbreviations: EQ-5D, EuroQol 5-Dimension; HRQoL, health-related quality of life; N/A, not applicable/available.

Source: [95].

10.3.1.4 HSUV and disutility results (BLAST)

The HSUV's and disutilities based on HRQoL data from the BLAST trial are presented within this section. For an overview of all HSUVs and disutilities used in the CEM, see Table 39 in section 10.3.3.

10.3.1.4.1 HSUV and disutility calculation (BLAST)

The Danish EQ-5D-3L utility values were generated using the approach in the following reference: Generation of a Danish TTO value set for EQ-5D health states - Kim U. Wittrup-Jensen, Jørgen Lauridsen, Claire Gudex, Kjeld M. Pedersen (2009) and estimated using generalized linear model/generalizing estimating equations with EQ-5D utility values as the dependent variable and covariates for baseline utility value, MRD response, a time-dependent variable for on versus off blinatumomab treatment, and a time-dependent variable for death within 6 months [99]

To generate the Danish EQ-5D scores, the *eq5d* package was used, with version equal to '3L' and type time trade-off (TTO) and applied to the filtered long format dataset, see

Appendix F. These were firstly generated for the UK, to replicate the original analysis, then for Denmark using the available Danish option in the package [99].

As a result of the method described above and in Appendix F the parameters in Table 33 were elicited through a mixed model. A utility decrement of -0.029 was applied to patients who are receiving blinatumomab to account for any disutility due to continuous intravenous (IV) infusion. MRD response was not associated with either an increase or a decrease 0.000 in EQ-5D-3L score. The less than 6 months to death covariate had the greatest impact, being associated with a reduction of a 0.075 EQ-5D-3L score.

The utility for the relapse-free health state was calculated using the average utility for patients in first complete response (CR1) of 0.828 added to the coefficient for MRD response, 0.000. The indicator for blinatumomab treatment was changed from positive, off-treatment, to a decrement, on-treatment, meaning it was associated with an average reduction of 0.029 in EQ-5D-3L score. The terminal care utility decrement was applied in the same way, meaning that having <6 months prior to death was again associated with an average reduction of 0.075 in EQ-5D-3L score.

$$\begin{aligned} &Relapse\ free\ health\ state\ utility\ (off\ treatment) \\ &\quad = intercept + baseline\ utility * mean\ utility\ value\ at\ baseline \\ &\quad + off\ treatment + MRD\ response \\ &Relapse\ free\ health\ state\ utility\ (off\ treatment) \\ &\quad = 0.444 + 0.475 * 0.828 + 0.029 + 0.000 = 0.865 \end{aligned}$$

Table 33. Parameter estimates from regression on EQ-5D-3L utility values in BLAST

	Value	SE
Intercept	0.444	N/A
Baseline utility	0.475	N/A
Blinatumomab on-treatment utility decrement	-0.029	-0.006
MRD response versus no MRD response	0.000	N/A
Terminal care utility decrement (≤ 6 months prior to death)	-0.075	-0.015

Abbreviations: MRD, minimal residual disease; N/A, not applicable; SE, standard error.

10.3.1.4.2 HSUV results (BLAST)

The HSUV's and disutilities from the BLAST trial used in the base case of the CEM is presented in Table 34.

Table 34. Overview of health state utility values and disutilities from the BLAST trial

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Relapse-free				
Blinatumomab (off treatment)	0.865 [0.442;1]	EQ-5D	DK	Estimate is based on mean value

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Blinatumomab (on treatment)	0.836 [0.443;0.0998]	EQ-5D	DK	Estimate is based on blinatumomab off treatment subtracted by blinatumomab on treatment decrement
Chemotherapy	0.865 [0.443;1]	EQ-5D	DK	Estimate is based on mean value
Death within ≤ 6 months				
For both arms	-0.075 [0.048;-0.107]	EQ-5D	DK	Estimate is based on mean of both trial arms

Abbreviations: CI, confidence interval; DK, Denamrk; EQ-5D, EuroQol 5-Dimension; N/A, not applicable.

10.3.2 HRQoL data and HSUV's from the TOWER trial

As noted above, post-relapse utility assessments in BLAST were limited and not likely representative of utility during the entire post-relapse period. For this reason, post-relapse utility estimates were calculated by matching Ph- BCP-ALL patients from TOWER to Ph- BCP-ALL patients from BLAST who were relapsed and with no prior salvage therapy mapped to UK tariffs, that was initially conducted to support the core BLAST CEM.

10.3.2.1 Study design (TOWER)

The TOWER study is a phase 3, open-label randomized controlled trial (RCT), comparing blinatumomab with chemotherapy in adults aged ≥ 18 years with R/R Ph- BCP-ALL, using the EORTC QLQ-C30 tool for HRQoL assessment. Blinatumomab was given as a continuous IV infusion for 4 weeks followed by a 2-week treatment-free period. Overall, the treatment with blinatumomab consisted of 2 induction cycles followed by up to 3 cycles of consolidation therapy and up to 4 cycles of maintenance therapy. In cycle 1, the initial dose of blinatumomab was 9 µg per day for week 1, followed by an increased dose of 28 µg per day for the remaining 3 weeks, and for all subsequent cycles [92].

The patient population of the TOWER trial differs to some extent from the population of the E1910 trial, primarily in regard to the TOWER population being slightly younger and being pre-treated, i.e. in R/R setting, and hence the use of the elicited utility from TOWER to the post relapse health state [4,23]. However, as for the BLAST trial population discussed in section 10.3.1.1, the age difference is likewise assessed to be negligible for the HRQoL outcomes because blinatumomab's efficacy has also been examined in adolescents and young adults, as mentioned in section 6.1.3. Thus, the transferability of study populations between the TOWER and the E1910 trials are assumed to be reasonable. In the TOWER trial, analysis of HRQoL was based on the reported change in each EORTC QLQ-C30 scale scores relative to baseline [23].

10.3.2.2 Data collection (TOWER)

HRQoL data was collected on day 1 (baseline), day 8 (cycle 1 only), day 15, and day 29 of each cycle. The analysis included patients at baseline (day 1 before the start of protocol-specified therapy) and at least one postbaseline result from any EORTC QLQ-C30 multi-item or single-item scale measure. 405 patients were randomized (271 blinatumomab; 134 chemotherapy), whereof 376 patients received ≥1 dose of study drug. Of these, 342 patients (247 blinatumomab, 95 chemotherapy) had pretreatment EORTC QLQ-C30 baseline scores and ≥1 postbaseline response [23]. Scores were calculated using the sum of responses from all related questions and standardized to a range of 0 to 100. For multi-item scales with answers for at least half of the items, missing responses were estimated based on the average of completed items; if more than half of the responses were missing, the score was recorded as missing [23].

The baseline characteristics were well matched between the two treatment groups. On average, patients in the blinatumomab group answered 94.1% of the subscale measures, while those in the chemotherapy group answered 93.5% [23]. Mean pretreatment EORTC QLQ-C30 scores were similar; baseline demographics and characteristics were consistent across both groups and comparable to the intent-to-treat population [100].

In cycle 1, questionnaire completion rates among surviving patients were high, especially given their condition. The blinatumomab group had slightly higher rates, ranging from 72% to 89%, compared to 60% to 85% for the chemotherapy group [100]. Subscale completion rates were higher for global health status (GHS)/QoL in the blinatumomab group, rates of cycle 1 ranged from 94% on day 1 to 79% on day 29, and for chemotherapy, rates of cycle 1 ranged from 94% on day 1 to 70% on day 29 [23]. Most patients who discontinued chemotherapy or blinatumomab after the first cycle did so due to disease progression or to receive additional therapy/allo-HSCT. The number of patients continuing beyond the first cycle in the EORTC QLQ-C30 population was insufficient for conducting meaningful HRQL analyses [100]. For an overview of the extent of missing EORTC QLQ-C30 data and completion from the TOWER trial, see Table 35.

Table 35. Pattern of missing data and completion from the TOWER trial

Time point	HRQoL population[a] N	Missing N (%)	Expected to complete[b] N	Completion[c] N (%)
	Number of patients at randomization	Number of patients for whom data is missing (% of patients at randomization) *	Number of patients "at risk" at time point X	Number of patients who completed (% of patients expected to complete)
Blinatumomab				
Baseline	247	28 (11%)	247	219 (89%)
Cycle 1, Day 8	247	40 (15%)	244	207 (85%)
Cycle 1, Day 15	247	44 (13%)	233	203 (87%)

Time point	HRQoL population[a] N	Missing N (%)	Expected to complete[b] N	Completion[c] N (%)
Cycle 1, Day 29	247	97 (28%)	209	150 (72%)
Chemotherapy				
Baseline	95	14 (15%)	95	81 (85%)
Cycle 1, Day 8	95	23 (24%)	95	72 (76%)
Cycle 1, Day 15	95	27 (28%)	94	68 (72%)
Cycle 1, Day 29	95	43 (40%)	86	52 (60%)

[a] The HRQoL analysis set includes all subjects who had both baseline and at least one post-baseline EORTC assessment. [b] The "number of patients expected to complete" at a visit includes patients with any data or measurements for that visit, such as a vital sign or medical visit form. [c] The "number of patients who completed" refers to those who answered every PRO question. The numbers used in analysis for each subscale are higher because some patients answered portions of the PRO questionnaires.
*Estimated as the remaining proportion of patients who did not complete, indicated in the row "number of patients who completed".
Abbreviations: HRQoL, health-related quality of life; N, number.
Source: [100].

10.3.2.3 HRQoL Results (TOWER)

In the blinatumomab arm, mean changes from baseline in GHS/QoL, functional scales, and symptom scales were minimal across cycle 1. In the chemotherapy arm, a drop in EORTC QLQ-C30 scores appeared with mean changes near or exceeding the 10-point threshold for deterioration in about half of the scale scores (see figure 2 and figure 3 in the publication of HRQoL results from the TOWER trial, Topp 2018 [23]). The trends in EORTC QLQ-C30 scores for both treatment arms from cycle 1 were similar in cycle 2, despite fewer patients remaining in the chemotherapy group (n=27 on day 1; n=15 on day 29) [23].
The time to clinically meaningful deterioration in HRQoL or death was extended for patients treated with blinatumomab compared to those receiving chemotherapy, across all EORTC QLQ-C30 scales. Specifically, a longer time to deterioration (TTD) in HRQoL or death was observed for patients treated with blinatumomab as opposed to chemotherapy (HR < 1.0; P < 0.05) for all functional scales (with the exception of social functioning) and for all symptom scales (excluding insomnia and financial difficulties) [23]. The between-group treatment effect for the change from baseline in cycle 1, as determined by the mixed model for repeated measures (MMRM), was consistent with the descriptive analyses. The results showed P < 0.05 favoring blinatumomab for all EORTC QLQ-C30 subscales, except for financial difficulties where no difference was observed [23]. In Table 36, a summary of the HRQoL results from the TOWER trial is presented.

Table 36. HRQoL EORTC QLQ-C30 summary statistics from the TOWER study

	Intervention (blinatumomab + chemotherapy)		Comparator (chemotherapy)		Intervention vs. comparator*
	N	Mean (SE)	N	Mean (SE)	Difference (95% CI) p-value

	Intervention (blinatumomab + chemotherapy)		Comparator (chemotherapy)		Intervention vs. comparator*
Baseline	247	N/A	95	N/A	N/A
GHS/QoL					
Cycle 1, Day 8	244	N/A	95	N/A	6.26 (N/A), p < 0.01
Cycle 1, Day 15	233	N/A	94	N/A	8.68 (N/A), p < 0.01 HR:
Cycle 1, Day 29	209	N/A	86	N/A	7.05 (N/A), p < 0.01

*Repeated measure analyses: Least Square mean estimation for EORTC QLQ-C30 GHS/QoL measure.
Abbreviations: CI, Confidence interval; GHS/QoL, Global Health Status/Quality of Life; N/A, not available; SE, Standard error.
Source: [23].

10.3.2.4 HSUV and disutility results (TOWER)

The relapsed BLAST patients were matched with 80 TOWER patients in the SoC arm who were not refractory at baseline. TOWER patients with no prior salvage therapy at baseline (S0) and relapsed BLAST patients with one prior remission at baseline (CR1) were considered similar, as were TOWER patients with prior salvage therapy at baseline (S1) and relapsed BLAST patients with two or more prior remissions at baseline (CR2) were considered similar. Of the 113 BLAST patients in primary efficacy FAS, 73 patients had one remission at baseline (CR1) while 40 had two or more remission at baseline (CR2), and 34 in CR1 and 30 in CR2 relapsed. Of the 34 relapsed patients in CR1, 13 patients relapsed more than 12 months after therapy initiation. Since TOWER inclusion criteria specify that patients with no prior salvage therapy must have relapsed within 12 months of remission, these 13 BLAST patients are not represented in TOWER study and excluded from the matching. See Appendix F.2 for the patient characteristics among BLAST and TOWER patients.

The 80 TOWER SOC patients and 51 relapsed BLAST patients were matched based on their health state: i.e. CR1/CR2 (BLAST) or S0/S1 (TOWER), age, and their receipt of HSCT (at baseline among TOWER patients and prior to relapse among BLAST patients).

Two logistic regression models were estimated among the above 51 BLAST patients (21 in CR1 and 30 in CR2) and 80 TOWER SOC relapsed patients with either IPTW (Inverse Probability of Treatment Weighting), ATT (Average Treatment Effect on the treated) or ATE (Average Treatment Effect) weights applied to BLAST CR1 patients to achieve balance with the historical cohort study patients. Using the estimated predicted probability of being in BLAST (vs TOWER), ATT weights were calculated for 80 TOWER patients. There were total of 233 utility assessments available among 80 TOWER SOC patients and their ATT weighted means are reported in Table 37.

Table 37. Mean mapped-EQ5D utility (UK tariffs) among TOWER SOC relapsed patients with ATT weight adjustment (vs relapsed BLAST patients)

IPTW weight: BLAST CR1 vs HC	S0/S1	N. of utility assessments	Mean	SD	95% CI	
					Lower	Upper
ATT	S0	134	0.692	0.021	0.649	0.734
	S1	99	0.613	0.029	0.556	0.670
	S0/S1	233	0.653	0.018	0.618	0.688
ATE	S0	134	0.697	0.021	0.656	0.739
	S1	99	0.613	0.029	0.556	0.670
	S0/S1	233	0.652	0.017	0.618	0.687

10.3.2.4.1 HSUV calculation and mapping (TOWER)

Utility values were mapped from EORTC QLQ-C30 to EQ-5D-3L using the algorithm from Longworth et al (2013) which provided the HSUV (with UK tariffs) used for the post relapse health state in this assessment [101]. Thereby, the HSUV for PR applies a UK tariff.

10.3.2.4.2 HSUV results (TOWER)

A mean EQ-5D-3L utility of 0.692 for the PR health state was estimated and used in this CEM, see Table 38.

Table 38. Overview of health state utility values from the TOWER trial

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Post-relapse (PR)	0.692 [N/A]	EQ-5D mapped from the EORTC QLQ-C30	UK	Estimate is based on mean of both trial arms.

Abbreviations: CI, confidence interval; DK, Denmark; EQ-5D, EuroQol 5-Dimension; N/A, not applicable.

For an overview of all HSUVs and disutilities used in the CEM, see Table 39 in section 10.3.3.

10.3.3 All HSUVs and disutilities used in the health economic model

All utilities and disutilities from the BLAST and TOWER trials were validated by the Danish clinical expert, who confirmed these utilities being reasonably to represent the HRQoL of the modeled population. In Table 39 below, an overview of all HSUV's and disutilities used in the base case of the CEM is presented. The modeled relapse-free utility was capped at the age matched general population utility and the post-relapse utility was capped at the modeled relapse-free utility. This ensures that the modeled utilities retain face-validity when varied during the PSA and one-way sensitivity analyses (OWSA). Finally, after three years, patients were considered clinically cured. These patients are

unlikely to have a negative utility impact from ALL. Thus, patients remaining relapse-free after three years were assumed to have the same utility as the age-matched general population, described in section 10.3.3.1 below.

Table 39. Overview of all health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Relapse-free (RF)				
Blinatumomab (off-treatment)	0.865 [0.442;1]	EQ-5D	DK	Estimate is based on mean value
Blinatumomab (on-treatment)	0.836 [0.443;0.998]	EQ-5D	DK	Estimate is based on blinatumomab off treatment subtracted by blinatumomab on treatment decrement
Chemotherapy	0.865 [0.442;1]	EQ-5D	DK	Estimate is based on mean value
Relapse free (RF), cured patients				
	Age-matched general population utility (see section 10.3.3.1 below)			
Post relapse (PR)				
For both arms	0.692 [N/A]	EQ-5D mapped from the EORTC QLQ-C30	UK	Estimate is based on mean of both trial arms
Death within ≤ 6 months				
For both arms	-0.075 [0.015]	EQ-5D	DK	Estimate is based on mean of both trial arms

Abbreviations: CI, confidence interval; DK, Denmark; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EQ-5D, EuroQol 5-Dimension; N/A, not available.

N/A as HSUV were available from the BLAST and TOWER trials.

Table 40. Overview of literature-based health state utility values (N/A)

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV A				
Study 1	0.761 [0.700-0.810]	EQ-5D-5L	DK	EQ-5D-5L data was collected in X trial. Estimate is based on mean of both trial arms.
Study 2				
Study 3				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUV B				
…				
[Disutility A]				
…				

10.3.3.1 General population utility

In accordance with the method guide from the DMC, the HSUVs were matched to those of the general population by age and sex. The HSUVs were adjusted to ensure that the HRQoL of the patient cohort at any given age does not exceed the HRQoL of the general Danish background population.

As outlined in section 4.1, the share of patients who are considered cured and therefore no longer experiencing reduced HRQoL due to ALL disease switch to HRQoL of the age- and sex- matched general population, and this is assumed to be starting after 4 years. While no published literature on long-term utility decrements for ALL patients exists in the literature, the model includes the assumption of a long-term disutility due to the residual effects of ALL of 97.8% multiplied by the age-matched general population utility, which was validated by the Danish clinical expert. However, no disutility for the cured patients may be considered just as valid, for which reason a scenario is applied excluding the disutility for cured patients. Disutilities due to adverse events

Disutilities associated with AEs were incorporated into the CEM by first multiplying the disutility decrement for each AE with its respective estimated duration and the proportion of patients who had experienced these AEs (as presented in Table 25 in section 9.1), and thereafter summed across all AEs to determine a one-off value that was applied in the first cycle of the model. Utility decrements for the different AEs were derived from the literature and previous technology assessments (TAs) and are listed in Table 41 with the corresponding duration of each AE occurrence.

Table 41. Utility decrements associated with adverse events included in the model

Adverse event	Utility (SE)	Duration (days)	Source
Alanine aminotransferase increased	-0.000 (0.000)	20.0	Utility: Assumed no disutility for abnormal lab tests Duration: TA893 [102]
Anemia	-0.120 (0.020)	14.9	Utility and duration: Swinburn 2010 [103]
Aphasia	-0.000 (0.000)	0.0	Utility and duration: Assumption

Aspartate aminotransferase increased	-0.000 (0.000)	20.0	Utility and duration: Assumed no disutility for abnormal lab tests
Cytokine release syndrome	-0.230 (0.023)	4.3	Utility and duration: Howell et al. 2022 [104]
Device-related infection	-0.090 (0.020)	6.2	Utility and duration: Assumed same as febrile neutropenia
Diarrhea	-0.050 (0.005)	7.0	Utility and duration: Nafees et al. 2008 [105]
Fatigue	-0.115 (0.012)	7.0	Utility: Lloyd et al. 2006 [106]. Duration: TA642 [107]
Febrile neutropenia	-0.090 (0.020)	6.2	Utility and duration: Nafees et al. 2008 [105]
Headache	-0.027 (0.003)	2.0	Utility and duration: Sullivan 2011 [108]
Hyperglycemia	-0.062 (0.010)	7.5	Utility and duration: Sullivan 2011 [108]
Hypertension	-0.070 (0.010)	4.0	Utility: Assumed same as hypotension. Duration: TA893 [102]
Hypertriglyceridemia	-0.000 (0.000)	0.0	Utility and duration: Assumed no disutility for abnormal lab tests
Hypotension	-0.070 (0.010)	2.3	Utility and duration: TA520 [109]
Nausea	-0.050 (0.010)	7.0	Utility and duration: Assumed same as diarrhea
Neutrophil count decreased	-0.050 (0.010)	9.8	Utility and duration: Assumed same as white blood cell count decreased
Platelet count decreased	-0.050 (0.010)	11.9	Utility and duration: TA653 [110]
Sepsis	-0.200 (0.040)	15.1	Utility and duration: Tolley 2013 [111]
White blood cell count decreased	-0.050 (0.010)	16.9	Utility and duration: TA520 [109]

Sources: [103–106,108–112] and the Danish clinical expert.

10.3.3.2 Disutilities due to HSCT

Patients who had received HSCT are assumed to incur a utility decrement to reflect known AEs or complications associated with HSCT. A utility decrement of -0.57 was applied for one year, as informed by Sung et al. and in line with previous NICE submissions [113–115]. The HSCT-related disutility is applied as a one-off decrement in the first cycle of the model and applied to the proportion of patients who received HSCT pre-relapse. For patients who received HSCT after relapse, the HSCT-related disutility is applied as a one-off decrement at the time of relapse up to the cure timepoint of three years.

11. Resource use and associated costs

The following costs are included in the model:

- Drug acquisition and administration costs for BLINCYTO® (as well as pre-medication with dexamethasone) and chemotherapy together with 1L HSCT for patients stratified by intent to receive HSCT at the time of randomization by their physician
- Drug acquisition and administration costs for maintenance therapy and other subsequent therapy, including post relapse HSCT (where 2L treatment serves as bridging therapy until the receipt of HSCT)
- Disease management costs
- Costs related to adverse events
- Cost related to patient time and transportation
- Terminal care costs

Patients that remain relapse free for 4 years are assumed not to be at risk for any ALL-related costs in the health economic model (i.e. subsequent therapy and terminal care costs as all other costs are included in the first three years of the model).

11.1 Medicines - intervention and comparator

Treatment duration and dosage regimen:

In the health economic model, the treatment duration of the 1L treatment includes consolidation and maintenance treatment and spans a maximum of 2.5 years.

In the E1910 trial, the consolidation therapy duration for chemotherapy regimen covers approximately 18 weeks of the total treatment duration (28 days in cycle 1,2 and 4 + 42 days in cycle 3). The treatment duration of the consolidation therapy with blinatumomab + chemotherapy is extended, as blinatumomab is first administered for two consecutive cycles of continuous IV infusion over 28 days followed by an infusion-free interval of 14 days between the first two blinatumomab cycles. After this, patients continue with consolidation chemotherapy alternating with an additional two cycles of blinatumomab, thus resulting in a total treatment duration of maximum 36 weeks. However as elaborated in section 3.4.2, the extended consolidation phase did not extend the overall duration of treatment within the blinatumomab + chemotherapy arm, as the duration of the subsequent maintenance therapy remains to continue for up to 2.5 years from the start of the intensification phase. Therefore, the overall duration of treatment is on average identical for the two treatment arms [4,5]. The consolidation therapy duration as well as dosage regimen used is from the E1910 trial [4]. In Table 42, the dose regimen for all medicines included in the CEM in relation to the consolidation chemotherapy regimen are summarized.

Prior to each blinatumomab treatment cycle patients receive 20 mg dexamethasone (IV) to prevent acute reaction to blinatumomab [76].

Rituximab 375 mg/m2 IV on day 5 if CD20-positive was optional in each chemo-cycle in the E1910 trial and is therefore not included in the health economic model. If it were to be included in the health economic model, this would yield a very minor impact on the result, because it would be added to all chemotherapy cycles in both treatment arms for a proportion of CD-20-positive patients. For all the MRD-agnostic patients, 27.6% received rituximab treatment in the blinatumomab + chemotherapy arm and 29.1% in the chemotherapy arm.

Table 42. Medicines used in the model

Medicine [4]	**Dose** [4]	**RDI** [Assumption in base case]	**Frequency** [4]	**Vial sharing** [22]
Pre-medication, Dexamethasone	20 mg	100%	Within one hour prior to start of all four cycles of blinatumomab treatment	No
BLINCYTO® (blinatumomab)	28 µg	100%	Two cycles of blinatumomab 28 µg/day for 4 weeks with a 2-week interval between the two first cycles, followed by 3 cycles of chemotherapy, 1 additional cycle of blinatumomab, 1 cycle chemotherapy and finally 1 cycle of blinatumomab	No
Cytarabine	75 mg/m^2	Blin+SoC: 100% SoC: 100%	Once daily on days 1-5 in cycle 1, 2 and 4 + once daily on days 30-33 and 37-40 in cycle 3	No
Etoposide	100 mg/m^2	Blin+SoC: 100% SoC: 100%	Once daily on days 1-5 in cycle 1, 2, and 4	No
Methotrexate	12.5 mg	Blin+SoC: 100% SoC: 100%	Once on day 1 in cycle 1, 2 and 4 and once on day 2 in cycle 3	No
Pegaspargase	2000 IU/m^2 (1000 IU/m2 if ≥55 years)	Blin+SoC: 100% SoC: 100%	Once on day 5 in cycle 1	No
Daunorubicin	25 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on days 1, 8, 15 and 22 in cycle 3	No
Vincristine	1.4 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on days 1, 8, 15 and 22 in cycle 3	No
Dexamethasone	10 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on days 1-7 and 15-21 (with a maximum dose on 20 mg) in cycle 3	N/A

Medicine [4]	Dose [4]	RDI [Assumption in base case]	Frequency [4]	Vial sharing [22]
Cyclophosphamide	650 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on day 29 in cycle 3	No
Mercaptopurine	60 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on days 29-42 in cycle 3	N/A

[a] Median relative dose intensity retrieved from the clinical study report of the E1910 trial [22].
Abbreviations: mg, milligram; N/A, not applicable; RDI, relative dose intensity; SoC, standard of care.
Source: [4,22].

Not all patients in the E1910 trial received all 4 cycles of BLINCYTO® and all 4 cycles of consolidation chemotherapy treatment. The drug acquisition and administration costs were therefore corrected by the observed proportion of patients starting each cycle of treatment in the E1910 trial, as shown in Table 43 below. This observed treatment already accounts for patients discontinuing due to relapse and therefore is modeled independently from RFS. Furthermore, the share of treatment use is capped, so that the modeled treatment use can never exceed the treatment use of the previous cycle.

Table 43. Proportion of randomized only patients receiving each cycle of treatment in the blinatumomab + chemotherapy and chemotherapy arm, respectively, as observed in the E1910 trial

BLINCYTO® + chemotherapy [90]		Chemotherapy [90]	
Consolidation cycle	% treatment received	Consolidation cycle	% treatment received
Cycle 1 – BLINCYTO®	[redacted]	Cycle 1 - chemotherapy	[redacted]
Cycle 2 – BLINCYTO®	[redacted]	Cycle 2 - chemotherapy	[redacted]
Cycle 3 - chemotherapy	[redacted]	Cycle 3 - chemotherapy	[redacted]
Cycle 4 - chemotherapy	[redacted]	Cycle 4 - chemotherapy	[redacted]
Cycle 5 - chemotherapy	[redacted]		
Cycle 6 – BLINCYTO®	[redacted]		
Cycle 7 - chemotherapy	[redacted]		
Cycle 8 – BLINCYTO®	[redacted]		

Medicine waste:

The model includes the option to include and exclude drug wastage. In the modeled base case, drug wastage is assumed for drugs administered intravenously, meaning that a full vial would be used when opened, without considering vial sharing. In practice it is expected that vial sharing will be applied whenever possible. For drugs with either body surface area (BSA-) or weight-based dosing, the method of moments technique was used to estimate the average number of vials required per dose. This method assumes a distribution rather than a point estimate of the BSA or weight of the patient population. Using the point estimate and variation of BSA and weight in the E1910 population, normal and log-normal distributions, respectively, were fitted to calculate the distribution of doses.

Packages and costs

The unit costs have been sourced from Medicinpriser.dk on the 22nd of November 2024[2] for and are reported in the pharmacy purchase price [79,116]. For medicines where more packages are available, these are all included in the model to calculate the average costs per mg or µg of each medicine to be used if the option of including drug wastage is applied. For the base case, the costs of the package resulting in the lowest cost per vial is applied. In the E1910 trial, patients could receive various types of dose modifications of blinatumomab, resulting in lower observed cumulative doses (due to factors such as [redacted] [22]. The model includes an option to adjust blinatumomab treatment costs based on the observed cumulative dose from E1910. This approach is employed because these dose modifications are likely to reduce the number of vials actually received by patients. To account for full wastage, the model conservatively assumes 1 full vial of blinatumomab per administration in the base case. However, the cumulative dose scenario is considered to be more aligned with real-world blinatumomab dosing and is therefore considered as a scenario.

11.2 Medicines– co-administration

Patients who were randomized to the blinatumomab + chemotherapy arm in the E1910 trial could receive HSCT after two cycles of blinatumomab, while those randomized to the chemotherapy arm could receive HSCT at any time point during consolidation chemotherapy. In the MRD-agnostic randomized only population of the E1910 trial, 26.12% in the blinatumomab + chemotherapy arm, and 29.10% in the chemotherapy arm, received 1L HSCT including patients who received HSCT on- and off-protocol, which captures patients receiving HSCT even if they discontinued their on-protocol treatment [90]. The Danish clinical expert stated that the proportion of patients receiving 1L HSCT may be higher in the Danish clinical practice compared to what was observed in the E1910 trial, with approximately up to ⅔ of patients undergoing HSCT, however, as no data are available for the Danish patient population in this regard, the proportions from the E1910 trial were used in the health economic model.

The cost of 1L HSCT was applied as a one-off cost at the start of the model. The cost of HSCT includes the cost of a HSCT procedure derived from the Danish diagnosis-related group (DRG) tariffs of 2025, being “Allogeneic stem cell transplantation” (26MP22, trim point 59 days) with a total cost of DKK 1,035,036 [117]. Stem cell harvesting was originally assumed to be a part of this DRG tariff, however, a previous approved DMC application within ALL using the 26MP22 tariff for autologous HSCT adds additional costs for the stem cell harvesting procedure [73]. Therefore, an additional tariff for stem cell harvesting before allo-HSCT of DKK 26,206 was applied, sourced from the tariff catalogue of Rigshospitalet (2016) [118]. Within the CEM, the costs of stem cell harvesting can be changed and is also a part of sensitivity analysis. Costs of follow-up visits were derived

[2] The price for BLINCYTO® has been updated the 29th of august 2025.

from the previous approved DMC application within ALL as well [73]. See Table 44 for an overview of costs associated with HSCT.

Table 44. HSCT cost

Component		Cost [DKK]	Source
Stem cell harvesting		26,206	Tariff catalogue of Rigshospitalet, 2016: "4210429 TILLÆG ALLOGEN KMT – L" [118]
Allogeneic HSCT procedure		1,035,036	DRG tariff "Allogeneic stem cell transplantation" (26MP22) [117]
HSCT follow-up	Year 1	414,089	Estimate from previous approved DMC application within ALL [73]
	Year 2	121,679	Estimate from previous approved DMC application within ALL [73]

Abbreviations: ALL, acute lymphoblastic leukemia; DKK, Danish krone; HSCT, hematopoietic stem cell transplantation.
Source: [73,117,118].

11.3 Administration costs

Blinatumomab is administered continuously via an IV pump for 4 weeks for up to 4 cycles [1,4]. In line with the E1910 protocol as well as the SmPC, it was assumed that blinatumomab would be administered on an inpatient basis for 3 days during the first cycle and for the first two days of every subsequent cycle [1,76]. The administration cost of the inpatient IV pump was estimated to be DKK 51,697 derived from the DRG tariffs of 2025, reflecting the DRG tariff of 17MA01 covering both "Medicine administration via pump" (BWAA80) and "Medication administration via IV through a permanent venous catheter" (BWAA61) for the diagnosis of "Acute lymphoblastic leukemia" (DC910) with a trim point of 11 days [117,119]. Consequently, the inpatients cost of the IV pump of DKK 51,697 is the same for the respective 3 days in cycle 1 and the two days in cycles 2, 3, and 4 due to the trim point being 11 days for this specific tariff.

During the remaining days of each cycle, all patients would necessitate bag changes. The Danish clinical expert stated that the different regions of Denmark have differing frequencies of bag changes. Therefore, a frequency of changing bag every 4 days was used as described per the SmPC [1]. As validated by the Danish clinical expert the bag changes are facilitated in the outpatient setting, assumed with a duration of approximately 3 hours. The cost of an outpatient visit (and thus the costs of each bag change) was estimated to be DKK 2,136 derived from the DRG tariff of 2025, reflecting the DRG tariff of 17MA01 covering "Refilling of pump for medication administration" (ZZ4071A) and for the diagnosis of "Acute lymphoblastic leukemia" (DC910) with a trim point of 1 day [117,119].

The consolidation chemotherapy cycles were assumed to require hospitalization for the first 2 days of every cycle. Following the inpatient stay, all remaining IV chemotherapy drugs were assumed to be administered on an outpatient basis, which is in line with the guidelines of the ALLTogether protocol used in DK [51]. The administration cost of the 2 days inpatient IV and IT chemotherapy was estimated to be DKK 51,697 derived from the

DRG tariffs of 2025, reflecting the DRG tariff of 17MA01 covering both "Medicine administration via IV" (BWAA60) and "Medicine administration via IT" (BWAA70) for the diagnosis of "Acute lymphoblastic leukemia" (DC910) with a trim point of 11 days [117,119]. Administration costs for oral medications were assumed to be zero.

Administration of chemotherapy in the outpatient setting only consisted of IV administration, as the IT administration was completed during the inpatient stay. The outpatient IV administration cost was estimated to be DKK 2,136 derived from the DRG tariffs of 2025, reflecting the DRG tariff of 17MA98 covering both "Medicine administration via IV" (BWAA60) and "Medicine administration via IT" (BWAA70) for the diagnosis of "Acute lymphoblastic leukemia" (DC910) with a trim point of 1 day [117,119]. Table 45 provides an overview of the administration costs related to the treatments

Table 45 Administration costs used in the model

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
Blinatumomab				
Inpatient IV infusion pump	First 3 days in cycle 1, followed by first 2 days in cycle 2,3, and 4. (The cost is the same irrespective of the inpatient stay being 3 or 2 days due to the trim point of 11 days)	51,697	17MA01	[117,120]
Outpatient bag change	6 times within each of the 4 cycles *	2,136	17MA98	[117,120]
SoC (chemotherapy regimen)				
Inpatient IV and IT	First 2 days of every of the 4 cycles (The cost is the same irrespective of the inpatient stay being 3 or 2 days due to the trim point of 11 days)	51,697	17MA01	[117,120]
PO	First 2 days of every of the 4 cycles	0	N/A	Assumption
Outpatient IV	3 times within cycle 1, 2, and 4, together with 12 times in cycle 3	2,136	17MA98	[117,120]

*The first bag is changed at the first inpatient stay. Abbreviations: DKK, Danish krone; DRG, diagnosis-related group; IT, intrathecal; IV, intravenous; N/A, not applicable; PO, per oral; SoC, standard of care

11.4 Disease management costs

The costs related to disease management are listed in Table 46. It is assumed that the frequencies of the used health resources are dependent on the health state that the patients are in. The applied frequencies are partially based on inputs from the clinical expert and the Danish Medicines Councils assessment of brexucabtagene autoleucel to treatment of ALL. According to the clinical expert, in Danish clinical practice, patients

who are considered cured—defined as being relapse-free for three years or more—are not expected to incur any further disease management costs, since at this point, their course of illness is regarded as complete.

Table 46 Disease management costs used in the model

Activity	Frequency pr. week	Unit cost [DKK]	DRG code	Reference
Frequencies in the RF health state				
Outpatient visit (Hematologist)	0-12 months: 0,77 13-24 months: 0,41 25+ months (not cured): 0,13	2,136	17MA98 MDC17 1-dagsgruppe pat. Mindst 7 år	DRG 2025
CSF	0-12 months: 0,12 13+ months: 0	5,879	09PR04 Biopsi og væskeudsugning overfladisk	DRG 2025
Bone marrow aspirate/biopsy	0-12 months: 0,08 13+ months: 0	16,156	17PR01 Udtagning af knoglemarv til diagnostisk undersøgelse	DRG 2025
Echocardiogram	0-12 months: 0,02 13+ months: 0	3,850	05PR03 Kardiologisk undersøgelse, kompliceret	DRG 2025
Electrocardiagram	0-12 months: 0,06 13+ months: 0	2,111	05PR04 Kardiologisk undersøgelse, udvidet	DRG 2025
Frequencies in the PR health state				
Outpatient visit(Hematologist)	0,77	2,136	17MA98 MDC17 1-dagsgruppe pat. Mindst 7 år	DRG 2025
CSF	0,23	5,879	09PR04 Biopsi og væskeudsugning overfladisk	DRG 2025
Bone marrow aspirate/biopsy	0,08	16,156	17PR01 Udtagning af knoglemarv til	DRG 2025

Activity	Frequency pr. week	Unit cost [DKK]	DRG code	Reference
			diagnostisk undersøgelse	
Echocardiogram	0,02	3,850	05PR03 Kardiologisk undersøgelse, kompliceret	DRG 2025
Electrocardiagram	0,06	2,111	05PR04 Kardiologisk undersøgelse, udvidet	DRG 2025

11.5 Costs associated with management of adverse events

The model includes all AEs of Grade 3 and above that occurred in ≥ 5% of patients in either treatment arm in the E1910 trial, see section 9.1. The cost of AE management was calculated by multiplying the frequency at which each AE occurred by treatment arm (presented in 9.1, Table 25) with the unit cost for the management of the AE, and thereafter applied as a one-off cost at the start of the model. Unit costs were sourced from Danish DRG tariffs of 2025 and are shown in Table 47 [117,119]. Specifically for the AE "Cytokine release syndrome", costs were based on estimates from a previous DMC assessment of tisagenlecleucel [73]. A one-time cost for treatment with tocilizumab was added to the cost of managing CRS. The cost of tocilizumn was sourced from Medicinpriser.dk [116].

Table 47 Cost associated with management of adverse events

	DRG-code	Unit cost/DRG tariff [DKK]
Alanine aminotransferase increased	17MA98 [1-dagsgruppe, pat. mindst 7 år]. Trim point: 1 day [117,119]	2,136
Anemia	16PR02 [Transfusion af blod, øvrig]. Trim point: 1 day [117,119]	4,221
Aphasia	01MA15 [Andre specifikke sygdomme i nervesystemet]. Trim point 9 days [117,119]	40,649
Aspartate aminotransferase increased	17MA98 [1-dagsgruppe, pat. mindst 7 år]. Trim point: 1 day [117,119]	2,136
Cytokine release syndrome	Estimate from previous DMC assessment of tisagenlecleucel [73]	122,022
Device related infection	09MA04 [Infektioner i hud og underhud, pat mindst 18 år]. Trim point 9 days [117,119]	35,738

	DRG-code	Unit cost/DRG tariff [DKK]
Diarrhea	06MA11 [Malabsorption og betændelse i spiserør, mave og tarm, pat. mindst 18 år, u. kompl. bidiag.]. Trim point 1 day [117,119]	4,977
Fatigue	23MA05 [Anden kontaktårsag til sundhedsvæsenet]. Trim point 4 days [117,119]	6,902
Febrile neutropenia	16MA03 [Granulo- og trombocytopeni]. Trim point 10 days [117,119]	37,482
Headache	17MA98 [1-dagsgruppe, pat. mindst 7 år]. Trim point: 1 day [117,119]	2,136
Hyperglycemia	10MA04 [Ernærings- og diverse metaboliske sygdomme]. Trim point 5 days [117,119]	26,972
Hypertension	05MA11 [Hypertension]. Trim point 4 days [117,119]	18,807
Hypertriglyceridemia	Assumed to be the same as "Hyperglycemia"	26,972
Hypotension	05MA08 [Andre hjertesygdomme]. Trim point 1 day [117,119]	2,140
Lymphocyte count decreased	16MA10 [Øvrige sygdomme i blod og bloddannende organer]. Trim point 6 days [117,119]	28,342
Nausea	23MA05 [Anden kontaktårsag til sundhedsvæsenet]. Trim point 4 days [117,119]	6,902
Neutrophil count decreased	16MA10 [Øvrige sygdomme i blod og bloddannende organer]. Trim point 6 days [117,119]	28,342
Platelet count decreased	16MA10 [Øvrige sygdomme i blod og bloddannende organer]. Trim point 6 days [117,119]	28,342
Sepsis	18MA01 [Sepsis]. Trim point 13 days [117,119]	53,570
White blood cell count decreased	16MA10 [Øvrige sygdomme i blod og bloddannende organer]. Trim point 6 days [117,119]	28,342

Abbreviations: DKK, Danish krone; DRG, diagnosis-related group.
Source: [73,117,119].

11.6 Subsequent treatment costs

For subsequent treatment it is assumed that those who were alive and relapse free after 4 years are cured, as explained in section 4.1 and 8.1. Cured patients will not receive any treatment and therefore do not incur costs related to subsequent treatment.

11.6.1 Maintenance therapy

In the E1910 trial, upon completion of consolidation therapy, patients in both treatment arms were assumed to go on to receive maintenance therapy for up to 2.5 years (initiating from start of intensification) or until relapse or death. In the blinatumomab + chemotherapy and in the chemotherapy-arm alone 73 and 71 MRD-agnostic randomized patients only initiated maintenance therapy after consolidation therapy, respectively. The dosing and administration schedule of maintenance chemotherapy used in the model follows the E1910 trial protocol [4]. See Table 48 for an overview of the dosage regimen used in the model.

Table 48 Medicines of subsequent treatments

Medicine	Dose	RDI[a] [Assumption]	Frequency	Vial sharing
Mercaptopurine [4]	75 mg/m^2	Blin+SoC: 100% SoC: 100%	Once daily	N/A
Methotrexate (IT) [4]	12.5 mg	Blin+SoC: 100% SoC: 100%	Once on day 1 every 3 months	No
Methotrexate (PO) [4]	20 mg/m^2		Once weekly	N/A
Vincristine [4]	1.4 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on day 1 every 3 months	No
Prednisolone [4]	60 mg/m^2	Blin+SoC: 100% SoC: 100%	Once on days 1-5, every 3 months	N/A

[a] Median relative dose intensity retrieved from the clinical study report of the E1910 trial [22].
Abbreviations: IT, intrathecal; mg, milligram; N/A, not applicable; RDI, relative dose intensity; PO, per oral; SoC, standard of care.
Source: [4].

Maintenance chemotherapy is assumed to be administered exclusively in the outpatient setting, validated by the Danish clinical expert. The cost of the IV and IT administration was estimated to be DKK 2,136 for each outpatient visit derived from the DRG tariffs of 2025, reflecting the DRG tariff of 17MA98 covering both “Medicine administration via IV” (BWAA60) and “Medicine administration via IT” (BWAA70) for the diagnosis of “Acute lymphoblastic leukemia” (DC910) with a trim point of 1 day [119]. Administration costs for oral medications were assumed to be zero.

All drug costs were sourced from Medicinpriser.dk [116]. The method of moments was also applied to determine the dose of all BSA or weight-based drugs. The total drug and administration costs for maintenance treatment were applied as an average weekly cost in the model.

11.6.2 Other subsequent treatments (2L treatment upon relapse)

Relapsed patients are eligible to receive subsequent treatment. The type of treatment and the proportion of patients receiving these therapies (except for HSCT. See subsection 11.6.2.5 for description of HSCT in 2L instead) are presented in Table 49. The subsequent treatments and the proportion of patients receiving these therapies are based on feedback from the Danish clinical expert.

In the health economic analysis, these subsequent treatment costs are applied as a one-off cost at the time of relapse to patients who relapse at each model cycle. To account for patients who die without relapsing, the model also includes the option to adjust all subsequent treatment costs and HSCT costs and disutility to apply only to patients who relapse, excluding patients who die without having relapsed. These rates are calculated by dividing the RF death events per arm by the total RF events.

Table 49. Proportion of patients receiving subsequent treatment*

Subsequent treatment	Blinatumomab + chemotherapy	Chemotherapy
Blinatumomab	5%**	42%
Inotuzumab ozogamicin	~45%	50%
FLAG-IDA	~45%	8%
CAR-T	5%	0%
No active treatment	0%	0%

*Post relapse HSCT not included, however, is described in subsection 11.6.2.5.
** For patients experiencing a late relapse and who are still CD19+, blinatumomab can be administered again.
Abbreviations: CAR-T, chimeric antigen receptor cell therapy; FLAG-IDA, fludarabine, cytarabine, idarubicin, and filgrastim; SoC, standard of care.
Source: based on feedback from the Danish clinical expert.

All drug costs were sourced from Medicinpriser.dk [116]. The method of moments was also applied to determine the dose of all BSA or weight-based drugs. See Table 51 and Table 52 for an overview of the dosage regimen and costs used in the model to reflect subsequent treatment.

11.6.2.1 Blinatumomab as subsequent therapy

The dosing regimen of blinatumomab monotherapy as a 2L treatment follows the dosing in the prospective, phase 3 TOWER trial of blinatumomab monotherapy vs. SoC salvage chemotherapy, in which blinatumomab was given at a dose of 9 µg/day on days 1-7 of the first cycle, followed by a dose of 28 µg/day for the remaining days of the first cycle and for all subsequent cycles (up to 9 cycles in total) [92]. In Danish clinical practice, blinatumomab in 2L is most often used as a bridge to HSCT [5]. It is assumed that the patients receiving treatment with blinatumomab in 2L will get up to two cycles of treatment. However, this is changeable in the CEM. The proportion of patients who receive blinatumomab in 2L is assumed to be the average percentages of patients starting and completing cycle 1 and 2 of blinatumomab respectively from TOWER, [90,92].

The administration of 2L blinatumomab is assumed to be similar to frontline administration of blinatumomab, with an initial inpatient period, followed by outpatient administration comprised of outpatient bag changes (further described in section 11.3). For 2L blinatumomab, patients were assumed to require 9 inpatient administration days in the first cycle, two inpatient days in the second cycle, and all outpatient administration for the remaining cycles following the SmPC for the treatment of patients with a relapse even though blinatumomab in 2L most often is used as bridge to HSCT in Denmark [1].

11.6.2.2 Inotuzumab ozogamicin as subsequent therapy

The model assumes that inotuzumab ozogamicin is administered as an IV infusion of 0.8 mg on day 1 of each cycle, together with 0.5 mg on days 8 and 15 of each cycle for a median of 3 cycles, which is based on the dosing regimen of a phase 3 trial of inotuzumab ozogamicin vs SoC for ALL [121]. In agreement with the Danish clinical expert, Inotuzumab ozogamicin is assumed to be administered in the outpatient setting on days 1 (0.8 mg), 8, and 15 (0.5 mg) of each cycle for a median of 3 cycles. As for frontline therapy, the outpatient IV administration cost is DKK 2,136, based on the 2025 tariffs of 17MA98 for the same procedure and diagnosis (further described in section 11.3) [119].

11.6.2.3 FLAG-IDA as subsequent therapy

The FLAG-IDA chemotherapy dosage regimen is based on Danish clinical practice [5,122], administered IV in the following schedule:

- Fludarabine: 30 mg/m^2 for 5 consecutive days per 28-day cycle
- Cytarabine: 2 g/m^2 for 5 consecutive days per 28-day cycle
- Filgrastim: 0.005 mg/kg for a maximum of 14 days
- Idarubicin: 8 mg/m^2 for 3 days per 28-day cycle

A maximum of 4 cycles was assumed. The proportion of patients who received FLAG-IDA was based on the exposure data of the SoC cohort in the TOWER trial, see Table 50 [94]. The Danish clinical expert stated that in most cases only 1-2 cycles are administered, however, agreed with the proportion of patients receiving treatment as presented in the table below, thus validating the proportion in the table, where few patients are receiving cycle 3 and 4.

Table 50 Proportion of patients receiving each cycle of subsequent FLAG-IDA therapy

Cycle	Patients receiving FLAG-IDA in model (%)
Cycle 1	81.3%
Cycle 2	20.9%
Cycle 3	2.2%
Cycle 4	1.5%

Abbreviations: FLAG-IDA, Fludarabine, cytarabine, idarubicin, and filgrastim
Source: [94].

In agreement with the Danish clinical expert, FLAG-IDA was assumed to be administered in an inpatient setting for the first 5 days of each cycle. The same inpatient administration cost of DKK 51,697 was applied as in the frontline setting, derived from the 2025 DRG tariffs of 17MA01 (further described in section 11.3) [119]. As filgrastim (part of FLAG-IDA treatment) was assumed to be administered in a total of 14 days per cycle, this specific administration was assumed to require 1 outpatient visits per cycle in addition to the inpatient administration. As for frontline therapy, the outpatient IV administration cost is DKK 2,136 based on the 2025 tariffs of 17MA98 for the same procedure and diagnosis [119].

11.6.2.4 CAR-T as subsequent therapy

CAR-T consists of the following stages of treatment:

- Leukapheresis
- Bridging chemotherapy
- Lymphodepleting chemotherapy
- CAR-T-cell infusion (tisagenlecleucel)

Each of these stages is associated with different drug acquisition and administration costs, discussed in more detail in the sections below.

Leukapheresis

Leukapheresis refers to the procedure where T-cells destined for modification are harvested from patients' blood samples. The cost of leukapheresis was estimated to be DKK 9,967 based on the average of estimated costs of DKK 4,957 for "Stem cell harvesting" from the DMC application of tisagenlecleucel, together with the 2025 DRG tariffs of 17PR01 for "Bone Marrow Harvest for diagnostics" of DKK 16,156 (trim point: 1 day) and 70OP02 (trim point: 1 day) for "Minor operations without connection to the main diagnosis" of DKK 8,787 [73,117,119]. For leukapheresis, a correcting factor of 127% was applied to account for patients who have received leukapheresis but failed to receive the CAR-T cell infusion, which was validated by the Danish clinical expert.

Bridging chemotherapy

Patients undergoing CAR-T treatment may be administered bridging chemotherapy during the manufacturing of CAR T-cells for disease stabilization, which is validated by the Danish clinical expert. The bridging chemotherapy regimen (including supplementary supportive treatments) used in the model is based on the regimen described in NICE TA554 of tisagenlecleucel [123] and is detailed below:

- Allopurinol 100 mg/m^2 orally 3 times daily for 5 days
- Dexamethasone 6 mg/m^2 orally daily for 14 days, then 3 mg/m^2 daily for 7 days
- Vincristine 1.5 mg/m^2 IV weekly for 3 weeks
- Methotrexate 12 mg IT on Days 1 and 8
- Co-trimoxazole (sulfamethoxazole & trimethoprim) 480 mg orally twice daily for 2 consecutive days each week for 3 weeks.

Following TA554, it was assumed that 87% of patients intended for CAR-T treatment received bridging chemotherapy [123]. The unit costs of drugs used were retrieved from Medicinpriser.dk [116], and all administration was assumed to occur in the outpatient setting. This resulted in final drug acquisition and administration costs for bridging chemotherapy of DKK 4,802 and DKK 20,442 respectively.

Lymphodepleting chemotherapy

Prior to receiving CAR-T treatment, patients are required to undergo lymphodepleting chemotherapy. The recommended regimen is the fludarabine/cyclophosphamide regimen, elaborated in both the SmPC together with in the DMC assessment of tisagenlecleucel, comprising 30 mg/m^2 daily of IV fludarabine for 4 days and 500 mg/m^2 of IV cyclophosphamide for 1 day [73,124].

Similar to leukapheresis, a correcting factor of 105% was applied to account for patients that have received lymphodepleting chemotherapy but failed to receive the CAR-T-cell

infusion. This resulted in total lymphodepleting chemotherapy drug costs of DKK 10,947.61.

As described in the DMC assessment of tisagenlecleucel, 76% of patients required hospitalization while receiving lymphodepletion chemotherapy as part of tisagenlecleucel treatment [73]. In accordance with the duration of treatment infusion, the average hospitalization stay was assumed to be 7 days, also utilized in the NICE TA893 [114]. The same inpatient administration cost of DKK 51,697 was applied as in the frontline setting, derived from the 2025 DRG tariffs of 17MA01 (further described in section 11.3) [119]. The remaining 24% of patients received lymphodepleting chemotherapy in the outpatient setting for an average of 4 days. As for frontline therapy, the outpatient IV administration cost is DKK 2,136 based on the 2025 tariffs of 17MA98 for the same procedure and diagnosis [119]. Total lymphodepletion chemotherapy drug acquisition and administration costs were therefore estimated to be DKK 290,933.

CAR-T-cell infusion

The drug costs of tisagenlecleucel as the available CAR-T treatment in the Danish clinical practice for ALL is DKK 1,983,463 [116]. The administration costs of tisagenlecleucel were based on the 2025 DRG tariffs of 26MP21 (trim point: 73 days) for "Treatment with CAR-T cell-therapy" of DKK 3,645,319 [117].

Altogether, the total cost per course of CAR-T treatment, including infusion and pre-treatment costs, was estimated to be DKK 5,734,065.

In Table 51 and Table 52 below, an overview of the dosage regimen and costs used in the model to reflect subsequent treatment is presented.

Table 51. Medicines of subsequent treatments (other subsequent treatments)

Medicine	Dose	RDI*	Frequency	Vial sharing
Blinatumomab** [90,92]	9 µg / 28 µg	100% Cycle 1: [redacted] Cycle 2: [redacted]	9 µg/day on days 1-7 of the first cycle, followed by 28 µg/day for the remaining days of the first cycle and for all subsequent cycles.	No
Inotuzumab ozogamicin [121]	0.8 mg / 0.5 mg	100% N/A	On days 1 (0.8 mg), 8, and 15 (0.5 mg) of each cycle for a median of 3 cycles.	No

Medicine			Dose	RDI*	Frequency	Vial sharing
FLAG-IDA [5,122]	Fludarabine		30 mg/m^2	100% Cycle 1: 81% Cycle 2: 21% Cycle 3: 2% Cycle 4: 1%	5 consecutive days per 28-day cycle for up to 4 cycles	No
	Cytarabine		2000 mg/m^2		5 consecutive days per 28-day cycle for up to 4 cycles	
	Filgrastim		0.005 mg/kg		For a maximum of 14 days	
	Idarubicin		8 mg/m^2		For 3 days per 28-day cycle for up to 4 cycles	
CAR-T treatment	Bridging chemotherapy (including supplementary supportive treatments) [123]	Allopurinol	100 mg/m^2	100% 87%	Orally 3x daily, for 5 days	N/A
		Dexamethasone	6 mg/m^2 / 3 mg/m^2	100% 87%	6 mg/m^2 orally daily for 14 days, then 3 mg/m^2 daily for 7 days	N/A
		Vincristine	1.5 mg/m^2	100% 87%	IV weekly for 3 weeks	No
		Methotrexate	12 mg	100% 87%	IT on Days 1 and 8	No
		Co-trimoxazole	480 mg	100% 87%	IV, 2 days each week, for 3 weeks	No
	Lymphodepleting chemotherapy [73,114,124].	fludarabine	30 mg/m^2	100% 105%***	Daily for 4 days (before CAR-T infusion)	N/A
		Cyclophos-phamide	500 mg/m^2		Once on day 1 (before CAR-T infusion)	
	CAR (tisagenlecleucel)		1 dose	100% 100%	Once	

* RDI in the health economic model is assumed to be 100% for all 2L treatments. The numbers below the RDIs of 100% in the above tabel are the proportion af patients who is starting each cycle of that particular treament. RDI for 2L blinatumomab and FLAG-IDA treatment are based on the exposure data of the TOWER trial [92].
** Dosing regimen based on dosing of the TOWER trial [93]. The proportion of patients who received blinatumomab was assumed to be the average of the percentages of patients starting and completing each cycle of blinatumomab from TOWER.

*** A correcting factor of 105% was applied to account for patients who have received lymphodepleting chemotherapy but failed to receive the CAR-T cell infusion.
Abbreviations: CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor cell therapy; IV, intravenous; IT, intrathecal; kg, kilogram; mg, milligram; µg, microgram; N/A, not applicable.Source: [5,73,92,114,121–124].

Table 52. Unit cost of drugs used as other subsequent treatments

Medicine			Strength	Amount in pack	Packaging size	Pharmacy purchasing price (DKK)
Blinatumomab [116]			38.5 µg*	1 each	1	15,833
Inotuzumab ozogamicin [116]			1 mg	1 each	1	6,380
FLAG-IDA [116]	Fludarabine		25 mg/ml	2.0 ml	5	6,551
	Cytarabine		20 mg/ml	5.0 ml	5	625
			100 mg/ml	10.0 ml	1	216
			100 mg/ml	20.0 ml	1	283
	Filgrastim		0.3 mg/ml	1.0 ml	5	2,447
	Idarubicin		1 mg/ml	5.0 ml	1	2,500
			1 mg/ml	10.0 ml	1	5,000
CAR-T treatment [116]	Lymphodeplete chemotherapy	Fludarabine	25.0 mg/ml	2.0 ml	5	6,551
		Cyclophos-phamide	500.0 mg	1 each	1	192
			1000.0 mg	1 each	1	335
	CAR (tisagenlecleucel)		1 dose	1 each	1	1,983,463

* Single-use vials containing 38.5 µg blinatumomab (28 µg dose content)
Abbreviations: CAR, chimeric antigen receptor; CAR-T, chimeric antigen receptor cell therapy; DKK, Danish krone; mg, milligram; ml, milliliter; µg, microgram.
Source: [116].

11.6.2.5 Post relapse HSCT

In addition to the subsequent treatment options outlined so far in 11.6.2, patients who relapse and are eligible may also receive HSCT. In the blinatumomab + chemotherapy arm, 15 patients experienced a relapse event over the course of the E1910 trial. Of these patients, 3 (20.0%) received HSCT after they relapsed. In the chemotherapy alone treatment arm, 32 patients relapsed during the E1910 trial time horizon. Of these patients, five (15.6%) went on to receive HSCT [22]. As patients may potentially receive any of the subsequent therapies described above and summarized in Table 51 and Table 52 as a bridge to HSCT, HSCT costs were calculated in addition to the subsequent therapy costs outlined in the previous sections. The cost of post-relapse HSCT was assumed to be the same as the 1L HSCT cost as described in section 11.2.

11.7 Patient costs

Patient costs are included within the sheets “Drug Costs” and “2L Treatment” in the CEM in Excel and consists of transportation to and from the hospital, together with the time spend for inpatient and outpatient visits, respectively. All costs are based on the DMC ”Værdisætning af enhedsomkostninger v. 1.8” [120].

The cost per kilometer is 3.79 DKK, with an average travel distance of 40 km assumed for a trip to and from the hospital. Additionally, the duration of the inpatient hospital visit is assumed to be 16 hours based on the average daily working hours. The duration of the outpatient hospital visit is assumed to be 3 hours based on estimations from the Danish clinical expert. The average Danish salary per hour applied is 188 DKK [120]. An overview of the applied assumptions for patient costs are summarized in Table 53 below. The days per stay and whether the patient is going to be treated inpatient or outpatient is as outlined in section 11.3 and 11.6.

Table 53. Patient costs used in the model

Activity	Units	Source
Distance to hospital	40 km	The DMCs Catalog for Valuation of Unit Costs "Værdisætning af enhedsomkostninger v. 1.8" [120]
Travel time speed	1 min/ km	Assumption
Cost per km	DKK 3.73	The DMCs Catalog for Valuation of Unit Costs "Værdisætning af enhedsomkostninger v. 1.8" [120]
Time spent on traveling	40 minutes	Assumption
Average Danish salary per hour	DKK 188	The DMCs Catalog for Valuation of Unit Costs "Værdisætning af enhedsomkostninger v. 1.8" [120]
Time spent on outpatient hospital visit	3 hours	Assumption, validated by Danish clinical expert
Time spent on inpatient hospital visit	16 hours	Assumption based on average daily working hours

Abbreviations: DKK, Danish krone; km, kilometer.
Source: [120].

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

All patients who die in the economic model prior to the possible cure were assumed to incur a one-time terminal care cost applied at the time of death. Given that patients who survive beyond the cure timepoint of 4 years are considered long-term survivors, it was assumed that these patients would not incur the costs of terminal care.

The cost of terminal care was estimated by taking the weighted average of the Danish DRG tariffs, 2025, of "Specialized Palliative Care, Large/Small or Medium/Other" (26MP45-26MP47) with a trim point of 1 to 27 days, resulting in an average terminal care cost of DKK 32,383 [117].

12. Results

12.1 Base case overview

The base case settings of the health economic model compare blinatumomab + consolidation chemotherapy with consolidation chemotherapy alone using a CUA approach, and the primary health outcome of the model is Quality-Adjusted Life Years (QALY)s. The model considers a lifetime time horizon of 50 years. Costs and QALYs are discounted at 3.5% annually after the first year. The costing year used is 2024/2025, and the model includes costs as described in section 11. An overview of the base case of the health economic model is provided in Table 54 below.

Table 54. Base case overview

Feature	Description
Comparator	Chemotherapy regimen (a Berlin-Frankfurt-Münster-like regimen adapted from the UKALL XII/ECOG E2993 clinical trial) [4]
Type of model	PSM applying MCMs
Time horizon	Lifetime (50 years)
Patient population	MRD-agnostic
Treatment line	1L consolidation therapy. Subsequent treatment lines included
Measurement and valuation of health effects	HRQoL measured with EQ-5D in BLAST trial, and with EORTC QLQ-C30 in the TOWER trial mapped to EQ-5D [23,24]. Danish population weights were used to estimate health-state utility values
Costs included	Drug acquisition and administration costs (including consolidation, maintenance and subsequent treatment costs), HSCT costs, costs of adverse events, patient costs, and terminal care costs
Dosage of medicine	Body surface area (BSA) or weight-based dosing
Average time on treatment	Blinatumomab + SoC: 2.2 years SoC: 1.9 years

Feature	Description
Parametric function for RFS	Blinatumomab + chemotherapy: Exponential MCM Chemotherapy: Exponential MCM
Parametric function for OS	Blinatumomab + chemotherapy: Log-normal MCM Chemotherapy: Exponential MCM
Inclusion of waste	Yes (i.e. assume no tablet splitting/vial sharing)
Average time in model health state: RF: PR:	Blinatumomab + chemotherapy: 23.1 years Chemotherapy: 13.4 years Blinatumomab + chemotherapy: 1.6 years Chemotherapy: 1.7 years

Abbreviations: 1L, first-line; EORTC QLC-C30, European Organisation For Research And Treatment Of Cancer Quality of Life Questionnaire; EQ-5D EuroQol 5-Dimension¸ HRQoL, health related Quality of Life; HSCT, hematopoietic stem-cell transplantation; MRD, minimal residual disease; OS, overall survival; RFS, relapse free survival.
Source: [23,24].

12.1.1 Base case results

A breakdown of the base case results is shown in Table 55. The total discounted costs of BLINCYTO® + chemotherapy were DKK 3,112,601 thus resulting in an increased discounted costs of DKK 1,256,066 compared to chemotherapy total discounted costs of DKK 1,856,536. BLINCYTO® + chemotherapy yielded 5.30 and 4.26 more discounted LYs and QALYs compared with chemotherapy. The base case incremental cost-effectiveness ratio (ICER) was DKK 294,874 per QALY gained.

Table 55. Base case results, discounted estimates

	BLINCYTO® + chemotherapy	Chemotherapy	Difference
Consolidation therapy acquisition costs	DKK 1,306,888	DKK 20,778	DKK 1,286,111
Consolidation therapy administration costs	DKK 366,597	DKK 231,843	DKK 134,754
Disease mannagement costs	DKK 493,324	DKK 495,661	-DKK 2,338
Costs associated with management of adverse events	DKK 86,828	DKK 88,217	-DKK 1,388
Maintenance therapy costs	DKK 63,786	DKK 62,664	DKK 1,122
1L HSCT costs	DKK 349,065	DKK 388,958	-DKK 39,893
Terminal care costs	DKK 5,773	DKK 12,157	-DKK 6,384

	BLINCYTO® + chemotherapy	Chemotherapy	Difference
Subsequent treatment (2L treatment) costs	DKK 213,257	DKK 357,255	-DKK 143,988
Patient costs	DKK 227,084	DKK 199,004	DKK 28,080
Total costs	**DKK 3,112,601**	**DKK 1,856,536**	**DKK 1,256,066**
Life years gained (RF)	14.05	8.64	5.41
Life years gained (PR)	0.97	1.08	-0.11
Total life years	**15.02**	**9.72**	**5.30**
QALYs (RF)	11.17	6.85	4.32
QALYs (PR)	0.63	0.69	-0.06
QALYs (adverse reactions)	-0.007	-0.007	0
Total QALYs	11.80	7.54	4.26
Incremental costs per life year gained		**DKK 236,989**	
Incremental cost per QALY gained (ICER)		**DKK 294,874**	

12.2 Sensitivity analyses

12.2.1 Deterministic sensitivity analyses

Deterministic OWSAs were conducted to examine the implications on the result of the health economic analysis, if parameters associated with uncertainty were altered. Only parameters that could be varied independently were varied in the OWSA, so survival parameters were excluded from the OWSA.

Results of the OWSA are presented in Table 56 below, together with being displayed in a tornado diagram, see Figure 6, where each parameter and its resulting impact was ranked from highest to lowest. The proportion of patients receiving HSCT by treatment arm had the largest impact on the ICER.

Table 56. One-way sensitivity analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	-	-	1,256,066	4.26	294,874
Relapse-free HSCT distribution: (Chemotherapy only)	95%CI	Most influential parameters	1,368,025 & 1,135,108	4.22 & 4.31	324,248 & 263,676

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Relapse-free HSCT distribution: (Blinatumomab + chemotherapy)	95%CI	Most influential parameters	1,148,607& 1,373,805	4.30 & 4.22	267,125 & 325,885
Post-relapse HSCT distribution (Chemotherapy only)	95%CI	Most influential parameters	1,318,339 & 1,169,085	4.23 & 4.30	311,395 & 272,133
Post-relapse HSCT distribution (Blinatumomab + chemotherapy)	95%CI	Most influential parameters	1,207,122 & 1,328,842	4.28 & 4.23	282,038 & 314,188
Proportion of blin patients receiving cycle 4 of blinatumomab	95%CI	Most influential parameters	1,174,782 & 1,279,176	4.26 & 4.26	275,771 & 300,306
Age at model start	95%CI	Most influential parameters	1,255,939& 1,256,132	4.37 & 4.13	287,199 & 304,020
Gen. pop. survival SMR	Lower bound: 1.00 Upper bound 1.34*	Most influential parameters	1,256,039 & 1,256,175	4.33 & 4.10	290,429 & 306,793
2L treatment distribution: CAR-T (Blinatumomab)	+/-20%	Most influential parameters	1,220,338 & 1,288,344	4.26 & 4.26	286,486 & 302,451
Time horizon	+/- 20%	Most influential parameters	1,255,729 & 1,256,066	4,33 & 4,10	310,281 & 294,874
Proportion of blin patients receiving cycle 2 of blinatumomab	95%CI	Most influential parameters	1,223,828 & 1,282,975	4.26 & 4.26	287,296 & 301,199

*An upper bound of 1.34 calculated as the weighted average of patients who received HSCT (26.12% in the blinatumomab + chemotherapy arm and 29.10% in the chemotherapy alone arm) multiplied by an SMR of 2 assumed for patients post-HSCT, based on statements from the Danish clinical expert, and patients who did not receive HSCT (73.88% in the blinatumomab + chemotherapy arm and 70.9% in the chemotherapy alone arm) multiplied by the base case SMR of 1.09. Lower bound of 1.00 was chosen as a SMR<1 would imply cured ALL patients would have better survival than the general population, which is not plausible.
Abbreviations: 2L, second-line; CAR-T, Chimeric antigen receptor cell therapy; DKK, Danish krone; Gen, general; HSCT, hematopoietic stem-cell transplantation; ICER, Incremental cost-effectiveness ratio; pop, population; QALY, Quality-adjusted life year; SMR, Standardized mortality ratio.

Figure 6. Tornado diagram of the ICER of BLINCYTO® + chemotherapy vs chemotherapy

Abbreviations: 2L, second-line; CAR-T, Chimeric antigen receptor cell therapy; Gen, general; HSCT, hematopoietic stem-cell transplantation; ICER, Incremental cost-effectiveness ratio; OWSA, One-way sensitivity analysis; pop, population; SMR, Standardized mortality ratio.

Further, uncertainties around the assumptions in the health economic model were examined through other sensitivity analyses. Key model assumptions or parameters were altered for each analysis, and the corresponding results were tabulated. An overview of the included sensitivity analyses is available in Table 57 below.

Table 57. Other sensitivity analyses

	Rationale	ICER (difference from vs base case)
Base case		DKK 294,874
Using a cure point of 5 years	Cure is modeled by assuming a 5-year cure point instead of the 4-year point used in the base-case.	DKK 290,811 (-4,063)
Max duration of 42 weeks for blinatumomab + chemotherapy consolidation treatment	A potentially 14 days treatment-free interval between all blinatumomab cycles was assumed, in line with the SmPC, corresponding to a max duration of 42 weeks for blinatumomab + chemotherapy consolidation treatment.	DKK 294,304 (-570)
MRD-negative population only	The randomized MRD- patients only as the publication of the E1910 trial.	DKK 293,633 (-1,241)
Adjust the blinatumomab dose by the observed dose per treatment cycle, from E1910	In E1910, there were several potential reasons why patients could receive a different dose than the recommended 28µg/day per dose. The base case only accounts for patients discontinuing treatment but assumes that patients who continue treatment all receive the full 28µg/day per blinatumomab dose. Here the dose is modeled down by the observed dose per treatment cycle from E1910, to	DKK

	ensure the modeled treatment use reflects the treatment use from the trial.	
Cap RFS at the percent alive, rather than the OS risk per cycle	Although RFS and OS are extrapolated independently, both endpoints are related. The model therefore includes several options to ensure the relationship between RFS and OS has face-validity, and to avoid implausible scenarios (e.g. RFS exceeding OS). In the modeled base case, this RFS-OS relationship is modeled by capping the RFS risk per cycle at the OS risk per cycle. Here, the impact of capping the percent RFS at the percent alive is explored instead.	DKK 329,864 (+34,990)
Using an alternative RFS distribution for (Gompertz for both arms)	The model includes various extrapolation options for RFS and OS. The best fitting OS and RFS option were selected for the modeled base case, however, to explore the impact of this curve selection on the model results, alternative distributions were considered as scenarios.	DKK 294,414 (-460)
Using an alternative OS distribution (Weibull for Blin, Log-logistic for SoC)		DKK 321,040 (+26,166)
Using an alternative RFS distribution (Log-Normal for both arms)		DKK 291,197 (-3,677)
Using an alternative OS distribution (Gamma for Blin, Exponential for SoC)		DKK 288,887 (-5,987)
Excluding the utility decrement for cured patients, relative to gen pop	Excluding a utility decrement to the general population utility for cured patients, to account for potential long-term quality of life impacts of ALL.	DKK 288,988 (-5,885)
Adjust 2L costs by the observed fatal	Excludes patients who died without having a recorded relapse from	DKK 297,503 (+2,629)

progression rate from E1910	receiving subsequent therapy costs and disutilities to test the sensitivity of the model to the assumption that patients generally relapse before death.	
Exclude disutilities related to AEs	If assumed captured in the HSUV elicited from the BLAST and TOWER studies.	DKK 294,921 (-48)

Abbreviations: 2L, second-line; MRD, minimal residual disease; OS, overall survival; PSM, parametric survival model; RFS, relapse-free survival; SmPC, Summary of Product Characteristics; SoC, standard of care.

Overall, the deterministic sensitivity analyses had a modest impact on the modeled ICER, indicating that the model is robust to changes in the underlying assumptions of the model. The sensitivity analyses impacting the base case ICER the most was the ones capping the RFS at the percent alive, rather than the OS risk per cycle as well as using alternative OS distribution (Weibull for blinatumomab and Log-Logistic for SoC) and adjusting the BLINCYTO® dose by the observed dose per treatment cycle from E1910 trial. Furthermore, the other scenarios relating to alternative survival curve extrapolations (OS and RFS) produced both higher and lower ICERs, supporting that the selected base-case distributions provide a balanced and clinically plausible representation of survival.

12.2.2 Probabilistic sensitivity analyses

A PSA was conducted using 10,000 Monte Carlo simulations to examine parameter uncertainty. In each simulation, model parameters were randomly drawn from an appropriate distribution within the prespecified upper and lower bounds. All cost and frequency inputs were varied using gamma distributions, while beta distributions were used for utility and probability parameters. Dirichlet distributions were used for multinomial parameters. Survival inputs were varied separately in the survival data sheets. The survival inputs were varied using the generated variance/covariance matrices per extrapolation and the MultiNormInv function, to account for the interdependence between the different survival parameters for one specific extrapolation. All parameters from the PSA can be assessed in Appendix G, with parameter input, point estimate, lower-, upper bound and belonging distribution.

Simulations from the PSA are plotted on the cost-effectiveness plane in Figure 7 below. Almost all of the simulations lie in the northeast quadrant of the cost-effectiveness plane, meaning that BLINCYTO® + chemotherapy is more costly and more effective than chemotherapy alone, with a mean ICER of DKK 310,937/QALY.

Results from the PSA were further transformed into CEACs, where the probability of treatment preference was plotted against various WTP thresholds, see Figure 8 below.

Figure 7. Cost-effectiveness plane

Abbreviations: DKK, Danish krone; QALY, quality-adjusted life years; SoC, standard of care; WTP, willingness to pay.

Figure 8. Cost-effectiveness acceptability curve

Abbreviations: DKK, Danish krone; SoC, standard of care.

13. Budget impact analysis

This section outlines the budgetary implications of introducing BLINCYTO® as monotherapy as part of consolidation therapy for the treatment of adult patients with newly diagnosed Ph- CD19+ BCP-ALL in Denmark. Thus, the section provides estimates of

the number of patients eligible for treatment together with estimations of the incremental budget impact for the patient population. The budget impact model (BIM) includes expenses on acquisition, administration, and AEs, along with predicted market share. In accordance with the guidelines of the DMC, patient costs are excluded from the budgetary implication calculations and costs are undiscounted [79].

Number of patients (including assumptions of market share)
As described in section 3.2, of the estimated yearly incidence of 15 adult patients newly diagnosed with Ph-negative CD19-positive BCP-ALL in Denmark, it is expected that all patients currently treated with the multiagent chemotherapy backbone as consolidation therapy are eligible candidates for treatment with BLINCYTO® as monotherapy as part of multiagent chemotherapy in the consolidation setting. This was agreed on by the Danish clinical expert.

As described in section 3.3, it must be emphasized that a significant proportion of the eligible patients are expected to be included in the current protocols available in Denmark. However, it is assumed that all patients being eligible for treatment should be offered BLINCYTO® regardless of protocol, resulting in a market share of 100% for BLINCYTO® and 0% for SoC within the scenario where BLINCYTO® alternating with consolidation chemotherapy is approved. This assumption was agreed on by the Danish clinical expert too.

If it is assessed that patients within the currently available protocols cannot deviate from the SoC treatment, and thereby not qualify for treatment with BLINCYTO®, the BIM includes an option to adjust the proportion of patients being eligible for treatment with blinatumomab.

In the currently Danish clinical practice where BLINCYTO® alternating with consolidation chemotherapy is not approved, all 15 patients are assumed to be treated with SoC, resulting in a market share of 100% for SoC and 0% for BLINCYTO®. See Table 58 below for an overview of the expected number of patients being treated over the next five-year period within the different scenarios.

Table 58 Number of new patients expected to be treated over the next five-year period if the medicine is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
BLINCYTO® + SoC	15	15	15	15	15
SoC	0	0	0	0	0
			Non-recommendation		
BLINCYTO® + SoC	0	0	0	0	0
SoC	15	15	15	15	15

Budget impact

The budgetary consequences covering the following five years, both in the scenario of recommendation and no recommendation of BLINCYTO®, derived from the BIM, are presented in Table 59 below.

Table 59 Expected budget impact of recommending the medicine for the indication

	Year 1	Year 2	Year 3	Year 4	Year 5
The medicine under consideration is recommended	DKK 34.111.984	DKK 35.932.186	DKK 37.051.561	DKK 37.739.777	DKK 37.929.821
The medicine under consideration is NOT recommended	DKK 16.801.615	DKK 19.754.271	DKK 21.266.196	DKK 22.337.457	DKK 22.580.082
Budget impact of the recommendation	**DKK 17.310.369**	**DKK 16.177.916**	**DKK 15.785.364**	**DKK 15.402.321**	**DKK 15.346.739**

14. List of experts

[redacted]

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Appendix A. Main characteristics of studies included

Table 60 Main characteristic of studies included

Trial name: E1910	**NCT number: NCT02003222**
Objective [4]	To investigate the efficacy and safety of consolidation chemotherapy with or without addition of blinatumomab for the treatment of adult patients (≥ 30 through ≤ 70 years of age) with newly diagnosed Ph-CD19 positive BCP- ALL.
Publications – title, author, journal, year [4]	Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults, Litzow MR, et al. N Engl J Med. 2024;391(4):320-33.
Study type and design [4]	Randomized, open-label, phase 3, controlled study with 1:1 randomization at consolidation to receive either blinatumomab + chemotherapy or chemotherapy alone. The blinatumomab + chemotherapy arm received 2 cycles of blinatumomab for 4 weeks of each cycle (with a 2-week interval between the 2 cycles) followed by 3 cycles of consolidation chemotherapy (the first 2 cycles were 4 weeks and then a cycle for 6 weeks), another 4-week cycle of blinatumomab followed by an additional four-week cycle of chemotherapy, and then a fourth 4-week cycle of blinatumomab. The chemotherapy alone arm received four cycles of consolidation chemotherapy (cycle 1 and 2 were 4 weeks, cycle 3 was 6 weeks and the last cycle was 4 weeks). Randomization was risk stratified based on patient age (<55 years vs ≥ 55 years, CD20 status (positive vs negative), rituximab use (yes or no), and whether allogeneic HSCT was intended (yes or no).
Sample size (n) [4,22]	Full Analysis Set (MRD-negative only): 224 (112 in each arm) Step 3 Analysis Set (MRD-agnostic): 286 (152 in Blinatumomab + chemotherapy arm; 134 in chemotherapy arm) Step 3 MRD Positive Analysis Set: 62 (40 in Blinatumomab + chemotherapy arm; 22 in chemotherapy arm)
Main inclusion criteria [22,76]	Step 1 (induction) • Newly diagnosed with Ph- BCP-ALL • Aged between 30 and 70 years • ECOG performance score 0 to 3 Step 2 (intensification) • Achieving CR/CRi after induction therapy • CNS negative • ECOG performance score 0 to 2

Trial name: E1910	NCT number: NCT02003222
	Step 3 (randomization) • Maintaining CR/CRi after intensification therapy • ECOG performance score 0 to 2
Main exclusion criteria [22,76]	• Subjects with Ph+/BCR::ABL1+ ALL, Burkitt leukemia/lymphoma, mature B-cell leukemia, T-cell ALL, T-cell lymphoblastic lymphoma, or B-cell lymphoblastic lymphoma*. • Subjects having a concurrent active malignancy for which they are receiving treatment. • Subjects with pre-existing significant CNS pathology or uncontrollable seizure disorders.
Intervention [4]	Blinatumomab is administered for 2 cycles (with a 2-week interval between the 2 cycles) followed by 3 cycles of consolidation chemotherapy, another cycle of blinatumomab followed by an additional cycle of chemotherapy, and then a fourth cycle of blinatumomab. Patients were allowed to receive HSCT after at least 2 cycles of blinatumomab.
Comparator(s) [4]	Consolidation chemotherapy alone. At any time after the commencement of consolidation chemotherapy, eligible patients may receive HSCT.
Follow-up time [1,4, 90]	**Primary endpoints:** • OS for MRD- patients (E1910 publication): Median follow-up: 43 months • OS for MRD- patients (SmPC data): Median follow-up: 4.5 years. **Selected secondary endpoints:** • RFS for MRD- patients (E1910 publication): Median follow-up: 43 months • RFS for MRD- **patients** (SmPC data): Median follow-up: 4.5 years **Selected post hoc analysis** (SmPC data and data on file)**:** • OS for MRD-agnostic randomized patients only: Median follow-up: 4.5 years in blinatumomab + chemotherapy and 4.6 years in the chemotherapy alone arm • RFS for MRD-agnostic randomized patients only: Median follow-up: 4.5 years in blinatumomab + chemotherapy and 4.6 years in the chemotherapy alone arm • OS for MRD+ patients: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm) • RFS for MRD+ patients: Median follow-up: 4.6 years (blinatumomab-arm)/5.0 years (chemotherapy-arm)
Is the study used in the health economic model?	Yes, especially the post hoc analyses from the E1910 study.

Trial name: E1910	NCT number: NCT02003222
Primary, secondary and exploratory endpoints [1,4,22,90]	**Primary endpoints:** • OS for MRD- patients (E1910 publication) • OS for MRD- patients (SmPC data) **Selected secondary endpoints:** • RFS for MRD- patients (E1910 publication) • RFS for MRD- patients (SmPC data) **Selected post hoc analysis** (SmPC data and data on file)**:** • OS for MRD-agnostic randomized patients only • RFS for MRD-agnostic randomized patients only • OS for MRD+ patients • RFS for MRD+ patient
Method of analysis [22]	**Efficacy:** Per protocol. KM-analysis were used to estimate RFS and OS. Full Analysis Set: all Step 3 randomized patients who were MRD-negative (< 10^{-4}). Step 3 Analysis Set (post hoc analysis): all Step 3 randomized or registered patients combined, regardless of MRD status. The Step 3 MRD Positive Analysis Set: all subjects from the Step 3 analysis set who are MRD+ at step 3 using the protocol-specified 10-4 cut-off. **Safety:** Consolidation therapy (Step 3) safety analysis set: all patients randomized/registered in the consolidation phase (Step 3) who received at least 1 dose of protocol-specified therapies.
Subgroup analyses [4,76]	Stratification factors: Age < 55 years vs. ≥ 55 years, CD20 status, rituximab use, and whether transplantation was intended. Prespecified subgroups: • Gender (female vs male) • MRD-status • Combined molecular risk • *BCR::ABL1*-genotype like Patient characteristics for the subgroups relevant for this application are listed in section 6.1.2.
Other relevant information	N/A

*In Danish clinical practice, abnomalities in BCR::ABL1 Ph+ was previously termed as Ph+ BCP-ALL, but now termed BCP-ALL with BCR::ABL1 fusion [5].

Abbreviations: ALL, acute lymphoblastic leukemia; BCR::ABL1, breakpoint cluster region-Abelson fusion gene; CD, cluster of differentiation; CNS, central nervous system; CR, complete remission; CRi, complete remission

with incomplete hematologic recovery; EGOC, Eastern Cooperative Oncology Group; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; OS, overall survival; Ph+/-, Philadelphia chromosome (positive/negative); RFS, relapse-free survival; SmPC, Summary of Product Characteristics.

Source: [1,4,22,76,90].

Appendix B. Efficacy results per study

B.1 Results of the E1910 trial – FAS (MRD- patients only)

A total of 224 subjects were randomized in step 3 with 112 subjects assigned to blinatumomab + chemotherapy and 112 to the chemotherapy alone arm. All were assessed as MRD-, centrally following induction and intensification chemotherapy and subsequently included in the FAS [4].

Primary Efficacy Endpoint: OS in MRD-negative subjects (third efficacy interim analysis, E1910 publication data):
57 deaths were reported overall (17 deaths in the blinatumomab + chemotherapy arm and 40 deaths in the chemotherapy arm). 3-year OS was 85% and 68% in the blinatumomab + chemotherapy arm and chemotherapy arm, respectively. Hence, treatment with blinatumomab + chemotherapy significantly improved OS as compared with chemotherapy alone (hazard ratio (HR): 0.41; 95% confidence interval (CI): 0.23 to 0.73; probability value (p-value) = 0.002) [4].

Primary Efficacy Endpoint: OS in MRD-negative subjects (23 June 2023 DCO, CSR and SmPC data):
As of the primary analysis data cutoff date (23 June 2023), a total of 59 deaths had been reported: 19 (17.0%) in the blinatumomab + chemotherapy arm and 40 (35.7%) in the chemotherapy arm [22]. The median follow-up duration was 4.5 years in both treatment arms [1]. The study met its primary endpoint, demonstrating a statistically significant improvement in OS for the blinatumomab + chemotherapy group compared to the chemotherapy group (p = 0.001, one sided stratified log-rank test). The stratified hazard ratio (HR) for OS, calculated using a Cox regression model was 0.44 (95% CI: 0.25, 0.76), indicating a 56% reduction in the HR for OS in the blinatumomab + chemotherapy arm. The median OS had not been reached in either treatment arm at the time of analysis [1].

At 5-years, the Kaplan-Meier estimate for OS was 82.4% (95 CI: 73.7, 88.4) in the blinatumomab + chemotherapy arm and 62.5% (95% CI: 52.0, 71.3) in the chemotherapy arm [1]. A KM plot illustrating the OS comparison between the two treatment arms is presented in Figure 9 in appendix B.6.1. Additional details on the KM estimates for OS, can be found in Table 61.

Table 61. Overall Survival for MRD Negative at Step 3 – Primary Analysis (Full Analysis Set)

	Blinatumomab + chemotherapy (N=112)	Chemotherapy (N=112)

KM estimate - % [1,22]		
At 0.5 year (95% CI)	98.2 (93.0, 99.5)	99.1 (93.8, 99.9)
At 1 year (95% CI)	96.4 (90.7, 98.6)	90.0 (82.6, 94.3)
At 2 year (95% CI)	90.1 (82.8, 94.4)	81.5 (72.8, 87.6)
At 3 year (95% CI)	85.5 (77.5, 90.9)	70.0 (60.3, 77.7)
At 4 year (95% CI)	82.4 (73.7, 88.4)	64.1 (53.9, 72.7)
At 5 year (95% CI)	82.4 (73.7, 88.4)	62.5 (52.0, 71.3)
At 6 year (95% CI)	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)
At 7 year (95% CI)	82.4 (73.7, 88.4)	53.3 (37.8, 66.5)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

Secondary Efficacy Endpoint: RFS in MRD-negative subjects (third efficacy interim analysis, E1910 publication data):
Among all step 3 randomized MRD− subjects, 3-year RFS was 80% and 64% in the blinatumomab + chemotherapy arm and chemotherapy arm, respectively. Hence, treatment with blinatumomab improved RFS as compared with chemotherapy alone (HR for relapse or death: 0.53; 95% CI: 0.32 to 0.87) [4].

Secondary Efficacy Endpoint: RFS in MRD-negative subjects (23 June 2023 DCO, CSR and SmPC data):
Among all step 3 randomized MRD- subjects, relapse or death from any cause occurred in 25 subjects (22.3%) in the blinatumomab + chemotherapy arm and in 43 subjects (38.4%) in the chemotherapy arm. The one-sided stratified log-rank test yielded a p-value of 0.006 [22]. Median follow-up was 4.5 years in both treatment arms [1]. The stratified HR for RFS, derived from a Cox regression model, was 0.53 (95% CI: 0.32, 0.88), indicating a 47% reduction in the hazard rate for RFS in the SoC blinatumomab + chemotherapy arm. At the time of analysis, the median RFS had not been reached in either treatment arm [22].

At 5 years, the KM estimate for RFS was 77.0% (95% CI: 67.8, 83.8) in the blinatumomab + chemotherapy arm and 60.5% (95% CI: 50.1, 69.4) in the Chemotherapy arm [1]. A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 10 in Appendix B.6.2. Additional details on the KM estimates for RFS can be found in Table 62.

Table 62. Relapse-free survival for MRD Negative at Step 3 - Primary Analysis (Full Analysis Set)

	Blinatumomab + chemotherapy (N=112)	Chemotherapy (N=112)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	92.8 (86.1, 96.3)	91.9 (85.1, 95.7)
At 1 year (95% CI)	90.1 (82.8, 94.4)	81.9 (73.4, 87.9)
At 2 year (95% CI)	82.0 (73.5, 88.0)	71.5 (61.9, 79.0)
At 3 year (95% CI)	81.1 (72.5, 87.2)	65.7 (55.9, 73.8)
At 4 year (95% CI)	77.0 (67.8, 83.8)	62.1 (52.0, 70.7)
At 5 year (95% CI)	77.0 (67.8, 83.8)	60.5 (50.1, 69.4)
At 6 year (95% CI)	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)
At 7 year (95% CI)	77.0 (67.8, 83.8)	52.7 (38.5, 65.0)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

For an overview of all results of the FAS, see the table below.

Table 63. Results of the E1910 trial - FAS (MRD- patients only)

Results of [trial name (NCT number)]											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Overall Survival at 5 years	Blinatumomab + chemotherapy	112	82.4% (73.7, 88.4)	19.9%	N/A	N/A	HR: 0.44	0.25, 0.76	0.003	The overall survival is based on the Kaplan-Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	112	62.5% (52.0, 71.3)								
Relapse free survival at 5 years	Blinatumomab + chemotherapy	112	77.0% (67.8, 83.8)	16.5%	N/A	N/A	HR: 0.53	0.32, 0.88	0.013	The relapse free survival is based on the Kaplan–Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	
	Chemotherapy	112	60.5% (50.1–69.4)								

Abbreviations: CI, Confidence interval; HR, hazard ratio; MRD, minimal residual disease; N, number; N/A; not available; OS, overall survival; RFS, relapse-free survival.
Source: [1,22].

B.2 Results of the E1910 trial – Step 3 Analysis Set (MRD-agnostic patients)

For an overview of all results of the Step 3 Analysis Set, see the table below.

Post hoc analyses: OS in MRD-agnostic subjects (23 June 2023 DCO, CSR and SmPC data):
Among all 286 subjects, a total of 83 deaths were reported: 30 [19.7%] in the blinatumomab + chemotherapy arm and 53 [39.6%] in the chemotherapy arm. The median follow-up time for OS was 4.5 years for both treatment arms [1,22]. In line with the findings from the primary analysis, the stratified HR for OS, based on Cox proportional hazards (PH) model was 0.47 (95% CI: 0.30, 0.74), favoring the blinatumomab + chemotherapy arm. At the time of analysis, the median OS had not been reached in either arm [1]. At 5 years, the KM estimate for OS was 79.1 % (95% CI: 71.4, 85.0) in the blinatumomab + chemotherapy arm and 58.3% (95% CI: 48.8, 66.7) in the chemotherapy arm [1]. A KM plot illustrating the OS comparison between the two treatment arms is presented in Figure 11 in appendix B.6.3. Additional details on the KM estimates for OS can be found in Table 64.

Table 64. Overall Survival in MRD-agnostic patients at Step 3 (Step 3 Analysis Set)

	Blinatumomab + chemotherapy (N=152)	Chemotherapy (N=134)
KM estimate - % [1,22]		
At 0.5 years (95% CI)	96.7 (92.2, 98.6)	96.2 (91.2, 98.4)
At 1 year (95% CI)	94.7 (89.6, 97.3)	84.7 (77.3, 89.9)
At 2 years (95% CI)	87.3 (80.9, 91.7)	76.1 (67.7, 82.5)
At 3 years (95% CI)	82.6 (75.5, 87.8)	65.7 (56.7, 73.2)
At 4 years (95% CI)	80.3 (72.8, 85.9)	60.9 (51.6, 68.9)
At 5 years (95% CI)	79.1 (71.4, 85.0)	58.3 (48.8, 66.7)
At 6 years (95% CI)	79.1 (71.4, 85.0)	51.3 (38.6, 62.6)
At 7 years (95% CI)	79.1 (71.4, 85.0)	51.3 (38.6, 62.6)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

Post hoc analyses: RFS in MRD-agnostic subjects (23 June 2023 DCO, CSR and SmPC data):

The median follow-up time for RFS was 4.5 years for both treatment arms [1]. Consistent with the FAS for the MRD- patients, the stratified HR for RFS, derived from a Cox PH model, favored the blinatumomab + chemotherapy arm with a HR of 0.53 [95% CI: 0.35, 0.81] [1]. At the time of analysis, the median RFS had not been reached in either arm [22]. At 5 years, the KM estimate for RFS was 75.6% (95% CI: 67.8, 81.8) in the blinatumomab + chemotherapy arm and 57.2% (95% CI: 47.9, 65.4) in the chemotherapy arm [1]. A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 12 in appendix B.6.4. Additional details on the KM estimates for RFS can be found in Table 65.

Table 65. Relapse-free Survival in MRD-agnostic patients at Step 3 (Step 3 Analysis Set)

	Blinatumomab + chemotherapy (N=152)	Chemotherapy (N=134)
KM estimate - % [1,22]		
At 0.5 years (95% CI)	90.7 (84.8, 94.4)	86.5 (79.5, 91.3)
At 1 year (95% CI)	88.0 (81.7, 92.3)	75.8 (67.5, 82.2)
At 2 years (95% CI)	81.4 (74.2, 86.7)	66.2 (57.4, 73.7)
At 3 years (95% CI)	78.7 (71.2, 84.4)	61.4 (52.4, 69.2)
At 4 years (95% CI)	75.6 (67.8, 81.8)	58.5 (49.3, 66.5)
At 5 years (95% CI)	75.6 (67.8, 81.8)	57.2 (47.9, 65.4)
At 6 years (95% CI)	75.6 (67.8, 81.8)	51.1 (39.3, 61.8)
At 7 years (95% CI)	75.6 (67.8, 81.8)	51.1 (39.3, 61.8)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

Table 66. Results of the E1910 trial - Step 3 Analysis Set (MRD-agnostic patients)

Results of E1910 trial [NCT02003222]											
				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		
Overall Survival at 5 years	Blinatumomab + chemotherapy	152	79.1% (71.4, 85.0)	20,8%	N/A	N/A	HR: 0.47	0.30, 0.74	<0.001	The overall survival is based on the Kaplan-Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	134	58.3% (48.8, 66.7)								
Relapse free survival at 5 years	Blinatumomab + chemotherapy	152	75.6% (67.8, 81.8)	18,4%	N/A	N/A	HR: 0.53	0.35, 0.81	0.003	The relapse free survival is based on the Kaplan–Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	134	57.2 %(47.9, 65.4)								

Abbreviations: CI, Confidence interval; HR, hazard ratio; MRD, minimal residual disease; N, number; N/A; not available; OS, overall survival; RFS, relapse-free survival.
Source: [1,22].

B.3 Results of the E1910 trial – Step 3 Analysis Set (MRD-agnostic randomized patients only)

In total, 62 (21.7%) out of 286 patients were MRD+ (40 patients [26.3%] in the blinatumomab + chemotherapy arm and 22 [16.4%] in the chemotherapy arm) [1]. Out of the 40 patients with MRD+ disease in the blinatumomab arm, 18 were not randomized but were assigned to this arm following the FDA's approval of blinatumomab for MRD+ ALL in March 2018 as described above [22] In this appendix, the 18 non-randomized patients are excluded. The results presented in this appendix make the foundation of the base case analysis in the health economic model.

Post hoc analysis: OS in MRD-agnostic randomized patients only (23 June 2023 DCO):
In the post hoc analysis of the MRD-agnostics randomized patients only, death from any cause occurred in 24 subjects (17.9%) in the blinatumomab + chemotherapy arm and in 53 subjects (39.6%) in the chemotherapy arm. Median follow-up was 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm [90]. The stratified HR for OS, derived from a Cox regression model, was 0.42 (95% CI: 0.26, 0.68), indicating a 58% reduction in the hazard rate for OS in the SoC blinatumomab + chemotherapy arm. At the time of analysis, the median OS had not been reached in either treatment arm [22].

Post hoc analysis: RFS in MRD-agnostic randomized patients (23 June 2023 DCO):
In the post hoc analysis of the MRD-agnostics randomized patients only, death from any cause occurred in 11 subjects (8.2%) in the blinatumomab + chemotherapy arm and in 14 subjects (10.4%) in the chemotherapy arm. Median follow-up was 4.6 years in the blinatumomab + chemotherapy arm and 4.5 years in the chemotherapy arm [90]. The stratified HR for RFS, derived from a Cox regression model, was 0.49 (95% CI: 0.31, 0.76), indicating a 51% reduction in the hazard rate for RFS in the SoC blinatumomab + chemotherapy arm. At the time of analysis, the median RFS had not been reached in either treatment arm [90].

At 5 years, the KM estimate for RFS was 76.9% (95% CI: 68.6, 83.2) in the blinatumomab + chemotherapy arm and 57.2% (95% CI: 47.9, 65.4) in the Chemotherapy arm [90]. A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 14 in appendix B.6.6.

Table 67. Relapse-free survival for MRD-agnostic randomized patients only (Step 3 Analysis Set)

	Blinatumomab + chemotherapy (N=134)	Chemotherapy (N=134)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	92.5 (86.4, 95.9)	86.5 (79.5, 91.3)
At 1 year (95% CI)	89.4 (82.8, 93.6)	75.8 (67.5, 82.2)

At 2 year (95% CI)	81.8 (74.1, 87.4)	66.2 (57.4, 73.7)
At 3 year (95% CI)	80.3 (72.5, 86.1)	61.4 (52.4, 69.2)
At 4 year (95% CI)	76.9 (68.6, 83.2)	58.5 (49.3, 66.5)
At 5 year (95% CI)	76.9 (68.6, 83.2)	57.2 (47.9, 65.4)
At 6 year (95% CI)	76.9 (68.6, 83.2)	51.1 (39.3, 61.8)
At 7 year (95% CI)	76.9 (68.6, 83.2)	51.1 (39.3, 61.8)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

For an overview of OS and RFS results of the Step 3 Analysis Set for the MRD-agnostic randomized patients only, see the table below.

Table 68. Results of the E1910 trial - Step 3 Analysis Set (MRD-agnostic randomized only patients)

Results of E1910 trial [NCT02003222]											
				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**		
Overall Survival at 5 years	Blinatumomab + chemotherapy	134	81.4% (73.5, 87.1)	23,1%	N/A	N/A	HR: 0.42	0.26, 0.68	<0.001	The overall survival is based on the Kaplan-Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[91]
	Chemotherapy	134	58.3% (48.8, 66.7)								

Results of E1910 trial [NCT02003222]											
				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**		
Relapse free survival at 5 years	Blinatumomab + chemotherapy	134	76.9% (68.6, 83.2)	19,7%	N/A	N/A	HR: 0.49	0.31, 0.76	0.002	The relapse free survival is based on the Kaplan–Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[90]
	Chemotherapy	134	57.2% (47.9, 65.4)								

Abbreviations: CI, Confidence interval; HR, hazard ratio; MRD, minimal residual disease; N, number; N/A; not available; OS, overall survival; RFS, relapse-free survival.
Source: [90].

B.4 Results of the E1910 trial – Step 3 Analysis Set (MRD+ patients only)

A total of 62 randomized or registered subjects (40 subjects in the blinatumomab + chemotherapy arm and 22 subjects in the chemotherapy arm) were identified as MRD+ at Step 3 based on the protocol-specified 10^{-4} cut-off (indicating MRD positivity) and were included in the Step 3 MRD Positive Analysis Set [1].

Post hoc analysis: OS in MRD+ subjects (23 June 2023 DCO, CSR and SmPC data):
Among the 62 subjects, a total of 24 deaths were reported: 11 (27.5%) in the blinatumomab + chemotherapy arm and 13 (59.1%) in the chemotherapy only arm [22]. The median follow-up time for OS was 4.6 years for the blinatumomab + chemotherapy arm and 5.0 years for the chemotherapy arm [1]. In line with the primary analysis, the stratified HR for OS, estimated using a Cox PH model, was 0.40 (95% CI: 0.14, 1.12), indicating a strong trend favoring the blinatumomab + chemotherapy arm [1]. At the time of the analysis, the median OS had not been reached in the blinatumomab + chemotherapy arm, while it was 1.9 years in the chemotherapy arm [22].

At 5 years, the KM estimate for OS was 70.1% (95% CI: 52.0, 82.5) in the blinatumomab + chemotherapy arm and 37.8% (95% CI: 17.8, 57.7) in the chemotherapy arm [1]. A KM plot illustrating the OS comparison between the two treatment arms is presented in Figure 15 in appendix B.6.7. Additional details on the KM estimates for OS can be found in Table 69.

Table 69. Overall Survival for MRD+ at Step 3 (Step 3 MRD Positive Analysis Set)

	Blinatumomab + chemotherapy (N=40)	Chemotherapy (N=22)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	92.4 (78.2, 97.5)	81.6 (58.0, 92.7)
At 1 year (95% CI)	89.8 (75.1, 96.0)	57.6 (34.2, 75.3)
At 2 year (95% CI)	79.5 (63.2, 89.2)	48.0 (26.0, 67.0)
At 3 year (95% CI)	74.2 (57.4, 85.2)	43.2 (22.2, 62.6)
At 4 year (95% CI)	74.2 (57.4, 85.2)	43.2 (22.2, 62.6)
At 5 year (95% CI)	70.1 (52.0, 82.5)	37.8 (17.8, 57.7)
At 6 year (95% CI)	70.1 (52.0, 82.5)	37.8 (17.8, 57.7)
At 7 year (95% CI)	70.1 (52.0, 82.5)	37.8 (17.8, 57.7)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [1,22].

Post hoc analysis: RFS in MRD+ subjects (23 June 2023 DCO, CSR and SmPC data):

The median follow-up time for RFS was 4.6 years for the blinatumomab + chemotherapy arm and 5.0 years for the chemotherapy arm. The RFS stratified hazard ratio from a Cox PH model showed a strong trend in favor of the blinatumomab + chemotherapy arm (hazard ratio 0.37 [95% CI: 0.13, 1.03], p = 0.056) [1,22]. The median RFS was not reached in SoC blinatumomab + chemotherapy arm and was 0.6 years in the chemotherapy arm [22].

At 5 years, the KM estimate for RFS was 71.8% (95% CI: 54.8, 83.3) in the blinatumomab + chemotherapy arm and 39.4% (95% CI: 19.3, 59.0) in the chemotherapy arm [1]. A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 16 in appendix B.6.8. Additional details on the KM estimates for RFS can be found in Table 70.

Table 70. Relapse-free Survival for MRD-positive at Step 3 (Step 3 MRD+ Analysis Set)

	Blinatumomab + chemotherapy (N=40)	Chemotherapy (N=22)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	84.9 (69.5, 92.9)	59.1 (36.1, 76.2)
At 1 year (95% CI)	82.4 (66.5, 91.2)	44.3 (23.2, 63.6)
At 2 year (95% CI)	79.8 (63.6, 89.3)	39.4 (19.3, 59.0)
At 3 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 4 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 5 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 6 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 7 year (95% CI)	71.8 (54.8, 83.3)	NE

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease; NE, not estimable.
Source: [1,22].

For an overview of all results of the Step 3 MRD+ Analysis Set, see the table below.

Table 71. Results of the E1910 trial – Step 3 MRD+ Analysis Set

Results of E1910 trial [NCT02003222]											
				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		
Overall Survival at 5 years	Blinatumomab + chemotherapy	40	70.1% (52.0, 82.5)	32.3%	N/A	N/A	HR: 0.40	0.14,1.12	0.082	The overall survival is based on the Kaplan-Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	22	37.8% (17.8, 57.7)								
Relapse free survival at 5 years	Blinatumomab + chemotherapy	40	71.8% (54.8, 83.3)	32.4%	N/A	N/A	HR: 0.37	0.13, 1.03	0.056	The relapse free survival is based on the Kaplan–Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	22	39.4% (19.3, 59.0)								

Abbreviations: CI, Confidence interval; HR, hazard ratio; MRD, minimal residual disease; N, number; N/A; not available; OS, overall survival; RFS, relapse-free survival.
Source: [1,22].

B.5 Results of the E1910 trial – Step 3 Analysis Set (MRD+ randomized patients only)

This appendix only reports results for the randomized MRD+ patients (22 subjects in the blinatumomab + chemotherapy arm and 22 subjects in the chemotherapy arm.

Post hoc analysis: OS in MRD+ subjects (23 June 2023 DCO, data on file):

Among the 44 subjects, a total of 18 deaths were reported: 5 (22.7%) in the blinatumomab + chemotherapy arm and 13 (59.1%) in the chemotherapy only arm [90]. In line with the primary analysis, the stratified HR for OS, estimated using a Cox PH model, was 0.34 (95% CI: 0.10, 1.08), indicating a strong trend favoring the blinatumomab + chemotherapy arm [90]. At the time of the analysis, the median OS had not been reached in the blinatumomab + chemotherapy arm, while it was 1.9 years in the chemotherapy arm [90].

At 5 years, the KM estimate for OS was 75.9% (95% CI: 51.4, 89.2) in the blinatumomab + chemotherapy arm and 37.8% (95% CI: 17.8, 57.7) in the chemotherapy arm [90]. A KM plot illustrating the OS comparison between the two treatment arms is presented in Figure 17 in appendix B.6.9. Additional details on the KM estimates for OS can be found in Table 72.

Table 72. Overall Survival for MRD+ randomized patients only at Step 3

	Blinatumomab + chemotherapy (N=22)	Chemotherapy (N=22)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	95.2 (70.7, 99.3)	81.6 (58.0, 92.7)
At 1 year (95% CI)	95.2 (70.7, 99.3)	57.6 (34.2, 75.3)
At 2 year (95% CI)	81.0 (56.9, 92.4)	48.0 (26.0, 67.0)
At 3 year (95% CI)	75.9 (51.4, 89.2)	43.2 (22.2, 62.6)
At 4 year (95% CI)	75.9 (51.4, 89.2)	43.2 (22.2, 62.6)
At 5 year (95% CI)	75.9 (51.4, 89.2)	37.8 (17.8, 57.7)
At 6 year (95% CI)	75.9 (51.4, 89.2)	37.8 (17.8, 57.7)
At 7 year (95% CI)	75.9 (51.4, 89.2)	NE (NE, NE)

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease.
Source: [90].

Post hoc analysis: RFS in MRD+ randomized patients only (23 June 2023 DCO, Amgen data on file):

In the post hoc analysis of the MRD-agnostics randomized patients only (RFS), death from any cause occurred in 1 subject (4.5%) in the blinatumomab + chemotherapy arm and in 3 subjects (13.6%) in the chemotherapy arm. The RFS stratified HR from a Cox PH model showed a trend in favor of the blinatumomab + chemotherapy arm (HR 0.30 [95% CI: 0.09, 0.97], p = 0.056) [90]. The median RFS was not reached in SoC blinatumomab + chemotherapy arm and was 0.6 years in the chemotherapy arm [90]

At 5 years, the KM estimate for RFS was 71.8% (95% CI: 54.8, 83.3) in the blinatumomab + chemotherapy arm and 39.4% (95% CI: 19.3, 59.0) in the chemotherapy arm [90]. A KM plot illustrating the RFS comparison between the two treatment arms is presented in Figure 18 in B.6.10.

Table 73. Relapse-free Survival for MRD-positive at Step 3

	Blinatumomab + chemotherapy (N=40)	Chemotherapy (N=22)
KM estimate - % [1,22]		
At 0.5 year (95% CI)	84.9 (69.5, 92.9)	59.1 (36.1, 76.2)
At 1 year (95% CI)	82.4 (66.5, 91.2)	44.3 (23.2, 63.6)
At 2 year (95% CI)	79.8 (63.6, 89.3)	39.4 (19.3, 59.0)
At 3 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 4 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 5 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 6 year (95% CI)	71.8 (54.8, 83.3)	39.4 (19.3, 59.0)
At 7 year (95% CI)	71.8 (54.8, 83.3)	NE

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; MRD, minimal residual disease; NE, not estimable.
Source: [90].

For an overview of the OS and RFS results of the Step 3 Analysis Set MRD+ randomized patients only, see the table below.

Table 74. Results of the E1910 trial – Step 3 Analysis Set MRD+ randomized patients only

Results of E1910 trial [NCT02003222]											
				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**		
Overall Survival at 5 years	Blinatumomab + chemotherapy	22	75.9% (51.4, 89.2)	38.1%	N/A	N/A	HR: 0.34	0.10, 1.08	0.066	The overall survival is based on the Kaplan-Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	22	37.8% (17.8, 57.7)								
Relapse free survival at 5 years	Blinatumomab + chemotherapy	22	76.3% (51.9, 89.4)	36.9%	N/A	N/A	HR: 0.30	0.09, 0.97	0.056	The relapse free survival is based on the Kaplan–Meier estimator. The HR estimates are obtained from a stratified Cox regression model.	[1,22]
	Chemotherapy	22	39.4% (19.3, 59.0)								

Abbreviations: CI, Confidence interval; HR, hazard ratio; MRD, minimal residual disease; N, number; N/A; not available; OS, overall survival; RFS, relapse-free survival.
Source: [90].

B.6 KM plots of efficacy results

B.6.1 OS (Full Analysis Set MRD- patients)

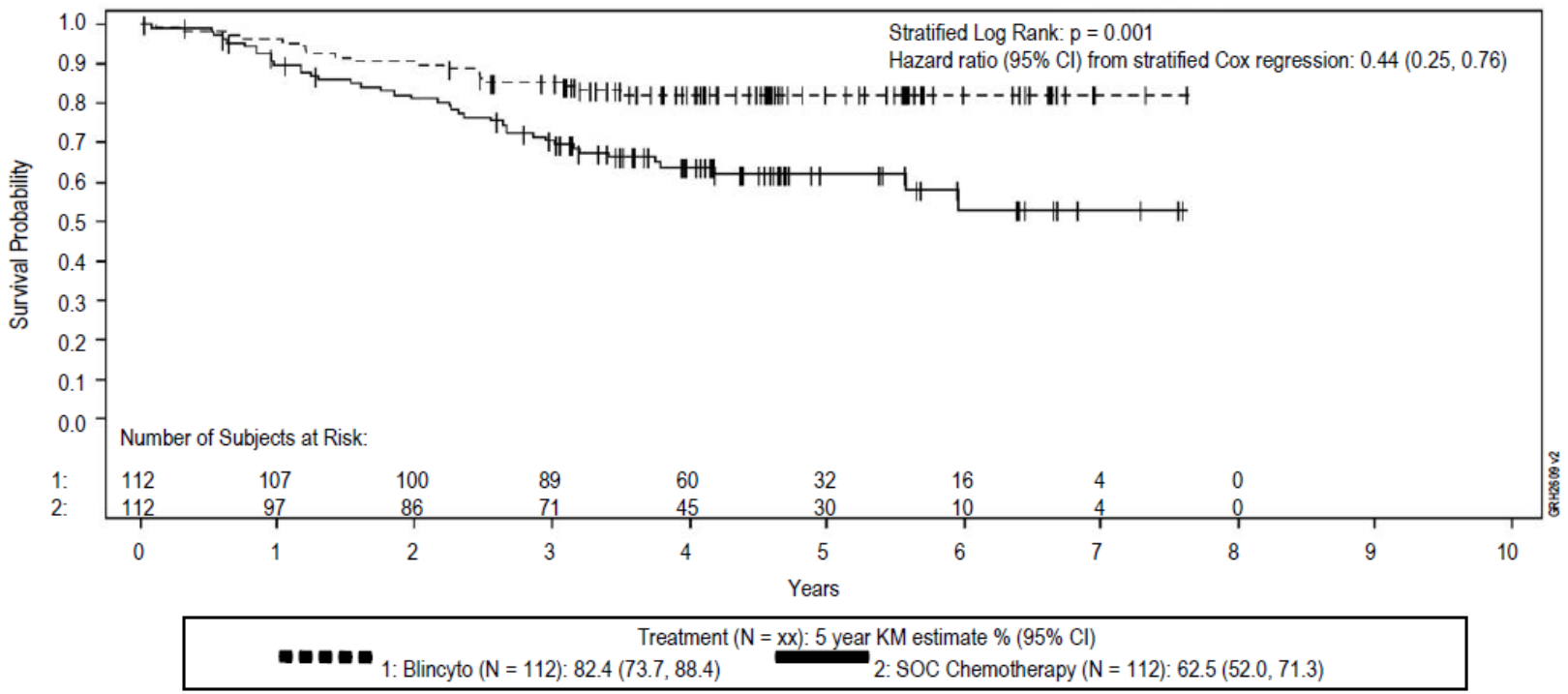

Figure 9. Kaplan-Meier for Overall Survival for MRD- at Step 3 – (FAS)

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

Source: [1].

B.6.2 RFS (Full Analysis Set MRD- patients)

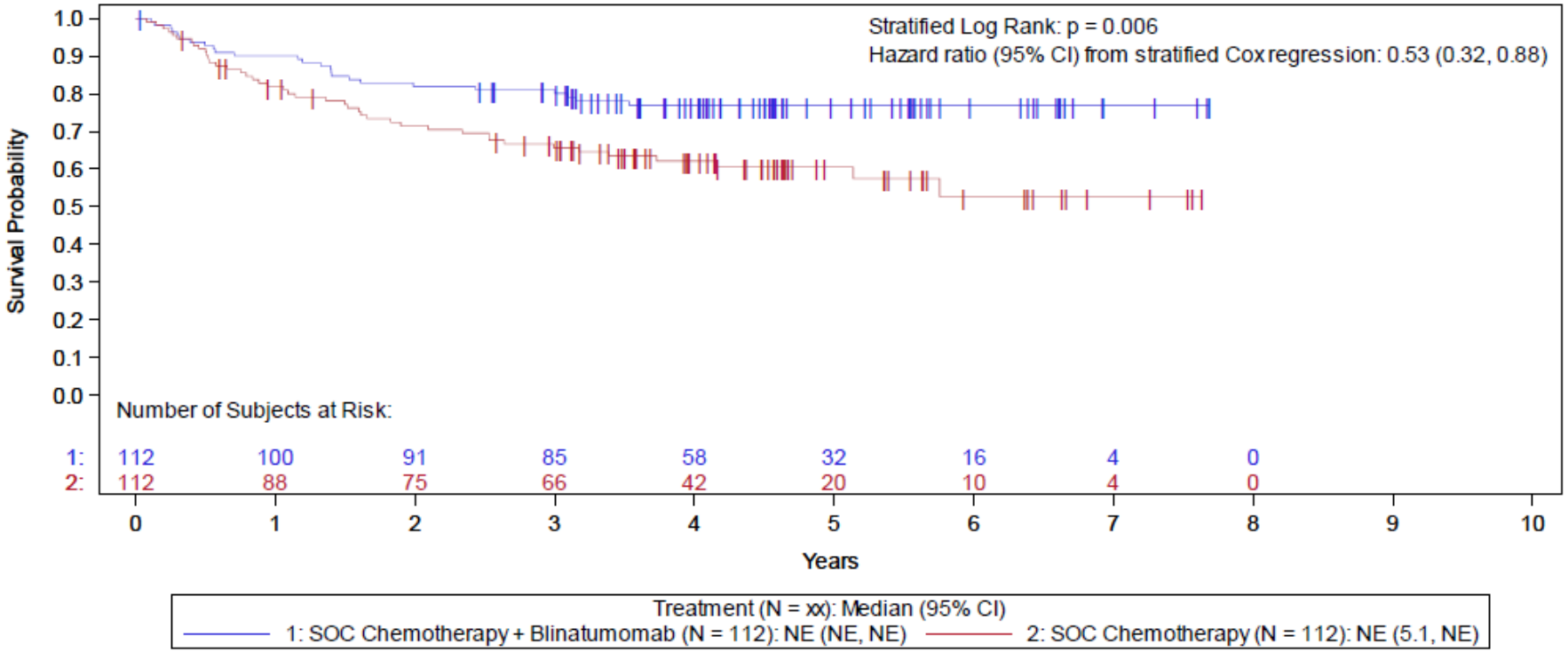

Figure 10. Kaplan-Meier for Relapse-free Survival for MRD- at Step 3 – (FAS)

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

Source: Amgen, Data on file [22].

B.6.3 OS (Step 3 Analysis Set MRD-agnostic)

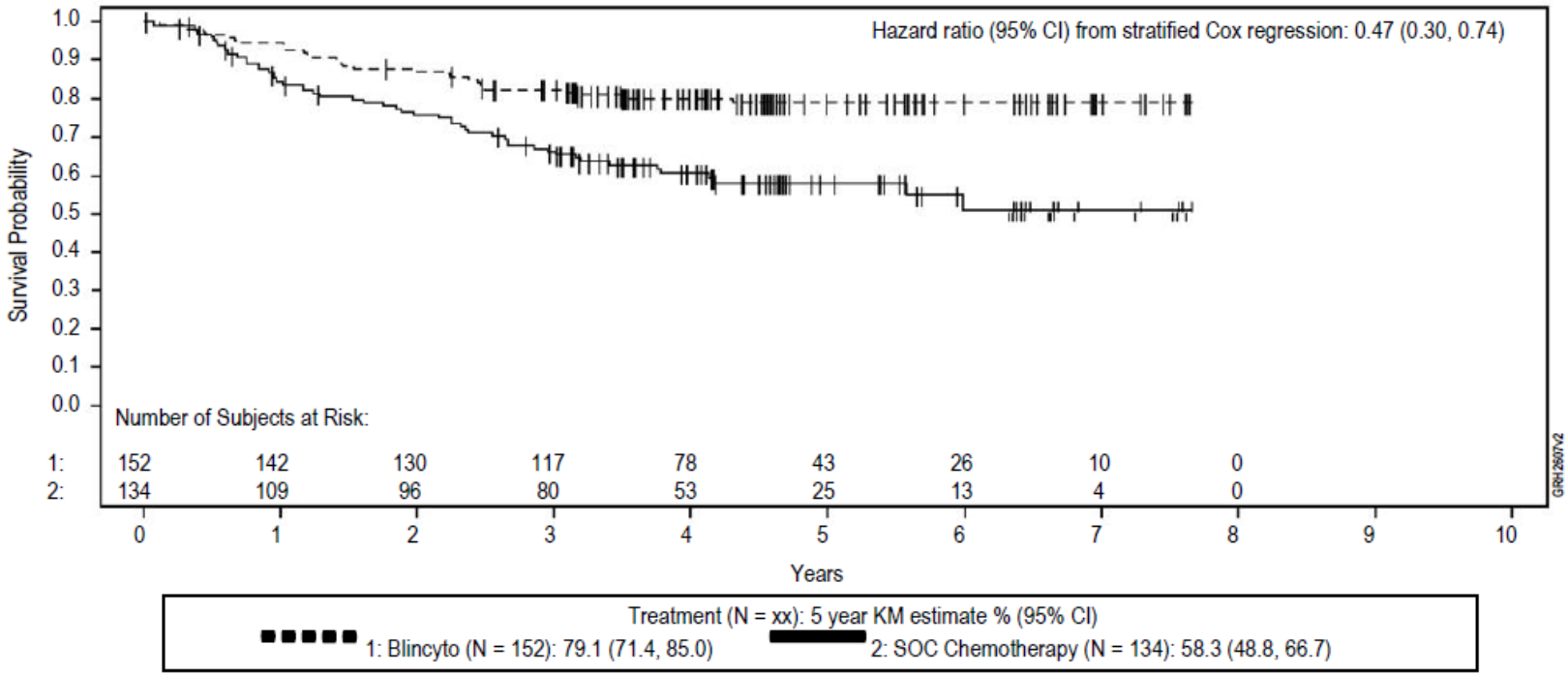

Figure 11. Kaplan-Meier for Overall Survival combining MRD-agnostic at Step 3

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, Number; NE, not estimated; SoC, standard of care.

Source: [1].

B.6.4 RFS (Step 3 Analysis Set MRD-agnostic)

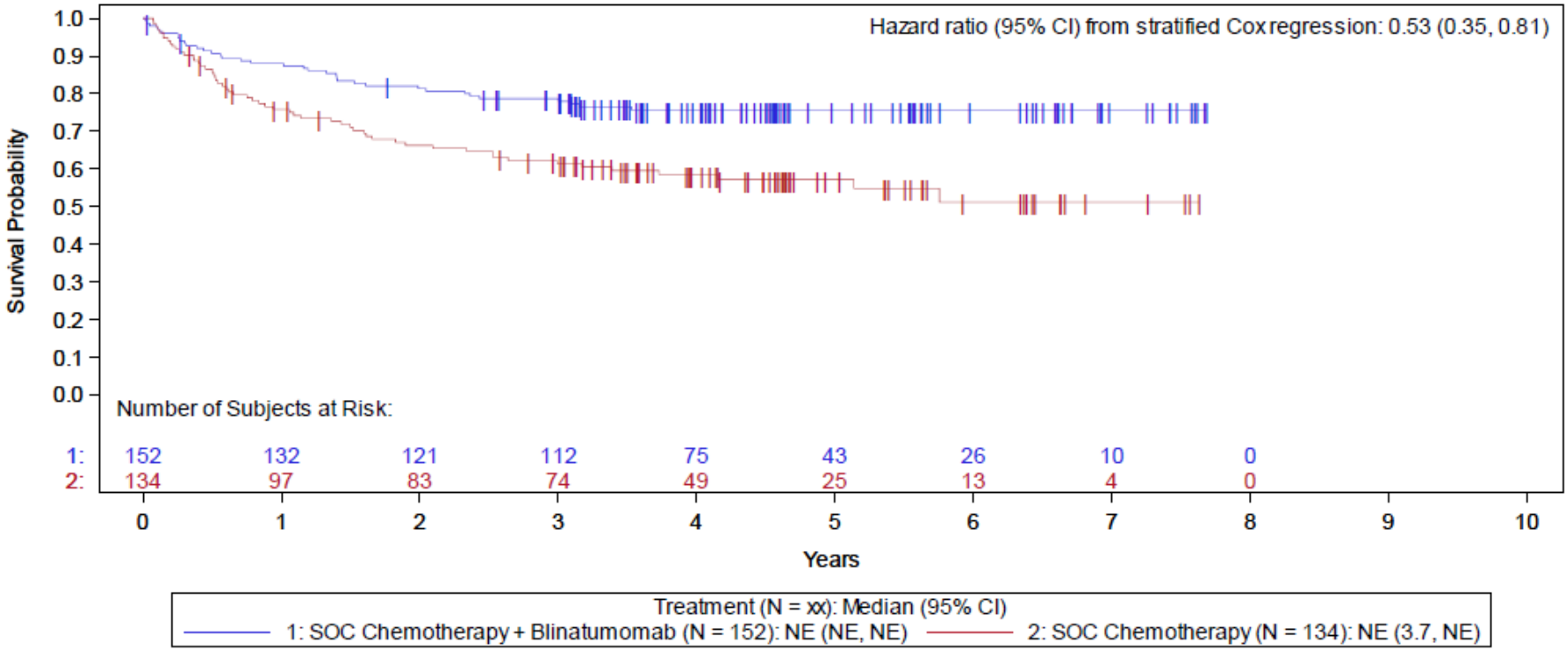

Figure 12. Kaplan-Meier for Relapse-free Survival combining MRD-agnostic at Step 3

Data cut-off date: 23 June 2023.
Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.
Source: Amgen, Data on file [22].

B.6.5 OS (Step 3 Analysis Set MRD-agnostic randomized patients only)

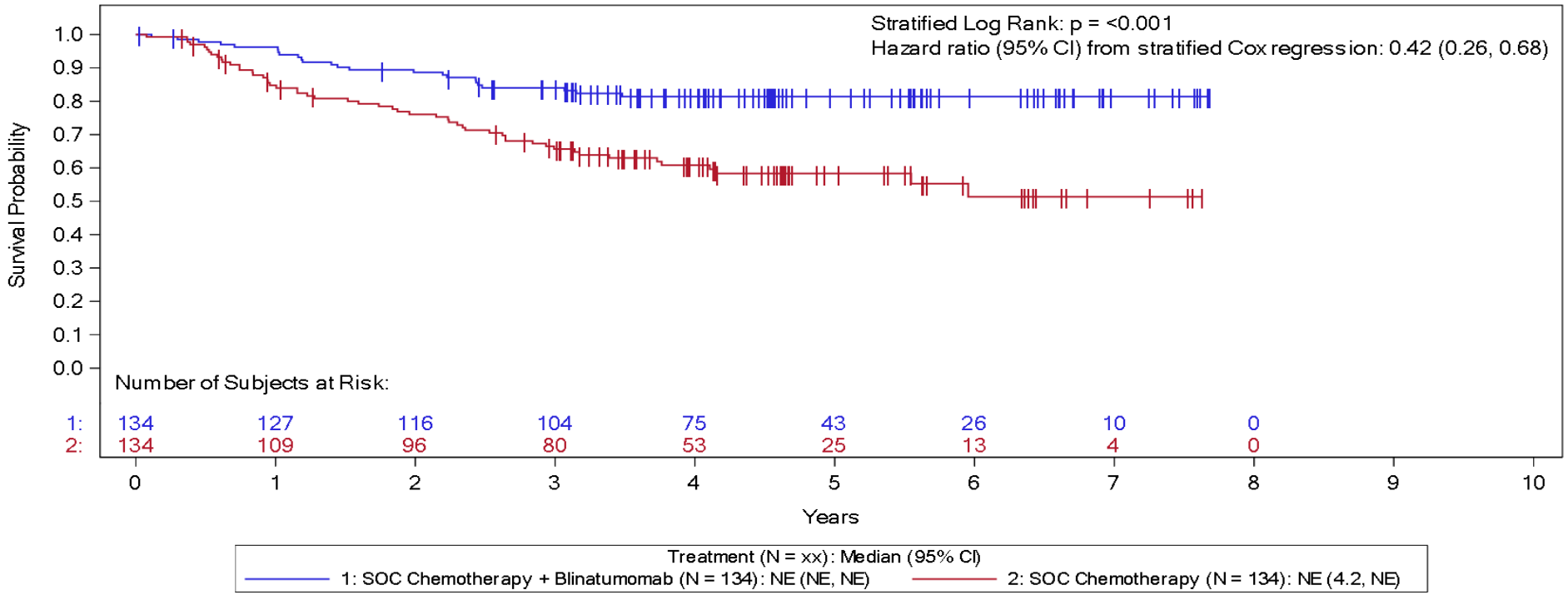

Figure 13. Kaplan-Meier for Overall Survival combining MRD-agnostic randomized only patients at Step 3 (Step 3 Analysis Set)

Data cut-off date: 23 June 2023.
Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.
Source: Amgen, Data on file [22].

B.6.6 RFS (Step 3 Analysis Set MRD-agnostic randomized patients only)

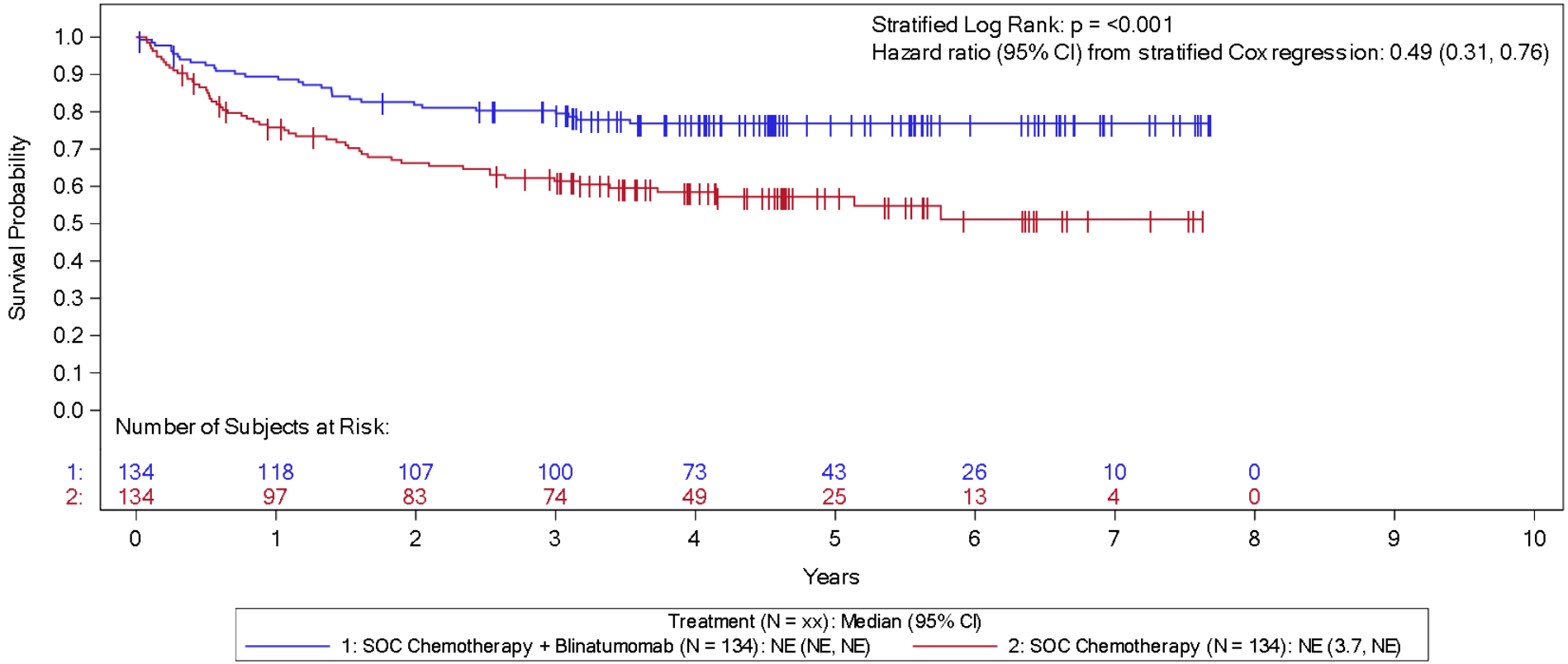

Figure 14. Kaplan-Meier for Relapse Free Survival combining MRD-agnostic randomized only patients at Step 3 (Step 3 Analysis Set)

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

B.6.7 OS (Step 3 Analysis Set MRD+ patients)

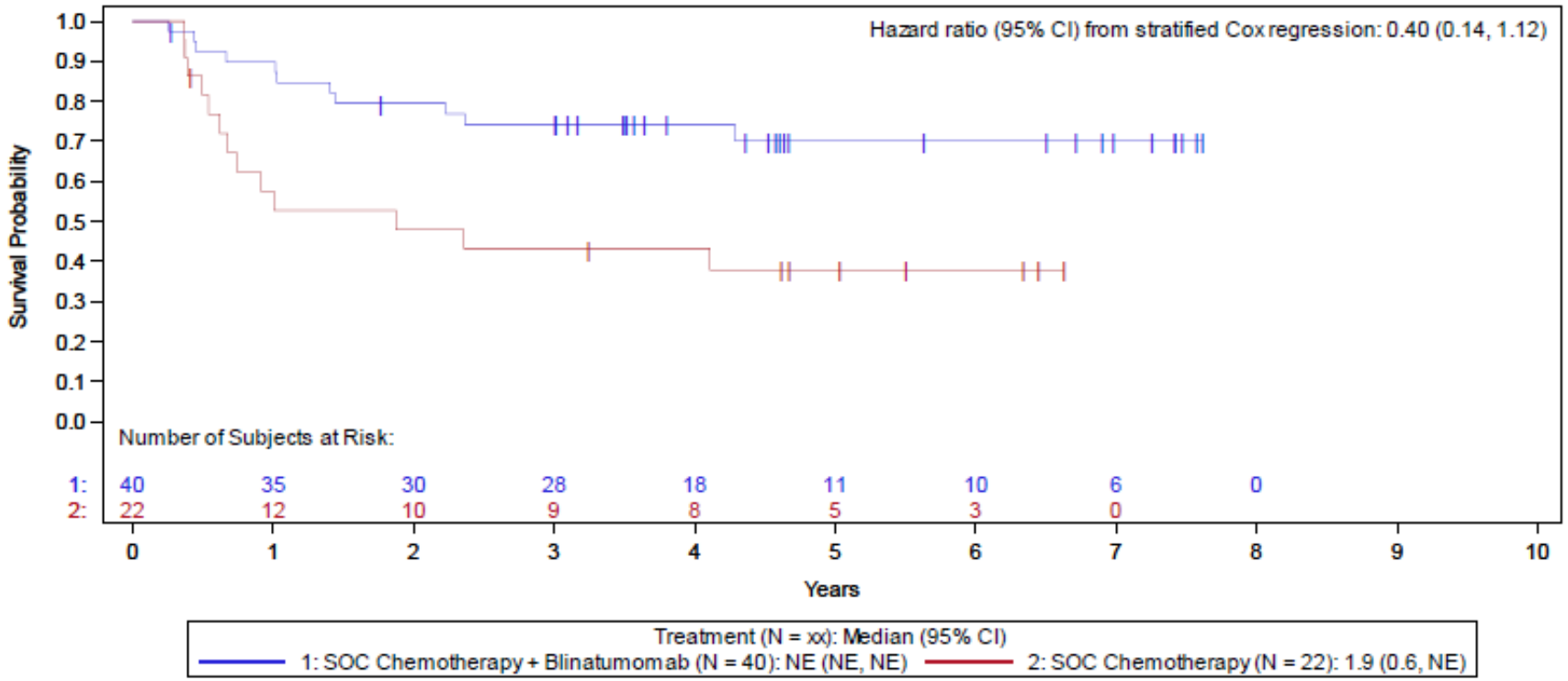

Figure 15. Kaplan-Meier for Overall Survival for MRD-positive at Step 3

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

Source: Amgen, Data on file [22].

B.6.8 RFS (Step 3 Analysis Set MRD+ patients)

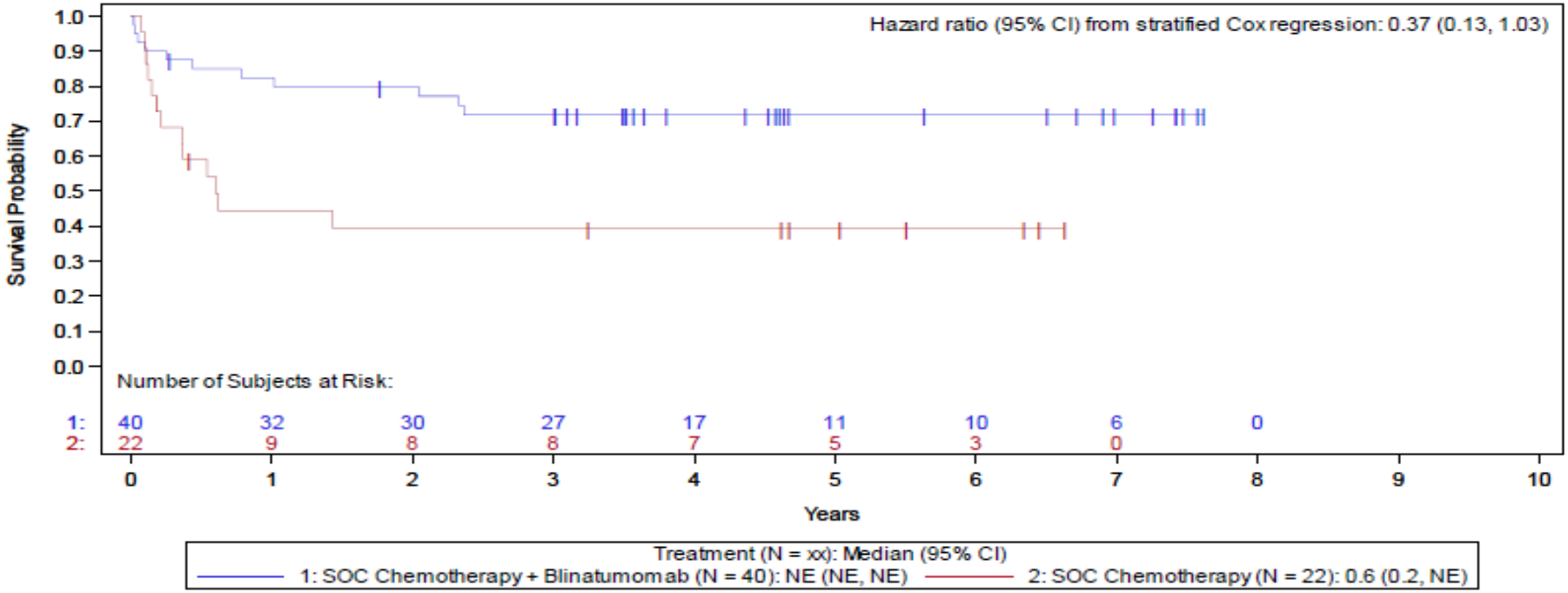

Figure 16. Kaplan-Meier for Relapse-Free Survival for MRD+ at Step 3

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

Source: Amgen, Data on file [22].

B.6.9 OS (Step 3 Analysis Set MRD+ randomized patients only)

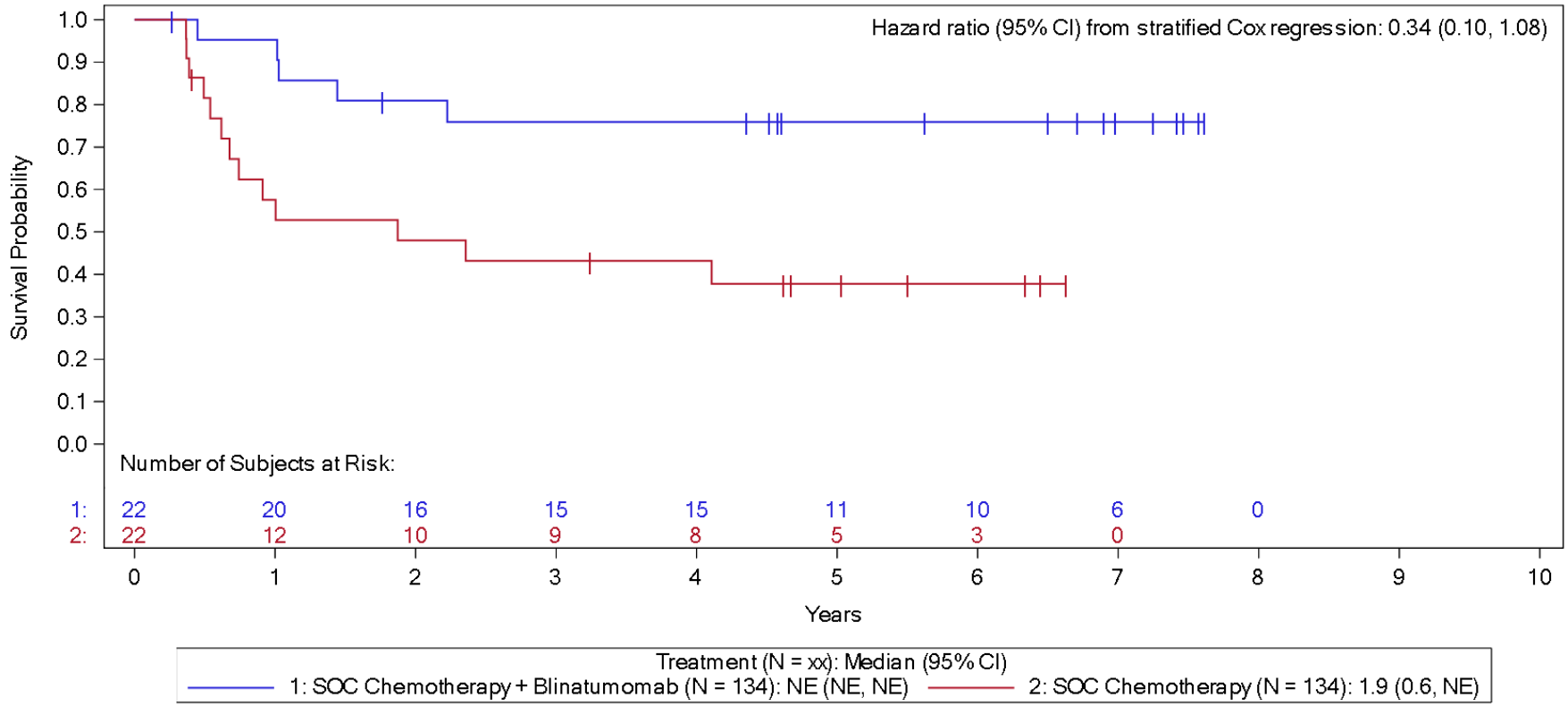

Figure 17. Kaplan-Meier for Overall Survival for MRD+ randomized patients only at Step 3

Data cut-off date: 23 June 2023.

Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.

Source: Amgen, Data on file [90].

B.6.10 RFS (Step 3 Analysis Set MRD+ randomized patients only)

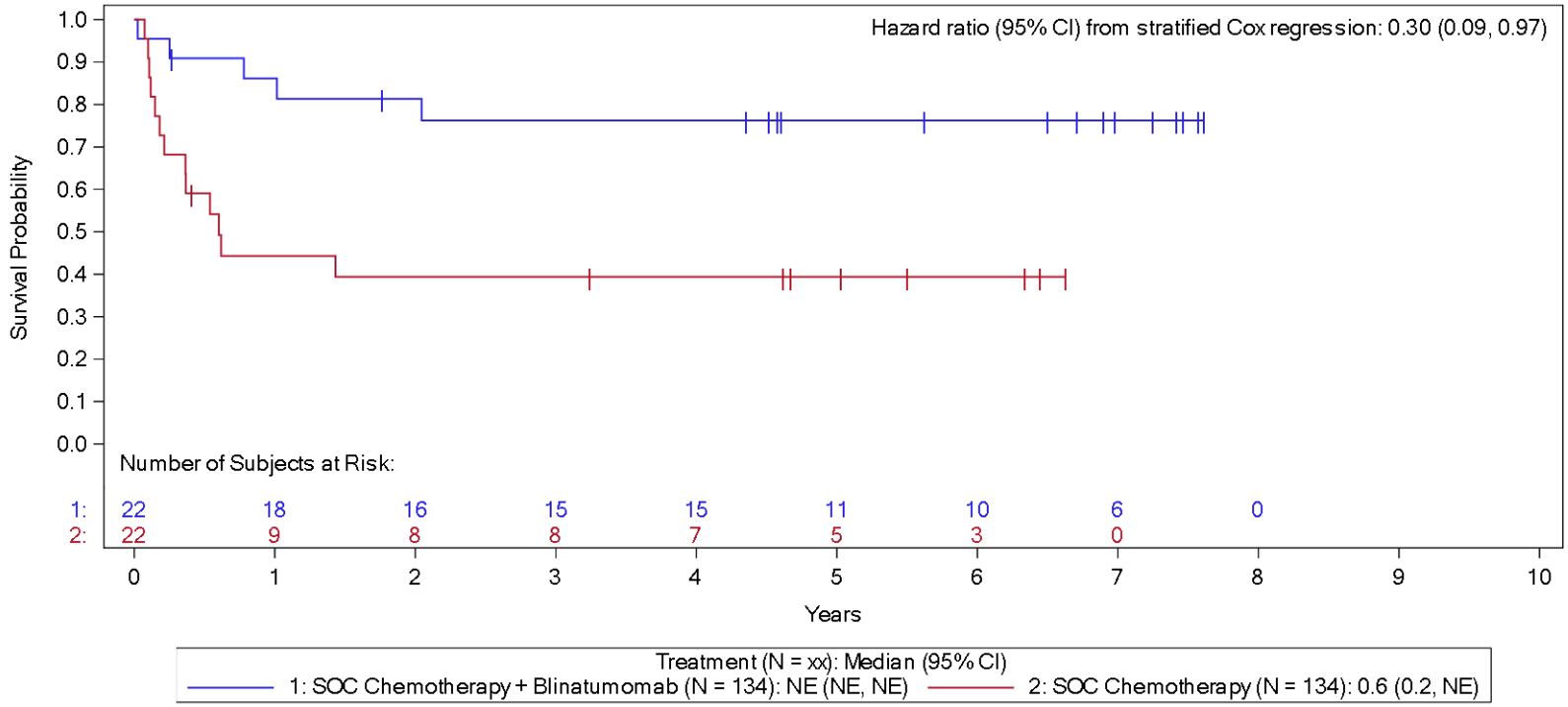

Figure 18. Kaplan-Meier for Relapse-Free Survival for MRD+ randomized patients only at Step 3

Data cut-off date: 23 June 2023.
Abbreviations: CI, confidence interval; N, number; NE, not estimated; SoC, standard of care.
Source: Amgen, Data on file [91].

Appendix C. Comparative analysis of efficacy (N/A)

As efficacy and safety differences between blinatumomab + chemotherapy and chemotherapy relevant to Danish clinical practice have been directly compared in a head-to-head study, this section is not applicable.

Appendix D. Extrapolation

For the base case analysis, Exponential MCMs were selected for modeling RFS in both treatment arms, whereas the Gompertz MCM and Log-normal MCM were selected for modeling OS in the blinatumomab + chemotherapy arm and chemotherapy arm, respectively. In the following section, details of the extrapolations used in the base case of the CEM are presented. In line with the recommendations in NICE DSU TSD 14, the choice of the most appropriate survival model for each arm and in each patient population was guided by the following:

- Clinical plausibility, which stipulates that the OS should neither underestimate nor exceed the SMR-adjusted general population survival and that there should be sufficient separation between the RFS and OS curves to reflect the possibility of post-relapse survival with subsequent therapies.
- Visual inspection against the observed KM curve and hazard plot. The fitted curves were overlaid onto the KM curve from the trial to assess similarity with the observed data.
- Goodness-of-fit statistics using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), where the lower the AIC or BIC, the better the model fit to the observed data. The goodness-of-fit statistics from the two arms of the same endpoint (i.e. OS or RFS) were added and subsequently ranked to determine which model had the best statistical fit in each of the two methods (MCM or PSM).

D.1 Extrapolation of OS

D.1.1 Data input

Extrapolation of the OS beyond the study period was required as the data from the E1910 trial did not provide accurate estimates hereof.

D.1.2 Model

As described in section 8.1, the E1910 trial data indicated that a group of patients achieved durable treatment remission. To better capture this plateau in survival, MCMs were considered in the base case analysis to inform long-term survival in the model. The cure fractions for the MCMs modeling OS in the MRD-agnostic population are presented in Table 75 below.

Table 75. Cure Fractions for MCMs for Modelling OS in the MRD-agnostic Population

Treatment Arm	Exponential	Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
Blinatumomab + chemotherapy	0.787	0.808	0.814	0.790	0.783	0.812

Chemotherapy	0.425	0.512	0.511	0.445	0.403	0.516

All standard parametric models, including Exponential, Weibull, Gompertz, Gamma, Log-Normal, Generalized Gamma, and Log-Logistic were tested, and are all available in the Excel model. However, the generalized gamma MCM was not considered in the model as it appeared to be over-fitting the data, leading to implausible results (with a low cure fraction) for the RFS distribution and it did not converge when fitting to the OS KM curve, leading to errors.

D.1.3 Proportional hazards

Figure 19 and Figure 20 present the LCH and Schoenfeld residual plots, respectively, for OS. The LCH plot (Figure 19) shows that the curves cross at the start of the follow-up period, which suggests violation of the PH assumption. After around 6 months, the curves appeared to be approximately parallel. Additionally, the Schoenfeld residual plot (Figure 20) formed an approximately horizontal line up to around 12 months, but the gradient from around 24 months raised some concerns. However, the Schoenfeld individual test provided no evidence against the PH assumption ($p > 0.05$). Given that there was some evidence that the PH assumption was violated, the analyses focused on fitting separate effect models to the data.

Figure 19. Log-cumulative hazard plot for OS in the MRD-agnostic population
Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; MRD-, MRD-negative; OS, overall survival; SoC, standard of care.
Source: Amgen, Data on file [90].

Figure 20. Schoenfeld residual plot for OS in the MRD-agnostic population

Notes: The blue dots indicate Schoenfeld residuals; the solid black line indicates time-varying log hazard ratio; the dashed black line indicates log-hazard ratio ± 2 standard errors; and the solid blue line indicates constant log-hazard ratio.
Abbreviations: MRD, minimal residual disease; MRD-, MRD-negative; OS, overall survival.
Source: Amgen, Data on file [90].

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

Table 76 summarizes the MCM fit statistics by treatment arm for the OS endpoint.

Table 76. Goodness-of-fit statistics – OS in MRD-agnostic population

Model	Blinatumomab + chemotherapy			
	AIC	BIC	AIC rank	BIC rank
Exponential	314.892	320.688	5	3
Gamma	312.199	320.893	3	4
Gompertz	310.362	319.056	1	1
Log-logistic	313.372	322.066	4	5
Log-normal	314.904	323.597	6	6
Weibull	311.211	319.904	2	2

Model	Chemotherapy			
	AIC	BIC	AIC rank	BIC rank
Exponential	596.518	602.314	5	1
Gamma	594.995	603.689	3	4
Gompertz	598.001	606.695	6	6
Log-logistic	594.425	603.119	2	3
Log-normal	593.764	602.458	1	2
Weibull	595.720	604.414	4	5

Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; MCM, mixture cure model; OS, overall survival.
Source: Amgen, Data on file [90].

The best statistically fitting MCM curve based on goodness-of-fit statistics alone was the Gompertz MCM based on both AIC and BIC for the blinatumomab + chemotherapy arm, and the log-normal MCM and exponential MCM for AIC and BIC, respectively, for the chemotherapy arm.

D.1.5 Evaluation of visual fit

Figure 21 and Figure 22 present all investigated extrapolated curves fit to the OS KM curve for blinatumomab + chemotherapy and chemotherapy alone, respectively. The OS KM curve is presented as the black solid line until the end of trial follow-up after which point the SMR-adjusted general population survival is shown as the black dotted line.

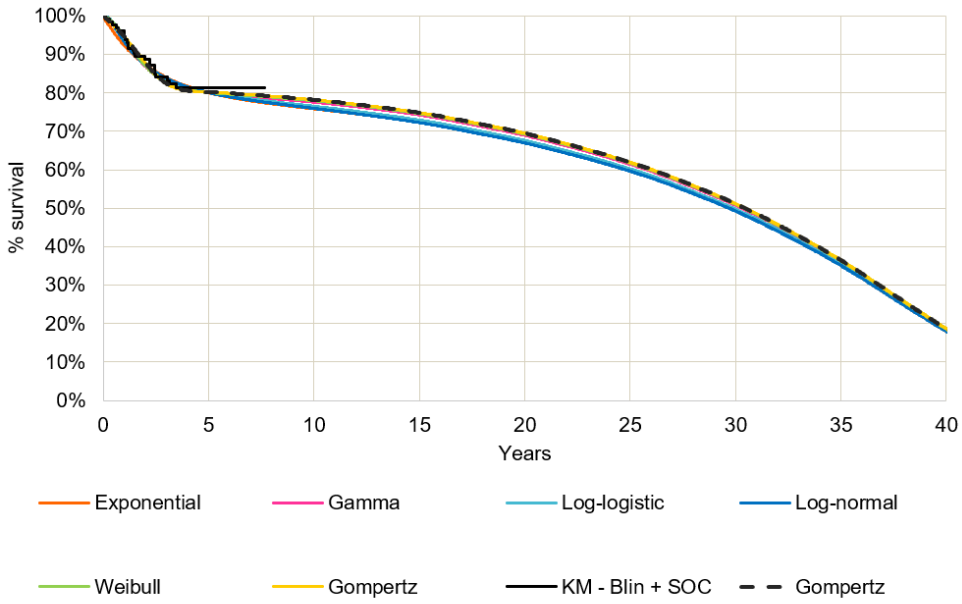

Figure 21. Extrapolated MCM (OS) – blinatumomab + SoC in MRD-agnostic population

Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; MCM, mixture cure model; OS, overall survival; SoC, standard of care.

Source: Amgen, Data on file [90].

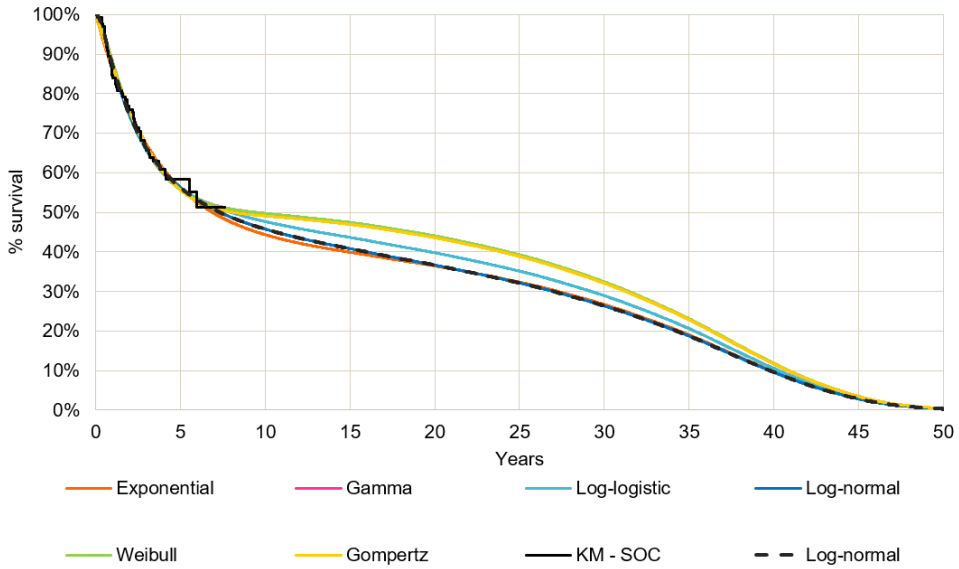

Figure 22. Extrapolated MCM (OS) – SoC in MRD-agnostic population

Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; MCM, mixture cure model; OS, overall survival; SoC, standard of care.

Source: Amgen, Data on file [90].

When assessing the visual fits relative to the general population survival with the added SMR, the exponential, log-normal, and log-logistic MCMs underestimated the long-term survival in the chemotherapy arm. The Weibull and Gompertz MCMs provide a better visual fit to the KM curves in both treatment arms, but especially in the blinatumomab + chemotherapy arm, and is aligned with the SMR-adjusted general population survival, without exceeding it.

D.1.6 Evaluation of hazard functions

Figure 23 displays the noisy and smoothed hazard plots for blinatumomab + chemotherapy and chemotherapy. The smoothed hazard curve for blinatumomab + chemotherapy shows that the hazard initially increased but then decreased over the remaining follow-up period. Similarly, the chemotherapy arm displays an initial increase then decrease until approximately 60 months. At this point, a spike in the smoothed hazard was observed (likely attributed to the small number of patients at risk). Throughout the observed follow-up period the smoothed hazard plot for chemotherapy consistently maintained a higher level than the blinatumomab + chemotherapy arm. Given that the hazard plots for both treatments showed an initial increase followed by a decrease, generalized gamma, log-normal or log-logistic were predicted to be the most appropriate parametric distributions to model the data.

Figure 23. Hazard plot for OS in the MRD-agnostic population
Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; MRD-, MRD-negative; OS, overall survival; SoC, standard of care.
Source: Amgen, Data on file [90].

D.1.7 Validation and discussion of extrapolated curves

When assessing the visual fits relative to the general population survival with the added SMR, the exponential MCM underestimated the long-term survival substantially in the chemotherapy arm. The Weibull and Gompertz MCM provide a better visual fit to the KM curves in both treatment arms and is aligned with the SMR-adjusted general population survival, without exceeding it. The best statistically fitting MCM curve was the Gompertz MCM for the blinatumomab + chemotherapy arm, and the log-normal MCM and exponential MCM for AIC and BIC, respectively, for the chemotherapy arm. Therefore, the Gompertz MCM and Log-normal MCM were selected for modeling OS in the blinatumomab + chemotherapy arm and chemotherapy arm, respectively. The Weibull and log-logistic MCM OS extrapolations in the blinatumomab + chemotherapy arm, together with the gamma and exponential MCM RFS extrapolations in the chemotherapy arm were explored as scenarios.

D.1.8 Adjustment of background mortality

The background mortality rates were derived from Statistics Denmark to reflect the general mortality within the Danish population and to ensure that the survival models do not exceed those of the general population.

D.1.9 Adjustment for treatment switching/cross-over (N/A)

Not applicable since there was no treatment switching/cross-over in the E1910 trial.

D.1.10 Waning effect (N/A)

Not applicable since there is no biological or clinical rationale for assuming a waning effect.

D.1.11 Cure-point

As mentioned in section 4, MCMs including cure fractions were selected for modeling survival in the base case based on their clinical validity, given the potential for long-term remission and cure in newly diagnosed ALL patients, and their best visual and statistical fit to the plateaus observed in the RFS and OS KM curves. Additionally, a cure point of 3 years was validated by the Danish clinical expert as being appropriate for the newly diagnosed adult Ph- B-ALL population.

D.2 Extrapolation of RFS

D.2.1 Data input

Extrapolation of the RFS beyond the study period was required as the data from the E1910 trial did not provide accurate estimates hereof.

D.2.2 Model

As described in section 8.1, the E1910 trial data indicated that a group of patients achieved durable treatment remission. To better capture this plateau in survival, MCMs were considered to inform long-term survival in the model. The cure fractions for the MCMs modeling OS in the MRD-agnostic population are presented in Table 77 below.

Table 77. Cure Fractions for Mixture Cure Models for Modelling Relapse free in the MRD-agnostic Population

Treatment Arm	Exponential	Gamma	Gompertz	Log-Logistic	Log-Normal	Weibull
Blinatumomab + chemotherapy	0.762	0.764	0.768	0.734	0.728	0.764
Chemotherapy	0.534	0.532	0.447	0.480	0.475	0.526

All standard parametric models, including Exponential, Weibull, Gompertz, Gamma, Log-Normal, Generalized Gamma, and Log-Logistic were tested, and are all available in the Excel model. However, the generalized gamma MCM was not considered in the model as it appeared to be over-fitting the data, leading to implausible results (with a low cure fraction) for the RFS distribution and it did not converge when fitting to the OS KM curve, leading to errors.

D.2.3 Proportional hazards

Figure 24 and Figure 25 present the LCH and Schoenfeld residual plots, respectively, for RFS in the MRD-agnostic population. Similar to OS, the LCH plot (Figure 24) displays curves that appeared to be approximately parallel and do not cross at all throughout the follow-up period, suggesting that the PH assumption holds. The Schoenfeld residual plot (Figure 25) formed an approximately horizontal line supporting the PH assumption, with the Schoenfeld individual test providing no evidence against the PH assumption ($p > 0.05$). Although there is limited evidence that that PH assumption is violated, the analyses focused on fitting separate effect models to the data.

Figure 24. Log-cumulative hazard plot for RFS in the MRD-agnostic population

Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; RFS, relapse-free survival; SoC, standard of care.

Source: Amgen, Data on file [90].

Figure 25. Schoenfeld residual plot for RFS in the MRD-agnostic population

Notes: The blue dots indicate Schoenfeld residuals; the solid black line indicates time-varying log hazard ratio; the dashed black line indicates log-hazard ratio ± 2 standard errors; and the solid blue line indicates constant log-hazard ratio.

Abbreviations: MRD, minimal residual disease; MRD-, MRD-negative; RFS, relapse-free survival.
Source: Amgen, Data on file [90].

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

Table 78 summarizes the MCM fit statistics by treatment arm for the RFS endpoint.

Table 78. Goodness-of-fit statistics – RFS in MRD-agnostic population

Model	Blinatumomab + chemotherapy			
	AIC	BIC	AIC rank	BIC rank
Exponential	364.000	369.780	1	1
Gamma	365.788	374.481	4	4
Gompertz	365.489	374.183	2	2
Log-logistic	366.721	375.414	5	5
Log-normal	367.248	375.942	6	6
Weibull	365.759	374.452	3	3
Model	**Chemotherapy**			
	AIC	**BIC**	**AIC rank**	**BIC rank**
Exponential	593.231	599.026	4	2
Gamma	589.584	603.854	1	6
Gompertz	591.909	602.210	3	4
Log-logistic	589.671	600.602	2	3
Log-normal	594.853	598.364	5	1
Weibull	595.161	603.547	6	5

Abbreviations: AIC, akaike information criterion; BIC, bayesian information criterion; MCM, mixture cure model; OS, overall survival.

The best statistically fitting MCM curve based on goodness-of-fit statistics alone was the exponential MCM based on both AIC and BIC for the blinatumomab + chemotherapy arm, and the gamma MCM and log-normal MCM for AIC and BIC, respectively, for the chemotherapy arm.

D.2.5 Evaluation of visual fit

Figure 26 and Figure 27 present all investigated extrapolated curves fit to the RFS KM curve for blinatumomab + chemotherapy and chemotherapy alone, respectively. The RFS KM curve is presented as the black solid line until the end of trial follow-up after which point the SMR-adjusted general population survival is shown as the black dotted line.

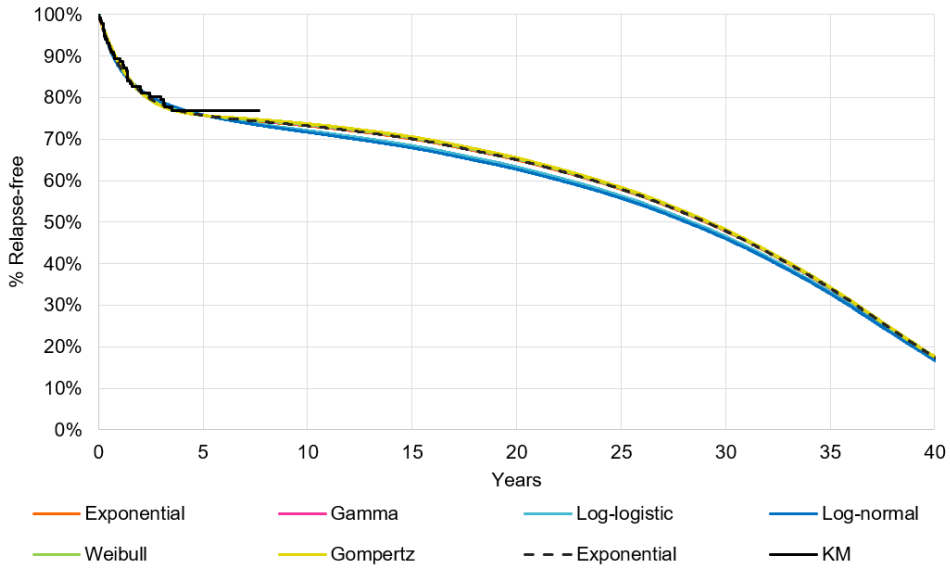

Figure 26. Extrapolated MCM (RFS) – blinatumomab + SoC in MRD-agnostic population

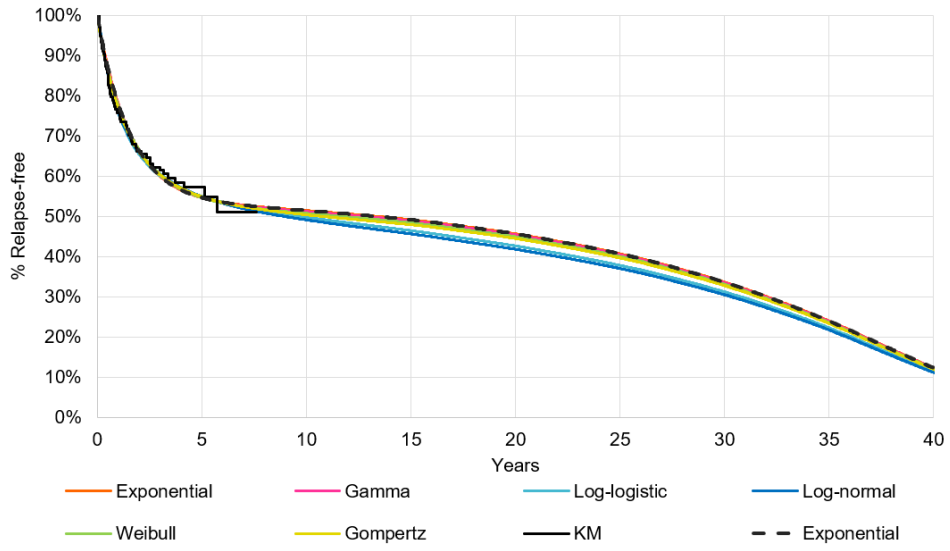

Figure 27. Extrapolated MCM (RFS) – SoC in MRD-agnostic population

All models provided a good visual fit to the trial data in both arms but overestimated RFS towards the tail of the KM curves. The log-normal and log-logistic MCMs are evaluated to provide the best visual fit to the KM curves in both treatment arms.

D.2.6 Evaluation of hazard functions

Noisy (4-week smoothing) and smoothed (1-year smoothing) hazard plots for each treatment are presented in Figure 28. The smoothed hazard plot for blinatumomab +

chemotherapy demonstrated a continuous and consistent decline in hazard throughout the follow-up period; a hazard of zero is observed after approximately 66 months (although there are few patients at risk at this time). Similarly, chemotherapy also exhibited a consistent decrease in hazard over time, but the hazard appeared to remain relatively constant after 36 months. The hazard rate for chemotherapy remains higher throughout the entire follow-up period than that of blinatumomab + chemotherapy. Notably, the observed plateau at approximately 66 months in the hazard curve for blinatumomab + chemotherapy is not observed to the same extent in the chemotherapy arm. Given that the smoothed hazards for both treatment arms showed a monotonically decreasing hazard, generalized gamma, Weibull, Gompertz, gamma or log-logistic were predicted to be the most appropriate parametric distributions to model the data, as well as mixture cure models.

Figure 28. Hazard plot for RFS in the MRD-agnostic population

Abbreviations: Blin, blinatumomab; MRD, minimal residual disease; MRD-, MRD-negative; RFS, relapse-free survival; SoC, standard of care.
Source: Amgen, Data on file [90].

D.2.7 Validation and discussion of extrapolated curves

All models provided a good statistical and visual fit to the trial data in both arms but underestimated RFS towards the tail of the KM curve for blinatumomab + chemotherapy, while overestimating the tail of the SoC KM curve. The Gompertz, exponential, and log-normal MCM distributions had the top three best statistical fits. Of these, exponential MCM was selected as the base case RFS curve, as it has a good statistical and visual fit, and provides a plausible survival extrapolation for both treatment arms. While all MCMs appear to overestimate RFS in the chemotherapy arm, the exponential MCM provides a close fit to the chemotherapy RFS KM curve. The Gompertz and log-normal MCM RFS extrapolations were explored as scenarios.

D.2.8 Adjustment of background mortality

The background mortality rates were derived from Statistics Denmark to reflect the general mortality within the Danish population and to ensure that the survival models do not exceed those of the general population.

D.2.9 Adjustment for treatment switching/cross-over (N/A)

Not applicable since there was no treatment switching/cross-over in the E1910 trial.

D.2.10 Waning effect (N/A)

Not applicable since there is no biological or clinical rationale for assuming a waning effect.

D.2.11 Cure-point

As mentioned in section section 4, MCMs including cure fractions were selected for modeling survival in the base case based on their clinical validity, given the potential for long-term remission and cure in newly diagnosed ALL patients, and their best visual and statistical fit to the plateaus observed in the RFS and OS KM curves. Additionally, a cure point of 4 years was validated by the Danish clinical expert as being appropriate for the newly diagnosed adult Ph- B-ALL population.

Appendix E. Serious adverse events

This appendix provides an overview of all serious adverse events observed in the E1910 trial (Safety Analysis Set), see Table 79 below [22].

Table 79. Serious adverse events

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Number of subjects reporting step 3 treatment-emergent adverse events requiring expedited reporting	**82 (55.8)**	**36 (28.1)**	**118 (42.9)**
Blood and lymphatic system disorders	20 (13.6)	15 (11.7)	35 (12.7)
Febrile neutropenia	18 (12.2)	15 (11.7)	33 (12.0)
Anemia	3 (2.0)	0 (0.0)	3 (1.1)
Coagulopathy	1 (0.7)	0 (0.0)	1 (0.4)
Cardiac disorders	4 (2.7)	3 (2.3)	7 (2.5)
Atrial fibrillation	2 (1.4)	0 (0.0)	2 (0.7)
Cardiac arrest	0 (0.0)	2 (1.6)	2 (0.7)
Sinus tachycardia	2 (1.4)	1 (0.8)	3 (1.1)
Ear and labyrinth disorders	1 (0.7)	0 (0.0)	1 (0.4)
Ear Pain	1 (0.7)	0 (0.0)	1 (0.4)
Endocrine disorders	1 (0.7)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Hypogonadism	1 (0.7)	0 (0.0)	1 (0.4)
Gastrointestinal disorders	10 (6.8)	3 (2.3)	13 (4.7)
Nausea	6 (4.1)	0 (0.0)	6 (2.2)
Vomiting	5 (3.4)	0 (0.0)	5 (1.8)
Diarrhoea	3 (2.0)	0 (0.0)	3 (1.1)
Abdominal pain	0 (0.0)	2 (1.6)	2 (0.7)
Enterocolitis	0 (0.0)	2 (1.6)	2 (0.7)
Constipation	1 (0.7)	0 (0.0)	1 (0.4)
Stomatitis	1 (0.7)	0 (0.0)	1 (0.4)
Colitis	1 (0.7)	0 (0.0)	1 (0.4)
Oral pain	1 (0.7)	0 (0.0)	1 (0.4)
General disorders and administration site conditions	20 (13.6)	3 (2.3)	23 (8.4)
Pyrexia	14 (9.5)	1 (0.8)	15 (5.5)
Fatigue	2 (1.4)	1 (0.8)	3 (1.1)
Chills	2 (1.4)	0 (0.0)	2 (0.7)
Generalised oedema	1 (0.7)	0 (0.0)	1 (0.4)
Non-cardiac chest pain	1 (0.7)	0 (0.0)	1 (0.4)
Gait disturbance	1 (0.7)	0 (0.0)	1 (0.4)
Influenza like illness	0 (0.0)	1 (0.8)	1 (0.4)
Hepatobiliary disorders	1 (0.7)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Hepatotoxicity	1 (0.7)	0 (0.0)	1 (0.4)
Immune system disorders	5 (3.4)	2 (1.6)	7 (2.5)
Cytokine release syndrome	5 (3.4)	0 (0.0)	5 (1.8)
Anaphylactic reaction	0 (0.0)	1 (0.8)	1 (0.4)
Hypersensitivity	0 (0.0)	1 (0.8)	1 (0.4)
Infections and infestations	33 (22.4)	19 (14.8)	52 (18.9)
Sepsis	13 (8.8)	9 (7.0)	22 (8.0)
Device related infection	12 (8.2)	5 (3.9)	17 (6.2)
Urinary tract infection	3 (2.0)	3 (2.3)	6 (2.2)
Pneumonia	2 (1.4)	2 (1.6)	4 (1.5)
Bacteraemia	3 (2.0)	0 (0.0)	3 (1.1)
Enterocolitis infectious	2 (1.4)	0 (0.0)	2 (0.7)
Upper respiratory tract infection	0 (0.0)	3 (2.3)	3 (1.1)
Appendicitis perforated	1 (0.7)	0 (0.0)	1 (0.4)
Bronchitis	1 (0.7)	0 (0.0)	1 (0.4)
Hepatic infection	1 (0.7)	0 (0.0)	1 (0.4)
Endocarditis	1 (0.7)	0 (0.0)	1 (0.4)
Pleural infection	0 (0.0)	1 (0.8)	1 (0.4)
Pseudomonal bacteraemia	1 (0.7)	0 (0.0)	1 (0.4)
Sinusitis	1 (0.7)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Injury, poisoning and procedural complications	4 (2.7)	1 (0.8)	5 (1.8)
Infusion related reaction	1 (0.7)	1 (0.8)	2 (0.7)
Vascular access complication	2 (1.4)	0 (0.0)	2 (0.7)
Contusion	1 (0.7)	0 (0.0)	1 (0.4)
Investigations	23 (15.6)	6 (4.7)	29 (10.5)
Neutrophil count decreased	12 (8.2)	2 (1.6)	14 (5.1)
Alanine aminotransferase increased	9 (6.1)	0 (0.0)	9 (3.3)
Platelet count decreased	5 (3.4)	5 (3.9)	10 (3.6)
Aspartate aminotransferase increased	5 (3.4)	0 (0.0)	5 (1.8)
Blood bilirubin increased	1 (0.7)	1 (0.8)	2 (0.7)
Blood creatinine increased	2 (1.4)	0 (0.0)	2 (0.7)
White blood cell count decreased	0 (0.0)	2 (1.6)	2 (0.7)
Gamma-glutamyltransferase increased	1 (0.7)	0 (0.0)	1 (0.4)
Lymphocyte count decreased	0 (0.0)	1 (0.8)	1 (0.4)
Metabolism and nutrition disorders	8 (5.4)	3 (2.3)	11 (4.0)
Hyperglycaemia	2 (1.4)	1 (0.8)	3 (1.1)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Hypertriglyceridaemia	2 (1.4)	1 (0.8)	3 (1.1)
Dehydration	2 (1.4)	0 (0.0)	2 (0.7)
Hypocalcaemia	2 (1.4)	0 (0.0)	2 (0.7)
Hyponatraemia	2 (1.4)	0 (0.0)	2 (0.7)
Failure to thrive	0 (0.0)	1 (0.8)	1 (0.4)
Hyperphosphataemia	1 (0.7)	0 (0.0)	1 (0.4)
Hyperuricaemia	1 (0.7)	0 (0.0)	1 (0.4)
Vitamin D deficiency	1 (0.7)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	8 (5.4)	1 (0.8)	9 (3.3)
Muscular weakness	3 (2.0)	0 (0.0)	3 (1.1)
Back pain	0 (0.0)	1 (0.8)	1 (0.4)
Flank pain	1 (0.7)	0 (0.0)	1 (0.4)
Myalgia	1 (0.7)	0 (0.0)	1 (0.4)
Neck pain	1 (0.7)	0 (0.0)	1 (0.4)
Osteonecrosis	1 (0.7)	0 (0.0)	1 (0.4)
Pain in extremity	1 (0.7)	0 (0.0)	1 (0.4)
Nervous system disorders	22 (15.0)	0 (0.0)	22 (8.0)
Aphasia	8 (5.4)	0 (0.0)	8 (2.9)
Headache	5 (3.4)	0 (0.0)	5 (1.8)
Tremor	6 (4.1)	0 (0.0)	6 (2.2)
Ataxia	3 (2.0)	0 (0.0)	3 (1.1)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Cognitive disorder	3 (2.0)	0 (0.0)	3 (1.1)
Depressed level of consciousness	3 (2.0)	0 (0.0)	3 (1.1)
Dizziness	3 (2.0)	0 (0.0)	3 (1.1)
Dysarthria	3 (2.0)	0 (0.0)	3 (1.1)
Encephalopathy	2 (1.4)	0 (0.0)	2 (0.7)
Seizure	2 (1.4)	0 (0.0)	2 (0.7)
Amnesia	1 (0.7)	0 (0.0)	1 (0.4)
Haemorrhage intracranial	1 (0.7)	0 (0.0)	1 (0.4)
Lethargy	1 (0.7)	0 (0.0)	1 (0.4)
Memory impairment	1 (0.7)	0 (0.0)	1 (0.4)
Neurotoxicity	2 (1.4)	0 (0.0)	2 (0.7)
Peripheral sensory neuropathy	1 (0.7)	0 (0.0)	1 (0.4)
Presyncope	1 (0.7)	0 (0.0)	1 (0.4)
Psychiatric disorders	9 (6.1)	1 (0.8)	10 (3.6)
Confusional state	6 (4.1)	0 (0.0)	6 (2.2)
Mental status changes	2 (1.4)	0 (0.0)	2 (0.7)
Anxiety	1 (0.7)	0 (0.0)	1 (0.4)
Depression	0 (0.0)	1 (0.8)	1 (0.4)
Renal and urinary disorders	4 (2.7)	0 (0.0)	4 (1.5)
Acute kidney injury	4 (2.7)	0 (0.0)	4 (1.5)
Chronic kidney disease	1 (0.7)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Respiratory, thoracic and mediastinal disorders	9 (6.1)	2 (1.6)	11 (4.0)
Hypoxia	3 (2.0)	0 (0.0)	3 (1.1)
Dyspnoea	1 (0.7)	1 (0.8)	2 (0.7)
Epistaxis	2 (1.4)	0 (0.0)	2 (0.7)
Pulmonary oedema	1 (0.7)	1 (0.8)	2 (0.7)
Asthma	1 (0.7)	0 (0.0)	1 (0.4)
Pleural effusion	0 (0.0)	1 (0.8)	1 (0.4)
Respiratory failure	1 (0.7)	0 (0.0)	1 (0.4)
Skin and subcutaneous tissue disorders	2 (1.4)	0 (0.0)	2 (0.7)
Dermatitis acneiform	1 (0.7)	0 (0.0)	1 (0.4)
Rash maculo-papular	1 (0.7)	0 (0.0)	1 (0.4)
Vascular disorders	7 (4.8)	1 (0.8)	8 (2.9)
Hypotension	4 (2.7)	0 (0.0)	4 (1.5)
Hypertension	2 (1.4)	0 (0.0)	2 (0.7)
Embolism	0 (0.0)	1 (0.8)	1 (0.4)
Flushing	1 (0.7)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	Blinatumomab + chemotherapy (N=147), n (%) [22]	Chemotherapy (N=128), n (%) [22]	Overall (N = 275), n (%) [22]
Number of subjects reporting step 3 treatment-emergent fatal adverse events	**3 (2.0)**	**2 (1.6)**	**5 (1.8)**
Cardiac disorders	0 (0.0)	1 (0.8)	1 (0.4)
Cardiac arrest	0 (0.0)	1 (0.8)	1 (0.4)
Infections and infestations	2 (1.4)	1 (0.8)	3 (1.1)
Sepsis	2 (1.4)	1 (0.8)	3 (1.1)
Nervous system disorders	1 (0.7)	0 (0.0)	1 (0.4)
Haemorrhage intracranial	1 (0.7)	0 (0.0)	1 (0.4)

Safety analysis set includes all subjects in the full analysis set who receive at least 1 dose of protocol-specified therapies. N = Number of subjects in the analysis set. n = Number of subjects with observed data.
Step 3 treatment-emergent adverse event is any AE recorded during the Step 3 treatment period including blinatumomab cycles, consolidation cycles, allogeneic SCT or late adverse events with onset within 30 days of end of Step 3 treatment. Expedited adverse event: A serious adverse event meeting requiring expedited reporting via CTEP AERS is called an expedited adverse event. Data cut-off date: 23JUN2023.
Abbreviations: N, number.
Source: [22].

Appendix F. Health-related quality of life

F.1 BLAST

The 'BLAST MT203-EQ-5d-questionnaire with relapse dataset.xlsx' file was filtered in R with the *dplyr* and *tidyverse* packages, to obtain the correct subset of patients for the utility analysis.

The 'BLAST MT203-EQ-5d-questionnaire with relapse dataset.xlsx' file was filtered in R with the *dplyr* and *tidyverse* packages, to obtain the correct subset of patients for the utility analysis. Firstly, the number of relapses (NPRELAP) variable was transformed, replacing patients with a value of 1 (for first relapse), with a value of 2, patients with a value of 2 (second relapse) with a value of 3. This was done because relapse-free patients, were assigned 'NA' in the original dataset; to include the patients who were relapse-free in the analysis, we needed to assign them a value of 1 and subsequently re-assign the relapse patients, as described. The dataset was then filtered to include only patients who were relapse-free (NPRELAP = 1 after transformation), resulting in a total of XX patients. The dataset was then filtered to include observations with the 'EQ5DFL' variable flag equal to 'Y', indicating that they had an EQ-5D assessment, reducing the number of patients to XX. Observations with the PARAMCD variable equal to 'EQ5D_VAS' were also removed as visual analog scale (VAS) scores were not required for the analysis. Assessments for re-treated patients, where the VISIT variable was equal to 'SCREENING', 'RE-TREATMENT CYCLE 1 DAY 29', or 'RE-TREATMENT FOLLOW-UP' were also removed.

The dataset was then reshaped from long data format to wide, so that each row was only one visit or utility assessment, containing the five indicator scores for EQ-5D. If any of these indicators contained a missing value, the assessment was removed, leading to a dataset of XX patients (X patients did not have the full set of values). There were XX patients in total for which EQ-5D values were available (1 patient was missing from the MRD response dataset 'ADRS_203.xlsx'). The EQ-5D indicator scores were then checked for validity by removing any observations with a score of <1 or >5 (none were found). These were then renamed ('MO', 'SC', 'UA', 'PD', 'AD') and defined as a subset of columns so that these could be used to calculate scores with the *eq5d* package.

Defining the covariates

In the BLAST trial, all patients started as MRD+ and were assessed for MRD response at the end of Cycle 1 and Cycle 2 of blinatumomab therapy. To generate the MRD response covariate, the previously combined dataset was merged with the 'ADRS_203.xlsx' file, by two common identifiers: 'Unique Subject Identifier (USUBJID)' and 'VISIT' variable, as the ADRS dataset had multiple assessments for each patient. Unneeded assessments were removed, such as re-treatments and survival follow-ups. The VISIT variable included extra assessments in this dataset such as 'DAY 3' and 'DAY 43', for example, whereas the

original dataset only had assessments for 'DAY 29' of each cycle. All visits ending with 'DAY 3', 'DAY 15', 'DAY 22', and 'DAY 43' were removed to match the original dataset. After joining the datasets, there were [redacted] missing values for MRD response, so it was assumed that the MRD status was the same as for the previous assessment using the date of assessment variable (QSDTC). Overall, this led to [redacted] assessments with a 'Y' for MRD response and [redacted] assessments with an 'N' for MRD response.

A binary on-treatment identifier variable was also created using the VISIT column, where observations, including 'FOLLOW-UP' OR 'END OF CORE STUDY', were labelled as assessments where patients were off treatment and assigned a value of 0; all other observations, such as those beginning with 'CYCLE' were assigned a value of 1 and labelled as on treatment. Overall, there were [redacted] assessments for patients who were off treatment, and [redacted] assessments for patients who were on treatment. These results are shown in Table 80.

To obtain covariate information for time to death less or greater than 6 months, the 'BLAST MT203-EQ-5d-questionnaire with relapse dataset.xlsx' dataset was merged with the 'ADSL_203.xlsx' file using unique subject identifier (USUBJID) (patient ID) as a common identifier variable. A time to death variable in months was then created, subtracting the time of death column from the quality-of-life assessment date (QSDTC) column from the original dataset, then dividing from days to months using a factor of (365.25/12) for the number of days in a month. Patients who did not die had a missing value for time of death, so were assigned a very large value (10,000) to indicate this was over 6 months. A binary variable was then created, where patients with a time to death of less than 6 months were assigned a value of 1, and patients with a time to death of over 6 months were assigned a value of 0. This led to [redacted] assessments with over 6 months to death, and [redacted] assessments of less than 6 months to death.

Table 80. Number of utility assessments for covariates used in the analysis

Variable	Assessments
Time to death (>6 months)	[redacted]
Time to death (<6 months)	[redacted]
Off treatment	[redacted]
On treatment	[redacted]
MRD Responder: Y	[redacted]
MRD Responder: N	[redacted]

Abbreviations: MRD, minimum residual disease.

Fitting the Generalized Linear Models

Distribution of EQ-5D scores

The distribution of EQ-5D scores exhibited a strong left skew as shown in Figure 29**,** with most of the scores at the higher end of the scale. This is a common finding with utility measures, which exhibit several non-normal characteristics due to large spikes typically at the upper bound and gaps in the range of feasible values, as well as having an upper and lower limit [4]. A formal statistical test for normality, the Shapiro–Wilk test, was conducted. This indicated that the EQ-5D scores deviated from normality at the 1% level of significance ($p<0.01$).

Figure 29. Histogram of EQ-5D-3L assessments

Given the non-normal nature of the distribution of scores, other models need to be considered when modeling EQ-5D. A Gamma distribution with a log link function was considered to be a more appropriate choice, as it accommodates the skewness of EQ-5D, and predictions are strictly positive. In addition, a mixed effects model can be considered, as these are flexible in handling nested data structures, such as repeated utility assessments for patients and specific individual random effects.

Residual plots

Overall, the residual plots shown in Figure 30 for all three models are relatively evenly spread around zero and are clustered to the right-hand side, due to the positively skewed nature of the data. There is a tailing off of the residuals as the utility scores approach 1, as this is the upper limit of the variable. It is impossible to obtain a score above 1 due to the nature of utility scores where this represents perfect health.

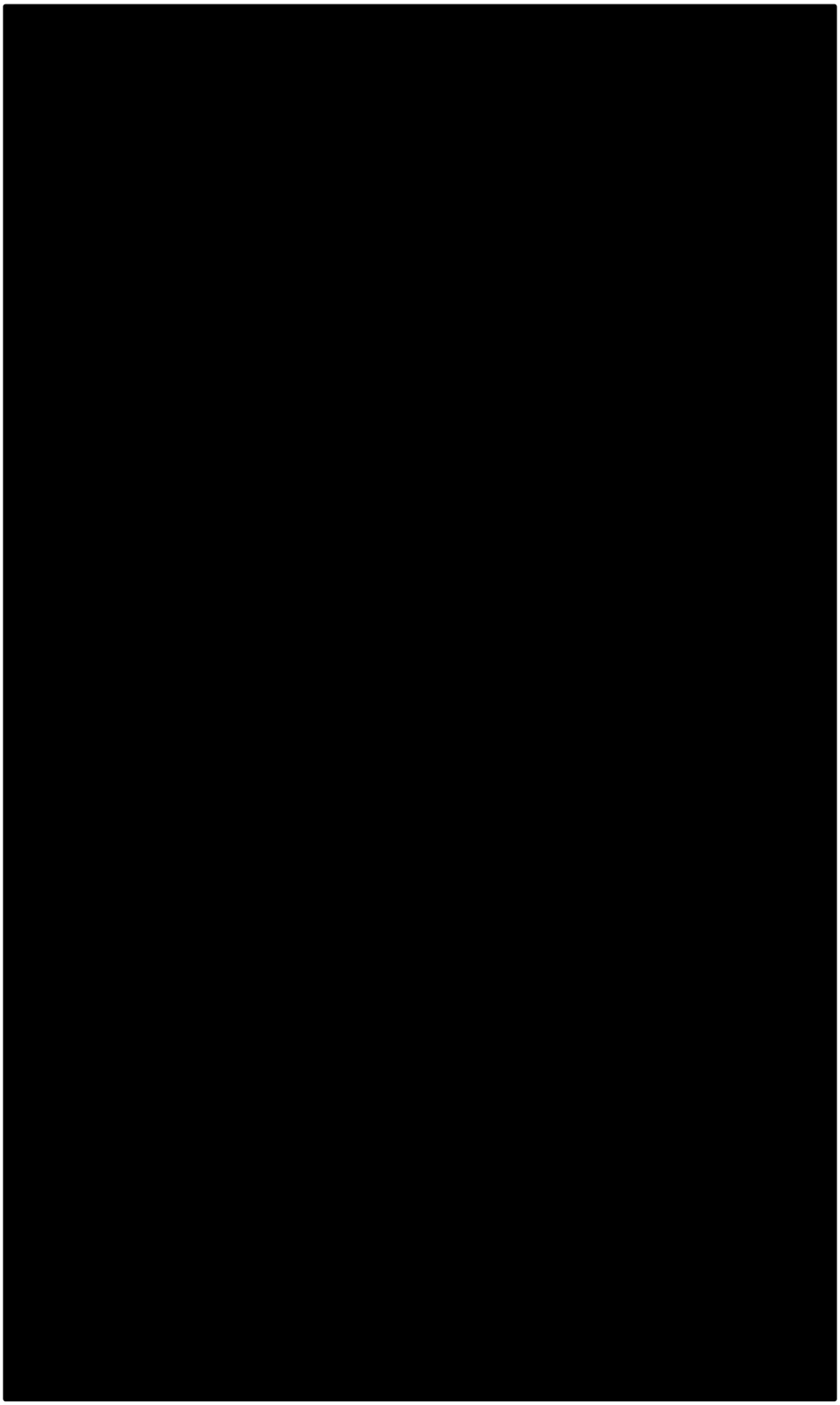

Figure 30. Residual plots for the three models

QQ plots of the residuals

The quantile–quantile (QQ) plots of the residuals show that, for most observations, the mixed, Gaussian, and Gamma models approximately follow a straight line, except for a few points at the low and high ends of the scale. This suggests that the residuals are approximately normally distributed. There is more of a deviation for the QQ plot of the mixed model random effects, however most points still follow a straight line suggesting no major assumption violations.

Figure 31. QQ plots for the three models
Abbreviations: QQ, quantile–quantile.

Model predictions versus actual values

To evaluate the three models, predictions were compared with actual utility values for each assessment, and the results were plotted to identify the most accurate model. The mixed model demonstrated the closest alignment with actual utility values, with most of its predictions falling within a range of 0.2 from the true utilities. In contrast, the Gaussian and Gamma GLMs showed larger deviations, although most of their predictions still fell within 0.3 of the actual values.

Figure 32. Mixed model predicted versus actual values

Figure 33. Gaussian model predicted versus actual values

Figure 34. Gamma model predicted versus actual values

Final model choice

Using the Gaussian GLM was not recommended, due to the nature of the data as strongly positively skewed, which violates the assumption of normality. The Gamma distribution was assessed as a better choice, however, the mixed model better accounts for individual variability for the repeated patient observations. The mixed model resulted in a clustering of patients into XX groups as expected, whereas the GLMs clustered assessments into XXX groups even though there were XX patients. This means that they may not account for individual variability and within cluster correlation as well as the mixed model, and this is reflected in the predictions versus actual values seen in Figure 32, Figure 33 and Figure 34. The outputs of the mixed model are also easier to interpret than the Gamma GLM and apply in the CEMs. Therefore, the mixed model was used.

F.2 TOWER

The 80 TOWER SOC patients and 51 relapsed BLAST patients were matched based on their health state: i.e. CR1/CR2 (BLAST) or S0/S1 (TOWER), age, and their receipt of HSCT (at baseline among TOWER patients and prior to relapse among BLAST patients). BLAST patients with one prior remission (CR1) were weighted to achieve balance with the historical cohort study patients with either IPTW ATT or ATE weights.

Table 81. Characteristics of relapsed BLAST patients vs TOWER patients (unweighted)

	Relapsed BLAST patients N (%)		TOWER SOC patients N (%)	
N	[redacted]	[redacted]	[redacted]	[redacted]
CR1 or S0	[redacted]	[redacted]	[redacted]	[redacted]
CR2 or S1	[redacted]	[redacted]	[redacted]	[redacted]
Age		[redacted]		[redacted]
≥ 18 and < 35 years	[redacted]	[redacted]	[redacted]	[redacted]
≥ 35 and < 55 years	[redacted]	[redacted]	[redacted]	[redacted]
≥ 55 and < 65 years	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65 years	[redacted]	[redacted]	[redacted]	[redacted]
With HSCT	[redacted]	[redacted]	[redacted]	[redacted]

Figure 35. Relapsed BLAST vs TOWER patients

Appendix G. Probabilistic sensitivity analyses

Table 82. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Patient characteristics				
Age at model start	50.00	48.64	51.36	Normal
Proportion male	50.00%	44.03%	55.97%	Beta
Weight	86.70	84.06	89.34	Normal
BSA	2.00	1.97	2.03	Normal
If MRD-agnostic, proportion of MRD positive patients	0.16	12.24%	21.07%	Beta
Drug characteristics				
Frequency of bag change	4.0	2.59	5.71	Gamma
Drug administration costs				
Cost per administration: Inpatient days	51,697.00 kr.	33,455.57 kr.	73,844.20 kr.	Gamma
Cost per administration: Outpatient bag change	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per administration: IV (Outpatient)	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per administration: IT (chemotherapy into CNS) (Outpatient)	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per administration: Oral	0.00 kr.	0.00 kr.	0.00 kr.	Gamma
Stem cell transplant costs				
Cost per administration: Stem cell harvesting cost	26,206.00 kr.	16,959.14 kr.	37,432.75 kr.	Gamma
Cost per administration: HSCT procedure	1,035,036.00 kr.	669,820.73 kr.	1,478,449.46 kr.	Gamma

Cost per administration: HSCT follow-up cost	236,483.21 kr.	153,039.46 kr.	337,793.54 kr.	Gamma
Other admin costs				
Cost per administration: Leucopheresis	9,966.67 kr.	6,449.90 kr.	14,236.43 kr.	Gamma
Treatment use				
Proportion of blinatumomab patients receiving Cycle 1 of Blinatumomab	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Cycle 2 of Blinatumomab	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 1	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 2	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 3	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 4 of Blinatumomab	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 5	[redacted]	[redacted]	[redacted]	Beta
Proportion of blinatumomab patients receiving Consolidation Cycle 6 of Blinatumomab	[redacted]	[redacted]	[redacted]	Beta
Proportion of SoC patients receiving Consolidation Cycle 1	[redacted]	[redacted]	[redacted]	Beta
Proportion of SoC patients receiving Consolidation Cycle 2	[redacted]	[redacted]	[redacted]	Beta
Proportion of SoC patients receiving Consolidation Cycle 3	[redacted]	[redacted]	[redacted]	Beta
Proportion of SoC patients receiving Consolidation Cycle 4	[redacted]	[redacted]	[redacted]	Beta
Resource use, frequencies				

Outpatient visit (hematologist), pre relaps, 1st year	0,77	0,50	1,10	Gamma
CSF, pre relaps, 1st year	0,12	0,08	0,17	Gamma
Bone marrow aspirate/biopsy, pre ralps 1st year	0,08	0,05	0,11	Gamma
Echocardiogram, pre relaps 1st year	0,02	0,01	0,03	Gamma
Electrocardiagram, pre relpas 1st year	0,06	0,04	0,09	Gamma
Outpatient visit (hematologist), pre relaps, 2nd year	0,41	0,27	0,59	Gamma
CSF, pre relaps, 2nd year	0,09	0,06	0,13	Gamma
Bone marrow aspirate/biopsy, pre relps 2nd year	0,00	0,00	0,00	Gamma
Echocardiogram, pre relaps 2nd year	0,00	0,00	0,00	Gamma
Electrocardiagram, pre relpas 2nd year	0,00	0,00	0,00	Gamma
Outpatient visit (hematologist), pre relaps, 2nd year	0,13	0,08	0,19	Gamma
CSF, pre relaps, 2nd year	0,00	0,00	0,00	Gamma
Bone marrow aspirate/biopsy, pre relps 2nd year	0,00	0,00	0,00	Gamma
Echocardiogram, pre relaps 2nd year	0,00	0,00	0,00	Gamma
Electrocardiagram, pre relpas 2nd year	0,00	0,00	0,00	Gamma
Outpatient visit (hematologist), post relaps	0,77	0,50	1,10	Gamma
CSF, post relaps	0,23	0,15	0,33	Gamma
Bone marrow aspirate/biopsy, post relaps	0,08	0,05	0,11	Gamma
Echocardiogram, post relaps	0,02	0,01	0,03	Gamma
Electrocardiagram, post relaps	0,06	0,04	0,09	Gamma

HSCT distribution				
Relapse-free HSCT distribution: (Blinatumomab)	26.12%	19.06%	33.85%	Beta
Relapse-free HSCT distribution: (Chemotherapy)	29.10%	21.75%	37.05%	Beta
2L therapy distribution (Blinatumomab)				
2L treatment distribution: Blinatumomab (Blinatumomab)	5.00%	2.36%	7.39%	Dirichlet
2L treatment distribution: Inotuzumab ozogamicin (Blinatumomab)	45.00%	47.64%	42.61%	Dirichlet
2L treatment distribution: CAR-T (Blinatumomab)	5.00%	2.36%	7.39%	Dirichlet
2L treatment distribution: FLAG-IDA (Blinatumomab)	45.00%	47.64%	42.61%	Dirichlet
2L treatment distribution: No active treatment (Blinatumomab)	0.00%	0.00%	0.00%	Dirichlet
2L therapy distribution (chemotherapy)				
2L treatment distribution: Blinatumomab (Chemotherapy)	42.00%	42.73%	41.25%	Dirichlet
2L treatment distribution: Inotuzumab ozogamicin (Chemotherapy)	50.00%	52.39%	48.05%	Dirichlet
2L treatment distribution: CAR-T (Chemotherapy)	0.00%	0.00%	0.00%	Dirichlet
2L treatment distribution: FLAG-IDA (Chemotherapy)	8.00%	4.88%	10.70%	Dirichlet
2L treatment distribution: No active treatment (Chemotherapy)	0.00%	0.00%	0.00%	Dirichlet
2L (Post-relapse) HSCT distribution				
Post-relapse HSCT distribution (Blinatumomab)	20.00%	4.66%	42.81%	Beta
Post-relapse HSCT distribution (Chemotherapy)	15.63%	5.45%	29.83%	Beta

Adverse event costs				
Cost per adverse event: Alanine aminotransferase increased	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per adverse event: Anaemia	4,221.00 kr.	2,731.61 kr.	6,029.29 kr.	Gamma
Cost per adverse event: Aphasia	40,649.00 kr.	26,305.89 kr.	58,063.19 kr.	Gamma
Cost per adverse event: Aspartate aminotransferase increased	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per adverse event: Cytokine release syndrome	122,022.00 kr.	78,966.20 kr.	174,296.70 kr.	Gamma
Cost per adverse event: Device related infection	35,738.00 kr.	23,127.75 kr.	51,048.30 kr.	Gamma
Cost per adverse event: Diarrhoea	4,977.00 kr.	3,220.85 kr.	7,109.17 kr.	Gamma
Cost per adverse event: Fatigue	6,902.00 kr.	4,466.61 kr.	9,858.84 kr.	Gamma
Cost per adverse event: Febrile neutropenia	37,482.00 kr.	24,256.37 kr.	53,539.44 kr.	Gamma
Cost per adverse event: Headache	2,136.00 kr.	1,382.31 kr.	3,051.07 kr.	Gamma
Cost per adverse event: Hyperglycaemia	26,972.00 kr.	17,454.86 kr.	38,526.91 kr.	Gamma
Cost per adverse event: Hypertension	18,807.00 kr.	12,170.90 kr.	26,863.99 kr.	Gamma
Cost per adverse event: Hypertriglyceridaemia	26,972.00 kr.	17,454.86 kr.	38,526.91 kr.	Gamma
Cost per adverse event: Hypotension	2,140.00 kr.	1,384.90 kr.	3,056.78 kr.	Gamma
Cost per adverse event: Lymphocyte count decreased	28,342.00 kr.	18,341.45 kr.	40,483.82 kr.	Gamma
Cost per adverse event: Nausea	6,902.00 kr.	4,466.61 kr.	9,858.84 kr.	Gamma
Cost per adverse event: Neutrophil count decreased	28,342.00 kr.	18,341.45 kr.	40,483.82 kr.	Gamma

Cost per adverse event: Platelet count decreased	28,342.00 kr.	18,341.45 kr.	40,483.82 kr.	Gamma
Cost per adverse event: Sepsis	53,570.00 kr.	34,667.68 kr.	76,519.60 kr.	Gamma
Cost per adverse event: White blood cell count decreased	28,342.00 kr.	18,341.45 kr.	40,483.82 kr.	Gamma
Adverse event utility decrements				
Adverse event utility decrement: Alanine aminotransferase increased	0.00	0.00	0.00	Beta
Adverse event utility decrement: Anaemia	0.12	0.08	0.16	Beta
Adverse event utility decrement: Aphasia	0.00	0.00	0.00	Beta
Adverse event utility decrement: Aspartate aminotransferase increased	0.00	0.00	0.00	Beta
Adverse event utility decrement: Cytokine release syndrome	0.23	0.15	0.33	Beta
Adverse event utility decrement: Device related infection	0.09	0.03	0.18	Beta
Adverse event utility decrement: Diarrhoea	0.05	0.03	0.07	Beta
Adverse event utility decrement: Fatigue	0.12	0.07	0.16	Beta
Adverse event utility decrement: Febrile neutropenia	0.09	0.05	0.13	Beta
Adverse event utility decrement: Headache	0.03	0.02	0.04	Beta
Adverse event utility decrement: Hyperglycaemia	0.06	0.04	0.08	Beta
Adverse event utility decrement: Hypertension	0.07	0.05	0.09	Beta
Adverse event utility decrement: Hypertriglyceridaemia	0.00	0.00	0.00	Beta
Adverse event utility decrement: Hypotension	0.07	0.05	0.09	Beta

Adverse event utility decrement: Lymphocyte count decreased	0.07	0.05	0.09	Beta
Adverse event utility decrement: Nausea	0.05	0.03	0.07	Beta
Adverse event utility decrement: Neutrophil count decreased	0.05	0.03	0.07	Beta
Adverse event utility decrement: Platelet count decreased	0.05	0.03	0.07	Beta
Adverse event utility decrement: Sepsis	0.20	0.13	0.28	Beta
Adverse event utility decrement: White blood cell count decreased	0.05	0.03	0.07	Beta
Adverse event durations				
Adverse event duration (days): Alanine aminotransferase increased	20.00	12.94	28.57	Gamma
Adverse event duration (days): Anaemia	14.90	9.64	21.28	Gamma
Adverse event duration (days): Aphasia	0.00	0.00	0.00	Gamma
Adverse event duration (days): Aspartate aminotransferase increased	20.00	12.94	28.57	Gamma
Adverse event duration (days): Cytokine release syndrome	4.30	2.78	6.14	Gamma
Adverse event duration (days): Device related infection	6.20	4.01	8.86	Gamma
Adverse event duration (days): Diarrhoea	7.00	4.53	10.00	Gamma
Adverse event duration (days): Fatigue	7.00	4.53	10.00	Gamma
Adverse event duration (days): Febrile neutropenia	6.20	4.01	8.86	Gamma
Adverse event duration (days): Headache	2.00	1.29	2.86	Gamma
Adverse event duration (days): Hyperglycaemia	7.50	4.85	10.71	Gamma

Adverse event duration (days): Hypertension	4.00	2.59	5.71	Gamma
Adverse event duration (days): Hypertriglyceridaemia	0.00	0.00	0.00	Gamma
Adverse event duration (days): Hypotension	2.30	1.49	3.29	Gamma
Adverse event duration (days): Lymphocyte count decreased	19.00	12.30	27.14	Gamma
Adverse event duration (days): Nausea	7.00	4.53	10.00	Gamma
Adverse event duration (days): Neutrophil count decreased	9.80	6.34	14.00	Gamma
Adverse event duration (days): Platelet count decreased	11.90	7.70	17.00	Gamma
Adverse event duration (days): Sepsis	15.10	9.77	21.57	Gamma
Adverse event duration (days): White blood cell count decreased	16.90	10.94	24.14	Gamma
Adverse event frequency: 1 - Blinatumomab				
Alanine aminotransferase increased incidence	6.72%	3.14%	11.51%	Beta
Anaemia incidence	29.10%	21.75%	37.05%	Beta
Aphasia incidence	5.22%	2.14%	9.56%	Beta
Aspartate aminotransferase increased incidence	4.48%	1.67%	8.56%	Beta
Cytokine release syndrome incidence	3.73%	1.23%	7.52%	Beta
Device related infection incidence	9.70%	5.31%	15.23%	Beta
Diarrhoea incidence	5.22%	2.14%	9.56%	Beta
Fatigue incidence	4.48%	1.67%	8.56%	Beta
Febrile neutropenia incidence	22.39%	15.77%	29.79%	Beta
Headache incidence	5.97%	2.63%	10.54%	Beta
Hyperglycaemia incidence	9.70%	5.31%	15.23%	Beta

Hypertension incidence	8.96%	4.75%	14.32%	Beta
Hypertriglyceridaemia incidence	2.99%	0.83%	6.45%	Beta
Hypotension incidence	4.48%	1.67%	8.56%	Beta
Lymphocyte count decreased incidence	29.10%	21.75%	37.05%	Beta
Nausea incidence	5.22%	2.14%	9.56%	Beta
Neutrophil count decreased incidence	84.33%	77.74%	89.95%	Beta
Platelet count decreased incidence	67.91%	59.80%	75.52%	Beta
Sepsis incidence	11.19%	6.45%	17.03%	Beta
White blood cell count decreased incidence	48.51%	40.11%	56.95%	Beta
Adverse event frequency: 2 - Chemotherapy				
Alanine aminotransferase increased incidence	5.97%	2.63%	10.54%	Beta
Anaemia incidence	40.30%	32.18%	48.70%	Beta
Aphasia incidence	0.00%	0.00%	0.00%	Beta
Aspartate aminotransferase increased incidence	2.24%	0.47%	5.33%	Beta
Cytokine release syndrome incidence	0.00%	0.00%	0.00%	Beta
Device related infection incidence	5.97%	2.63%	10.54%	Beta
Diarrhoea incidence	5.22%	2.14%	9.56%	Beta
Fatigue incidence	3.73%	1.23%	7.52%	Beta
Febrile neutropenia incidence	27.61%	20.40%	35.45%	Beta
Headache incidence	6.72%	3.14%	11.51%	Beta
Hyperglycaemia incidence	8.96%	4.75%	14.32%	Beta
Hypertension incidence	2.99%	0.83%	6.45%	Beta
Hypertriglyceridaemia incidence	4.48%	1.67%	8.56%	Beta
Hypotension incidence	2.24%	0.47%	5.33%	Beta

Lymphocyte count decreased incidence	26.12%	19.06%	33.85%	Beta
Nausea incidence	1.49%	0.18%	4.12%	Beta
Neutrophil count decreased incidence	88.81%	82.97%	93.55%	Beta
Platelet count decreased incidence	75.37%	67.77%	82.26%	Beta
Sepsis incidence	9.70%	5.31%	15.23%	Beta
White blood cell count decreased incidence	60.45%	52.07%	68.53%	Beta
End-of-life cost				
End-of-life costs	32,382.67 kr.	20,956.35 kr.	46,255.53 kr.	Gamma
Patient costs				
Distance to hospital	40 km	26 km	57 km	Normal
Travel time speed	1.0 min/km	0.6 min/km	1.4 min/km	Normal
Cost per km	3.73 kr.	2.41 kr.	5.33 kr.	Normal
Average Danish salary per hour	188.00 kr.	121.66 kr.	268.54 kr.	Normal
Time spent on outpatient hospital visit	180 minutes	116 minutes	257 minutes	Normal
Time spent on inpatient hospital visit	450 minutes	291 minutes	643 minutes	Normal
Utility values - treatment specific increments				
Relapse-free utility	[redacted]	[redacted]	[redacted]	Beta
Blinatumomab decrement	[redacted]	[redacted]	[redacted]	Beta
MRD decrement	[redacted]	[redacted]	[redacted]	Beta
Post HSCT decrement	[redacted]	[redacted]	[redacted]	Beta
Terminal care utility decrement (<6 months prior to death)	[redacted]	[redacted]	[redacted]	Beta
Post-relapse utility	0.692	0.407	0.865	Beta

Cured util, relative to gen pop (scenario)	98%	0,24	0,52	Gamma
MCMs				
Mixture cure fraction, exponentiel	0,787	0,51	1,12	Log-normal
Mixture cure fraction, gamma	0,808	0,52	1,15	Log-normal
Mixture cure fraction, gompertz	0,814	0,53	1,16	Log-normal
Mixture cure fraction, log-logistic	0,790	0,51	1,13	Log-normal
Mixture cure fraction, log-normal	0,783	0,51	1,12	Log-normal
Mixture cure fraction,weibull	0,812	0,53	1,16	Log-normal
2L fatal progression rates				
Blinatumomab fatal progression rate	0.37	0.24	0.52	Gamma
SoC fatal progression rate	0.25	0.16	0.36	Gamma
PSM				
Gen. pop. survival SMR	1.09	1.00	1.56	Gamma
Time horizon				
Time horizon	50	32.36	71.42	Normal

Abbreviations: 2L, second line; BSA, Body surface area; CAR-T, Chimeric antigen receptor cell therapy; CNS, central nervous system; FLAG-IDA, fludarabine, cytarabine, idarubicin, and filgrastim; Gen; general; HSCT, Hematopoietic stem cell transplantation IT, intrathecal; IV, intravenous; Km, kilometer; Min, minutes; MRD, minimal residual disease; OS, overall survival; Pop; population; PSA, probabilistic sensitivity analysis; RFS, relapse-free survival; SMR; standardized mortality ratio; SoC, standard of care.

Appendix H. Literature searches for the clinical assessment (N/A)

As efficacy and safety differences between blinatumomab + chemotherapy and chemotherapy relevant to Danish clinical practice have been directly compared in a head-to-head study, this section is not applicable.

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

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

An SLR was conducted with the objective to identify and summarize evidence in patients newly diagnosed with Ph- B-ALL ALL on the humanistic burden of illness from clinical trials and observational studies, including HRQoL and/or PRO measures.

Additionally, the SLR aimed to identify and summarize data on clinical efficacy and safety from clinical trials, real-world effectiveness and treatment patterns of frontline therapies from observational studies, and prognostic factors and treatment effect modifiers from clinical trials and observational studies. For this reason, the SLR was not solely focused on literature for HRQoL but also other outcome measures for clinical assessment, which is reflected in the search strategy and results of the SLR.

The SLR was performed on 27th of July 2023, and re-run on 12th of April 2024 using the Ovid® platform covering the databases listed in Table 83. Given that Amgen requested the submission date to the DMC to be ultimo March in the assessment request, no new SLR update was planned for the application, which was agreed upon by the DMC during the dialogue meeting in February. Due to a delay in the scheduled application time by the DMC, the SLR was not repeated.

Supplementary hand searches included congress searches, clinical trial registry searches, treatment guidelines, governmental bodies and other relevant reports, see Table 84 and Table 85.

Table 83 Bibliographic databases included in the literature search

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid®	1974 to 2024	27.07.2023 (re-run on 12.04.2024)
Medline		1946 to present	
Cochrane Library		1991 to 2024	

Abbreviations: HRQoL, health-related quality of life.

Table 84 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	https://clinicaltrials.gov/	Hand search using: Condition or disease: acute lymphoblastic leukaemia/leukemia	27.07.2023

Source name	Location/source	Search strategy	Date of search
		Study type: all studies Study results: studies with results	(re-run on 12.04.2024)
National Cancer Institute (NCI) clinical trial database	https://www.cancer.gov/research	Hand search using: Keywords: acute lymphoblastic leukaemia/leukemia	
National Institutes of Health (NIH)	https://clinicalstudies.info.nih.gov/	Hand search using: Keywords: acute lymphoblastic leukaemia/leukemia	
World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)	https://trialsearch.who.int/	Hand search using: Keywords: acute lymphoblastic leukaemia / leukemia Phases: all Recruitment status: all With results only: selected	
European Clinical Trials Register (EU CTR)	https://www.clinicaltrialsregister.eu/	Hand search using: Keywords: acute lymphoblastic leukaemia/leukemia Results status: trials with results	
Local treatment guidelines: US, Canada, UK, Germany, France, Italy, Spain, Portugal, Australia, China, Japan	N/A	Keywords: acute lymphoblastic leukemia	
National Comprehensive Cancer Network (NCCN)	https://www.nccn.org/guidelines/category_1	Keywords: acute lymphoblastic leukemia	
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines	Keywords: acute lymphoblastic leukemia	

Source name	Location/source	Search strategy	Date of search
University of York Centre for Reviews and Dissemination (CRD)	https://www.york.ac.uk/crd/	Keywords: acute lymphoblastic leukemia	
US Food and Drug Administration (FDA)	https://www.fda.gov/	Keywords: acute lymphoblastic leukemia	
European Medicines Agency (EMA)	https://www.ema.europa.eu/en	Keywords: acute lymphoblastic leukemia	
Center for Disease Control and Prevention (CDC)	https://www.cdc.gov/	Keywords: acute lymphoblastic leukemia	
World Health Organization (WHO)	https://www.who.int/ https://extranet.who.int/e-spar	Keywords: acute lymphoblastic leukemia	
Academy of Managed Care Pharmacy (AMCP)	https://www.amcp.org/	Keywords: acute lymphoblastic leukemia	
IHME Global Burden of Disease	https://www.healthdata.org/gbd	Keywords: acute lymphoblastic leukemia	
WHO Global Health Observatory	https://www.who.int/gho/mortality_burden_disease/en/	Keywords: acute lymphoblastic leukemia	

Abbreviations: HRQoL, health-related quality of life; N/A, not available.

Table 85 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
American Society of Clinical Oncology (ASCO) Annual meeting	https://www.asco.org/	Hand search using: Filter: publication date (month of publication in the journal) Media/article type: abstracts	Keywords: acute lymphoblastic leukemia	27.07.2023 (re-run on 12.04.2024)
American Society of Hematology (ASH) meetings	Meetings - Hematology.org			
European Hematology Association (EHA) meetings	EHA Meetings			

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
European Society for Blood and Marrow Transplantation (EBMT) events	Annual Meeting & Educational Events | EBMT			
European Society for Medical Oncology (ESMO)	https://oncologypro.esmo.org/meeting-resources			
Society for Immunotherapy of Cancer (SITC)	SITC Cancer Immunotherapy CONNECT - Society for Immunotherapy of Cancer (SITC)			
Asian Society for Pediatric Oncology (SIOP Asia)	Event | SIOP			
Nordic Society of Paediatric Haematology and Oncology (NOPHO) annual meeting	Home - NOPHO			

Abbreviations: HRQoL, health-related quality of life; N/A, not available.

I.1.1 Search strategies

The search strategy includes a mixture of Medical Subject Headings (MeSH) terms and free text terms, see Table 86 - Table 91.

Patient terms required studies to mention terms related to B-cell or Philadelphia chromosomes (or equivalent terms) and ALL, because not having this restriction led to very high numbers of search results (there was no restriction to 'newly diagnosed'). However, search terms were broader than simply specifying Ph-, because the search string included: (philadelphia and chromosome).mp. or philadelphia chromosome/ or philadelphia chromosome-negative/ or exp b lymphocyte/ or exp b-cell/ or exp b-precursor/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.

Studies that include Ph- subgroups within a broader ALL population were considered for inclusion for full-text review; however, both (1) B-cell or Ph- (or equivalent terms) and (2) ALL terms in the title or abstract were required to be captured in the search

Table 86 Search strategy for Embase for HRQoL inputs (original SLR)

No.	Query	Results
#1	exp acute lymphoblastic leukaemia/ or acute lymphoblastic leukaemia*.mp.	71841
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	89822
#3	1 or 2	91811
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or philadelphia chromosome-negative/ or exp b lymphocyte/ or exp b-cell/ or exp b-precursor/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	409890
#5	Clinical Trial/	1067796
#6	Randomized Controlled Trial/	775707
#7	controlled clinical trial/	470586
#8	multicenter study/	368046
#9	Phase 1 clinical trial/	70617
#10	Phase 2 clinical trial/	105857
#11	Phase 3 clinical trial/	68525
#12	Phase 4 clinical trial/	5356
#13	exp RANDOMIZATION/	98338
#14	Single Blind Procedure/	51208
#15	Double Blind Procedure/	209007
#16	Crossover Procedure/	74790
#17	PLACEBO/	400118
#18	randomi?ed controlled trial$.tw.	321653
#19	rct.tw.	53422
#20	(random$ adj2 allocat$).tw.	54465
#21	single blind$.tw.	31443
#22	double blind$.tw.	243350

No.	Query	Results
#23	((treble or triple) adj blind$).tw.	1894
#24	placebo$.tw.	365014
#25	Prospective Study/	867486
#26	(single arm or single-arm or noncomparative or non-comparative).tw.	34602
#27	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	1387754
#28	Clinical study/ or Case control study/ or Family study/ or Longitudinal study/ or Retrospective study/ or (Prospective study/ not Randomized controlled trials/) or Cohort analysis/ or (Cohort adj (study or studies)).mp. or (Case control adj (study or studies)).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or (epidemiologic$ adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	5180471
#29	or/5-28	7188409
#30	Case study/	95245
#31	Case report.tw.	534970
#32	Letter/	1204555
#33	or/30-32	1819950
#34	29 not 33	7036545
#35	3 and 4 and 34	7283
#36	(animal$ not human$).sh,hw.	4838115
#37	35 not 36	7170
#38	limit 37 to english language	6976

No.	Query	Results
#39	limit 38 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone)	792
#40	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	702589
#41	39 not 40	728
#42	38 not 41	6248
#43	conference abstract.pt.	4832191
#44	limit 43 to yr="2021 -Current"	688607
#45	43 not 44	4143584
#46	42 not 45	3834
#47	remove duplicates from 46	3641
#48	limit 47 to yr="2012 -Current"	2921

Table 87. Search strategy for Embase for HRQoL inputs (SLR update)

No.	Query	Results
#1	exp acute lymphoblastic leukaemia/ or acute lymphoblastic leukaemia*.mp.	76406
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	95051
#3	1 or 2	97051
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or philadelphia chromosome-negative/ or exp b lymphocyte/ or exp b-cell/ or exp b-precursor/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	431307
#5	Clinical Trial/	1080881
#6	Randomized Controlled Trial/	816604
#7	controlled clinical trial/	472837
#8	multicenter study/	389506
#9	Phase 1 clinical trial/	75764

No.	Query	Results
#10	Phase 2 clinical trial/	113182
#11	Phase 3 clinical trial/	74930
#12	Phase 4 clinical trial/	7090
#13	exp RANDOMIZATION/	99486
#14	Single Blind Procedure/	54272
#15	Double Blind Procedure/	217824
#16	Crossover Procedure/	77613
#17	PLACEBO/	411371
#18	randomi?ed controlled trial$.tw.	342988
#19	rct.tw.	57189
#20	(random$ adj2 allocat$).tw.	57028
#21	single blind$.tw.	32946
#22	double blind$.tw.	250981
#23	((treble or triple) adj blind$).tw.	2074
#24	placebo$.tw.	377589
#25	Prospective Study/	912937
#26	(single arm or single-arm or noncomparative or non-comparative).tw.	38104
#27	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	1464908
#28	Clinical study/ or Case control study/ or Family study/ or Longitudinal study/ or Retrospective study/ or (Prospective study/ not Randomized controlled trials/) or Cohort analysis/ or (Cohort adj (study or studies)).mp. or (Case control adj (study or studies)).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or	5540228

No.	Query	Results
	(epidemiologic$ adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	
#29	or/5-28	7612258
#30	Case study/	100330
#31	Case report.tw.	565526
#32	Letter/	1235083
#33	or/30-32	1885010
#34	29 not 33	7452481
#35	3 and 4 and 34	8219
#36	(animal$ not human$).sh,hw.	4942372
#37	35 not 36	8104
#38	limit 37 to english language	7890
#39	limit 38 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone)	840
#40	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	756485
#41	39 not 40	772
#42	38 not 41	7118
#43	conference abstract.pt.	5105199
#44	limit 43 to yr="2021 -Current"	940015
#45	43 not 44	4165184
#46	42 not 45	4696
#47	remove duplicates from 46	4500
#48	limit 47 to yr="2012 -Current"	3778

No.	Query	Results
#49	limit 48 to yr="2023 -Current"	917

Table 88. Search strategy for Medline for HRQoL inputs (original SLR)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	36704
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	47226
#3	1 or 2	49377
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	303338
#5	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or (phase i* or phase 1*).mp. or (phase ii* or phase 2*).mp. or (phase iii* or phase 3*).mp. or (phase iv* or phase 4*).mp. or controlled clinical trial.mp. or randomized controlled trial.mp. or multicenter study.mp. or clinical trial.mp. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or PLACEBOS/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw. or (single arm or single-arm or noncomparative or non-comparative).tw.	2182563
#6	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	1020692
#7	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi	4849983

No.	Query	Results
	adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	
#8	5 or 6 or 7	6476202
#9	Case study/	2395967
#10	Case report.tw.	422814
#11	Letter/	1248685
#12	or/9-11	3477744
#13	8 not 12	6223300
#14	3 and 4 and 13	3313
#15	(animal$ not human$).sh,hw.	5166502
#16	14 not 15	3300
#17	limit 16 to english language	3103
#18	limit 17 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone) [Limit not valid in Ovid MEDLINE(R); records were retained]	445
#19	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	480602
#20	18 not 19	427
#21	17 not 20	2676
#22	congress.pt.	67545
#23	limit 22 to yr="2021 -Current"	890
#24	22 not 23	66655
#25	21 not 24	2675
#26	remove duplicates from 25	2671
#27	limit 26 to yr="2012 -Current"	1627
#28	limit 27 to yr="2023 -Current"	225

Table 89. Search strategy for Medline for HRQoL inputs (SLR update)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	36704
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	47226
#3	1 or 2	49377
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	303338
#5	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or (phase i* or phase 1*).mp. or (phase ii* or phase 2*).mp. or (phase iii* or phase 3*).mp. or (phase iv* or phase 4*).mp. or controlled clinical trial.mp. or randomized controlled trial.mp. or multicenter study.mp. or clinical trial.mp. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or PLACEBOS/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw. or (single arm or single-arm or noncomparative or non-comparative).tw.	2182563
#6	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	1020692
#7	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	4849983
#8	5 or 6 or 7	6476202
#9	Case study/	2395967

No.	Query	Results
#10	Case report.tw.	422814
#11	Letter/	1248685
#12	or/9-11	3477744
#13	8 not 12	6223300
#14	3 and 4 and 13	3313
#15	(animal$ not human$).sh,hw.	5166502
#16	14 not 15	3300
#17	limit 16 to english language	3103
#18	limit 17 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone) [Limit not valid in Ovid MEDLINE(R); records were retained]	445
#19	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	480602
#20	18 not 19	427
#21	17 not 20	2676
#22	congress.pt.	67545
#23	limit 22 to yr="2021 -Current"	890
#24	22 not 23	66655
#25	21 not 24	2675
#26	remove duplicates from 25	2671
#27	limit 26 to yr="2012 -Current"	1627
#28	limit 27 to yr="2023 -Current"	225

Table 90. Search strategy for Cochrane for HRQoL inputs (original SLR)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	1658
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	3231
#3	1 or 2	3389
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	8969
#5	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or (phase i* or phase 1*).mp. or (phase ii* or phase 2*).mp. or (phase iii* or phase 3*).mp. or (phase iv* or phase 4*).mp. or controlled clinical trial.mp. or randomized controlled trial.mp. or multicenter study.mp. or clinical trial.mp. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or PLACEBOS/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw. or (single arm or single-arm or noncomparative or non-comparative).tw.	1182737
#6	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	726346
#7	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	351358
#8	5 or 6 or 7	1401209
#9	Case study/	259

No.	Query	Results
#10	Case report.tw.	2913
#11	Letter/	316
#12	or/9-11	3484
#13	8 not 12	1398432
#14	3 and 4 and 13	642
#15	(animal$ not human$).sh,hw.	2782
#16	14 not 15	642
#17	limit 16 to english language [Limit not valid in DARE,CLCMR,ACP Journal Club,CDSR; records were retained]	637
#18	limit 17 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone) [Limit not valid in DARE,CLEED,CLHTA,CLCMR,ACP Journal Club,CCTR,CDSR; records were retained]	8
#19	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	26706
#20	18 not 19	8
#21	17 not 20	629
#22	conference abstract.pt.	0
#23	limit 22 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	0
#24	22 not 23	0
#25	21 not 24	629
#26	remove duplicates from 25	623
#27	limit 26 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	445

Table 91. Search strategy for Cochrane for HRQoL inputs (SLR update)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	1781
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	3350
#3	1 or 2	3504
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	9527
#5	Randomized Controlled Trials as Topic/ or randomized controlled trial/ or Random Allocation/ or Double Blind Method/ or Single Blind Method/ or clinical trial/ or (phase i* or phase 1*).mp. or (phase ii* or phase 2*).mp. or (phase iii* or phase 3*).mp. or (phase iv* or phase 4*).mp. or controlled clinical trial.mp. or randomized controlled trial.mp. or multicenter study.mp. or clinical trial.mp. or exp Clinical Trials as topic/ or (clinical adj trial$).tw. or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. or PLACEBOS/ or placebo$.tw. or randomly allocated.tw. or (allocated adj2 random$).tw. or (single arm or single-arm or noncomparative or non-comparative).tw.	1250136
#6	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom* or (phase adj3 (study or studies or trial*)) or ((crossover or cross-over) adj3 (study or studies or trial*)) or ((multicent* or multi-cent*) adj3 (study or studies or trial*))).ti,ab,hw,kf. or allocated.ti,ab,hw. or ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf. or ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf. or (pragmatic study or pragmatic studies).ti,ab,hw,kf. or ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf. or ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf. or trial.ti,kf.	776522
#7	Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ or (registry or register$ or survey).ti,ab. or (real world or RWE).ti,ab. or Real-life.ti,ab. or exp seroepidemiologic studies/ or (descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf. or ((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf.	387485
#8	5 or 6 or 7	1481340
#9	Case study/	0

No.	Query	Results
#10	Case report.tw.	3074
#11	Letter/	0
#12	or/9-11	3074
#13	8 not 12	1478969
#14	3 and 4 and 13	669
#15	(animal$ not human$).sh,hw.	3349
#16	14 not 15	669
#17	limit 16 to english language [Limit not valid in DARE,CLCMR,ACP Journal Club,CDSR; records were retained]	663
#18	limit 17 to (editorial or erratum or letter or note or patent or reports or "review" or short survey or tombstone) [Limit not valid in DARE,CLEED,CLHTA,CLCMR,ACP Journal Club,CCTR,CDSR; records were retained]	5
#19	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw.	29110
#20	18 not 19	5
#21	17 not 20	658
#22	conference abstract.pt.	0
#23	limit 22 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	0
#24	22 not 23	0
#25	21 not 24	658
#26	remove duplicates from 25	647
#27	limit 26 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	470
#28	limit 27 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	36

I.1.2 Systematic selection of studies

Implementation and reporting of the SLR followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) standards. Records were screened based on the population, intervention, comparators, outcomes, and study design (PICOS) criteria.

Results from the database searches were downloaded via EndNote into a Microsoft Excel 2016® spreadsheet, at which point duplicates were identified and removed. The spreadsheet was used to manage citation screening during the first and second stages of screening. The captured literature was selected according to the inclusion/exclusion criteria presented in Table 92. At the first screening stage, the publications were selected based on the information in the title and abstract; publications included for the second stage screening were selected based on the information in the full text. Relevant SLRs, meta-analyses, and indirect treatment comparisons were reviewed to obtain references of the studies of interest for inclusion into this SLR. Reference lists of SLRs and meta-analyses were reviewed for any relevant articles based on title only. If relevant articles were identified based on the title, the full publication was reviewed, and the relevant data were extracted.

Both screening stages were performed by 2 reviewers in a double-blind manner to determine whether screened studies met the predefined inclusion and exclusion criteria. Any discrepancies in screening decisions were resolved by a third reviewer. The study selection process was reported in a PRISMA flow diagram, see Figure 36. Following study selection, final citation lists were developed that denoted studies excluded at the title/abstract level, studies excluded at the full-text level, reasons for exclusion, and studies included after 2 levels of screening.

Table 92. Inclusion and exclusion criteria used for assessment of studies for HRQoL inputs

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients with newly diagnosed Ph- B-ALL	R/R disease T-ALL only Studies of mixed B and T-ALL, without reporting subgroup results for B-ALL patients Studies reporting data from Ph+ patients or if results reported from a mixed Ph+ and Ph- population, without reporting	N/A

		subgroup results for Ph- patients	
Intervention	Any pharmacologic first-line therapy (irrespective of whether the therapy has received regulatory approval), including induction, consolidation, and maintenance treatment	Second-line or later therapy Studies of mixed lines of therapies without reporting subgroup results for first-line therapies	NA
Comparators	Any first-line therapy	N/A	N/A
Outcomes	Clinical efficacy Real-world effectiveness Safety and tolerability Treatment regimen, treatment patterns, and treatment pathways Potential prognostic factors and treatment effect modifiers associated with poor outcomes Humanistic outcomes, including HRQL, patient-reported outcomes, and caregiver burden	N/A	N/A
Study design/publication type	RCTs Non-randomized trials including non-blinded, single-blinded, and double-blinded trials SATs (except phase 1 studies) Observational/real-world evidence (including cohort studies) SLRs, meta-analyses, and indirect treatment comparisons	Animal/in vitro studies Case series and case reports General reviews, editorials, and letters Phase 1 studies	N/A
Language restrictions	English only	N/A	N/A

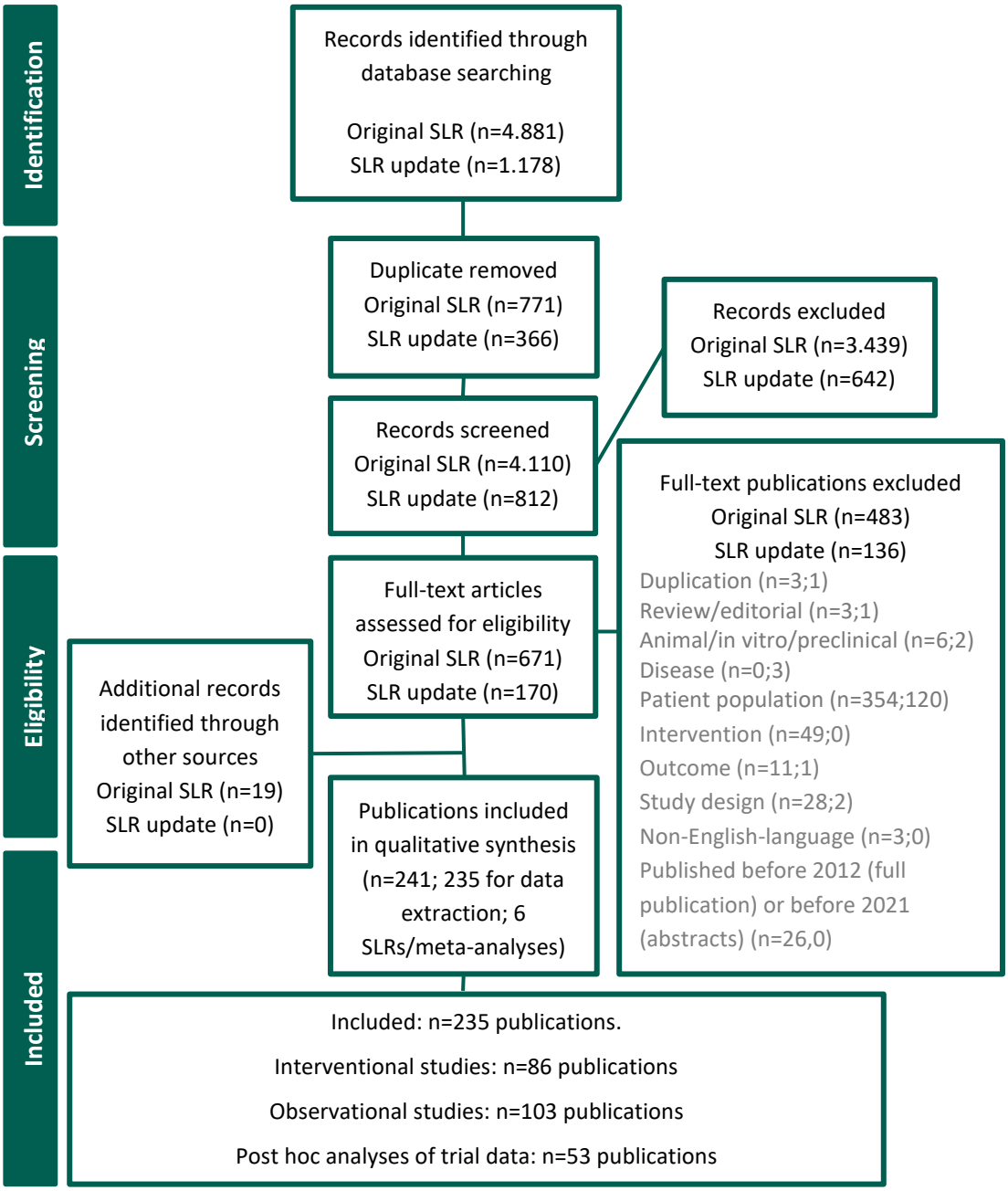

Figure 36. PRISMA diagram for HRQoL

No evidence was identified for humanistic burden, including outcomes of HRQoL. Thus, the table below is N/A.

I.1.2.1 Strengths and weaknesses of the literature search and the selection

This review followed robust methodologies and standards from the DMC and the PRISMA statement, including an extensive literature search covering trial registries, conference abstracts, and treatment guidelines, hereby capturing various study designs, including RCTs, SATs, and observational evidence. The interventions/comparators of interest were any pharmacologic treatments (irrespective of whether the therapy has

received regulatory approval) used in the first line for induction, consolidation, or maintenance treatment. The interventions of interest may have been given as monotherapy or in combination with other treatments. Thus, the search strings did not include search terms specifically for the intervention and comparators, e.g. generic and trade names, of interest for this specific application. This approach enabled a more expansive search to identify all studies of interest to minimize overlooking relevant studies. However, a limitation of this approach is that it may result in a larger number of irrelevant results, which increases the effort required to screen the results.

One limitation may be associated with the search being restricted to publications from 2012 onwards. However, the rationale for limiting searches to the last 12 years was to capture evidence from the most relevant and currently used therapies and therefore minimize inappropriate comparisons. While having strict inclusion and exclusion criteria is a methodologic strength in this review, the review may have missed some potentially relevant evidence for adults from studies reporting mixed populations (B/T ALL populations; Ph-/Ph+ populations).

Despite attempts to reduce the risk of bias in this review by using robust and accepted systematic review methods, as with all systematic reviews, the results are limited by the quantity and quality of the evidence from the included studies. Some included RCTs were only available as abstracts, and therefore were not assessed for risk of bias, because they lacked the detail of a journal manuscript. Risk of bias in the included RCTs varied; however, only 2 RCTs were rated as having a high risk of bias owing to the open-label design.

I.1.3 Excluded full text references

Table 93. Overview of the excluded full-text references with reasons (Original SLR)

Author	Year	Title	Journal	Citation	Final reviewer decision
Almajed	2022	Cost-effectiveness evidence on approved cancer drugs in Ireland: the limits of data availability and implications for public accountability	European Journal of Health Economics	23(3):375-431.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Anonymous	2016	Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: An economic analysis	Ontario Health Technology Assessment Series	16(8):1-83.	I2 – Include (SLR, Meta-analysis, ITC; all study types)
Athale	2022	Healthcare utilization and costs associated with acute lymphoblastic leukemia in children with and without Down syndrome	Pediatric Blood & Cancer	69:e29829.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Baba Moussa	2022	EE263 Cost-Effectiveness Analyses (CEAs) of CAR-T Therapies Over the Past Four Years: What's New?	Value in Health	25(12 Supplement):S105.	E5 – Disease (e.g. not ALL, not B-cell)
Baraka	2017	Detection of minimal residual disease in childhood B-acute lymphoblastic leukemia by 4-color flowcytometry	International Journal of Hematology	105(6):784-91.	E11 – Outcome (i.e. no economic outcomes mentioned)
Barakat	2022	Is hypoalbuminemia a risk factor for high-dose methotrexate toxicity in children with acute lymphoblastic leukemia?	Journal of the Egyptian National Cancer Institute	34(1) (no pagination):	E11 – Outcome (i.e. no economic outcomes mentioned)
Barba	2022	Impact of Center Characteristics and Macroeconomic Factors on the Outcome of Adult Patients with Acute Lymphoblastic Leukemia Treated with Pediatric-Inspired Protocols	HemaSphere	6(Supplement	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

				3):2985-6.	
Buldini	2018	Minimal residual disease by MFC in acute lymphoblastic leukemia in children	Haematologica	103:S1-S2.	E11 – Outcome (i.e. no economic outcomes mentioned)
Chakumatha	2022	Towards zero percent treatment abandonment of patients with common and curable childhood cancer types in Blantyre, Malawi	Pediatric Blood & Cancer	69:e29899.	E11 – Outcome (i.e. no economic outcomes mentioned)
Chen	2021	Cost-effectiveness and drug wastage of immunotherapeutic agents for hematologic malignancies: a systematic review	Expert Review of Pharmacoeconomics and Outcomes Research	21(5):923-41.	I2 – Include (SLR, Meta-analysis, ITC; all study types)
Chen	2022	Solving coagulation conundrums: comparing prophylaxis strategies in adult patients receiving PEG-asparaginase	Leukemia and Lymphoma	63(11):2663-70.	E11 – Outcome (i.e. no economic outcomes mentioned)
Cherla	2020	Cost-effectiveness of cancer drugs: Comparative analysis of the United States and England	EClinicalMedicine	29-30 (no paginatio n):	E6 – Disease status (i.e. R/R)
DuMontier	2019	Function, Survival, and Care Utilization Among Older Adults With Hematologic Malignancies	Journal of the American Geriatrics Society	67(5):889-97.	E5 – Disease (e.g. not ALL, not B-cell)
Goswami	2020	Quality-of-life issues and symptoms reported by patients living with haematological malignancy: a qualitative study	Therapeutic Advances in Hematology	11:	E5 – Disease (e.g. not ALL, not B-cell)
Gupta	2021	Efficacy of Single Low-Dose Rasburicase in Management of Tumor Lysis Syndrome in Leukemia and Lymphoma Patients	Clinical Lymphoma, Myeloma and Leukemia	21(1):e99-e104.	E5 – Disease (e.g. not ALL, not B-cell)

Gupta	2023	Racial and ethnic disparities in childhood and young adult acute lymphocytic leukaemia: secondary analyses of eight Children's Oncology Group cohort trials	The Lancet Haematology	10(2):e129-e41.	E11 – Outcome (i.e. no economic outcomes mentioned)
Halford	2021	A Systematic Review of Blinatumomab in the Treatment of Acute Lymphoblastic Leukemia: Engaging an Old Problem With New Solutions	Annals of Pharmacotherapy	55(10):1236-53.	E6 – Disease status (i.e. R/R)
Health Quality	2016	Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: an economic analysis (Structured abstract)	E1 – Duplicate		
Heine	2021	Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future	HemaSphere	5(2) (no pagination):	E6 – Disease status (i.e. R/R)
Hettle	2017	The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal	Health Technology Assessment (Winchester, England)	21:1-204.	E6 – Disease status (i.e. R/R)
Ho	2021	Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review	PharmacoEconomics	39(9):995-1019.	E6 – Disease status (i.e. R/R)
Jabbour	2023	Payer and Provider Solutions to Utilization Management Challenges in the Management of Rare Hematologic Cancers	American Journal of Managed Care	29(Suppl 4):S551-S60.	E2 – Review/editorial
Kako	2022	Decision Analysis for Unrelated Bone Marrow Transplantation or Immediate Cord Blood Transplantation for Patients with Philadelphia Chromosome-Negative Acute Lymphoblastic Leukemia in First Complete Remission	Transplantation and Cellular Therapy	28(3):161.e1-.e10.	E6 – Disease status (i.e. R/R)

Kriegsmann	2019	Collection, Cryostorage, Transplantation, and Disposal of Hematopoietic Stem Cell Products	Biology of Blood and Marrow Transplantation	25(2):382-90.	E11 – Outcome (i.e. no economic outcomes mentioned)
Liao	2022	Association of Minimal Residual Disease by a Single-Tube 8-Color Flow Cytometric Analysis With Clinical Outcome in Adult B-Cell Acute Lymphoblastic Leukemia	Archives of pathology & laboratory medicine.	13:	E10 – Study design (e.g. trial protocols)
Luskin	2022	EXABS-132-ALL Approach to Acute Lymphoblastic Leukemia in The Elderly	Clinical Lymphoma, Myeloma and Leukemia	E2 – Review/editorial	
Mayerhoff	2019	Cost associated with hematopoietic stem cell transplantation: A retrospective claims data analysis in Germany	Journal of Comparative Effectiveness Research	8(2):121-31.	E11 – Outcome (i.e. no economic outcomes mentioned)
Nam		Cost-effectiveness of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia	Value in health	Vol.20:A1 11p.	E4 – Published before 2012 (FP) or before 2021 (abstracts)
Nam	2017	Cost-effectiveness of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia	Haematologica	102:2017-05.	E4 – Published before 2012 (FP) or before 2021 (abstracts)
Ouchveridze	2022	Financial toxicity in hematological malignancies: a systematic review	Blood Cancer Journal	12(4) (no paginatio n):	I2 – Include (SLR, Meta-analysis, ITC; all study types)
Paganin	2014	Postinduction minimal residual disease monitoring by polymerase chain reaction in children with acute lymphoblastic leukemia	Journal of Clinical Oncology	32(31):3553-8.	E11 – Outcome (i.e. no economic outcomes mentioned)

Patkar	2012	Standardizing minimal residual disease by flow cytometry for precursor B lineage acute lymphoblastic leukemia in a developing country	Cytometry Part B, Clinical Cytometry	82:252-8.	E11 – Outcome (i.e. no economic outcomes mentioned)
Paula	2015	Comparison between qualitative and real-time polymerase chain reaction to evaluate minimal residual disease in children with acute lymphoblastic leukemia	Revista Brasileira de Hematologia e Hemoterapia	37:373-80.	E11 – Outcome (i.e. no economic outcomes mentioned)
Radhakrishnan	2021	Systematic Review of the Burden and Treatment Patterns of Adult and Adolescent Acute Lymphoblastic Leukemia in India: Comprehending the Challenges in an Emerging Economy	Clinical Lymphoma, Myeloma and Leukemia	21(1):e85-e98.	E11 – Outcome (i.e. no economic outcomes mentioned)
Ragoonanan	2022	A multicenter study of ICU resource utilization in pediatric, adolescent and young adult patients post CAR-T therapy	Frontiers in Oncology	12 (no paginatio n):	E6 – Disease status (i.e. R/R)
Tariq	2022	Efficacy of Furosemide in Methotrexate Clearance in Patients Treated with High Dose Methotrexate: A Cohort Study	Pakistan Journal of Medical and Health Sciences	16(4):485-7.	E5 – Disease (e.g. not ALL, not B-cell)
Totadri	2021	A single assessment of methotrexate levels at 42 hours permits safe administration and early discharge in children with lymphoblastic lymphoma and leukemia receiving high-dose methotrexate	Pediatric Hematology & Oncology	38:434-43.	E5 – Disease (e.g. not ALL, not B-cell)
Umaretiya	2021	Household material hardship and parental distress in a multicenter clinical trial for pediatric acute lymphoblastic leukemia	Journal of Clinical Oncology. Conference: Annual Meeting of the American Society of Clinical Oncology, ASCO	39:	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

Vokinger	2021	Analysis of Launch and Postapproval Cancer Drug Pricing, Clinical Benefit, and Policy Implications in the US and Europe	JAMA Oncology	7:	E5 – Disease (e.g. not ALL, not B-cell)
Vu	2022	Health economic evidence for the use of molecular biomarker tests in hematological malignancies: A systematic review	European Journal of Haematology	108(6):469-85.	E5 – Disease (e.g. not ALL, not B-cell)
Wilson	2022	The expense of sending cerebrospinal fluid for analysis on all lumbar punctures in pediatric acute lymphoblastic leukemia patients	Pediatric Blood and Cancer	69(8) (no pagination):	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Yang	2023	Impact of Infection Patterns on the Outcomes of Patients with Hematological Malignancies in Southwest China: A 10-Year Retrospective Case-Control Study	Infection and Drug Resistance	16:3659-69.	E11 – Outcome (i.e. no economic outcomes mentioned)
Zhang	2018	Economic Burden of Veno-occlusive Disease in Patients With B-cell Acute Lymphoblastic Leukemia in the United States	Clinical Therapeutics	40(10):1711-9.e1.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

Table 94. Overview of the excluded full-text references with reasons (SLR update)

Author	Year	Title	Journal	Citation	Final reviewer decision
Arjunji	2019	Assessment of Cost-Effectiveness Results from Icer Advanced Therapies Medicinal Products Reviews	Value in Health Regional Issues	19(Supplement):S75.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Batra	2023	Teleconsultation in pediatric acute lymphoblastic leukemia (ALL) - Its feasibility and impact	Pediatric Hematology Oncology Journal	8(4 Supplement):S15.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)

Borga	2019	Pbi71 Exploring Uncertainties and Solutions Allowing Patient Access to Car T-Cell Therapies: Learning Today How to Improve Tomorrow	Value in Health	22(Supplement 3):S430.	E5 – Disease (i.e. not ALL)
Caillon		Cost-Effectiveness of Blinatumomab in Pediatric Patients with High-Risk First-Relapse B-Cell Precursor Acute Lymphoblastic Leukemia in France	PharmacoEconomics - open	Vol.7:639-53p.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Clou	2018	Standardization of blinatumomab preparation for saving cost	European Journal of Oncology Pharmacy	1(3 Supplement 1):44.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Davitt	2023	Drivers of Differential Time to Diagnosis in Pediatric ALL Tied to Race and Ethnicity	Journal of Pediatric Hematology/Oncology	45(7):E879-E84.	E8 – Outcome
Duffy	2023	Evaluating Blinatumomab Treatment Adoption in Varied Resource Settings Using the RE-AIM Framework	Blood	142(Supplement 1):3713.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Guerra	2020	Risk Factors Associated with 30-Day Unplanned Readmissions for Adult Acute Lymphoblastic Leukemia (ALL)	Blood	136(Supplement 1):3-4.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Hall	2019	Minimizing drug waste and optimizing cost effectiveness of blinatumomab in a tertiary care center	Pediatric Blood and Cancer	66(Supplement 2):S30.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Jain	2023	Association of Age with Acuity and Severity of Illness at Initial Presentation in Children, Adolescents, and Young Adults with Leukemia	Blood	142(Supplement 1):3769.	E8 – Outcome

Janitz	2020	Exploring disparities among American indian children with cancer	Pediatric Blood and Cancer. Conference	67:	E8 – Outcome
Krakora	2019	Impact of Insurance Status on Survival Outcomes in Adults with Acute Lymphoblastic Leukemia (ALL): A Single Center Experience	Blood	134(Supplement 1):5071.	E8 – Outcome
Libanore	2023	HTA6 Balancing National Financial Stability with Commercial Expectations of Return on R&D Investment: A Review of Price Discounts for the Reimbursement of Oncology Drugs in Brazil	Value in Health	26(6 Supplement):S259-S60.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Mayerhoff	2018	Cost Associated with Hematopoietic Stem Cell Transplantation (Hsct) - a Retrospective Claims Data Analysis in Germany	Value in Health	21(Supplement 3):S36.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Mungle	2023	Comparative treatment costs of risk-stratified therapy for childhood acute lymphoblastic leukemia in India	Cancer Medicine	12(3):3499-508.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Pigneux	2019	Healthcare resource utilization (HRU) associated with minimal residual disease (MRD) status in adults with B-cell precursor (BCP) acute lymphoblastic leukemia (ALL)	HemaSphere	3(Supplement 1):1012.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Rompola	2018	Pediatric intensive care admissions in children with acute lymphoblastic leukemia	HemaSphere	2(Supplement 2):544.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Rompola	2020	Intensive care admissions for children with acute lymphoblastic leukaemia: A 13 years single centre experience	British Journal of Haematology	189(Supplement 1):133.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)

Salcedo	2019	Pcn126 Lifetime Costs for Diffuse Large B-Cell Lymphoma and B-Cell Acute Lymphoblastic Leukemia: A Literature Review to Inform Potential Financial Impact of Curative Therapies	Value in Health	22(Supplement 2):S79-S80.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Shah	2019	Thirty Day Resource Utilization after Chimeric Antigen Receptor (CAR) T Cell Infusion for Hematologic Malignancies	Biology of Blood and Marrow Transplantation	25(3 Supplement):S38-S9.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Wakase	2018	Costs of Hematopoietic Stem Cell Transplantation (Hsct) in Patients with Acute Lymphoblastic Leukemia (All), Diffuse Large B-Cell Lymphoma (Dlbcl) and Follicular Lymphoma (Fl) - a Retrospective Analysis of Japanese Claims Data	Value in Health	21(Supplement 3):S36.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Yingying	2019	Comparison between Hypercvad and CALLG2008 Protocol in Adult Patients with Newly Diagnosed Acute Lymphoblastic Leukemia:a Single Center Study	Blood	134(Supplement 1):5122.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Zhang	2019	Pcn120 Economic Burden for Patients with Newly Diagnosed Acute Lymphoblastic Leukemia (All) in Complete Remission (Cr)	Value in Health	22(Supplement 2):S78.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)

I.1.4 Quality assessment and generalizability of estimates

Clinical evidence for each included full publication was critically appraised using the second version of the Cochrane risk of bias (RoB 2) tool to assess the risk of bias for RCTs, the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool for interventional non-randomized/SATs, and the Newcastle-Ottawa Scale series for all non-interventional clinical evidence. Quality assessment was carried out in a double-blind manner.

I.1.5 Unpublished data (N/A)

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

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

J.1.1 Systematic literature search for health economic inputs

An SLR was conducted with the objective to identify and summarize evidence of economic burden of illness, economic evaluations, and HSUVs for patients with newly diagnosed Ph- B-cell ALL.

The SLR was performed on 12th of September 2023, and re-run on 16th of April 2024 using the Ovid® platform covering the databases listed in Table 95. Based on the submission date of September 2025, it can be argued that the last SLR update is outdated since the SLR re-run was conducted more than one year prior to this submission date. However, given that Amgen requested the submission date to the DMC to be ultimo March in the assessment request, no new SLR update was planned for the application, which was agreed upon by the DMC during the dialogue meeting in February.

Supplementary hand searches included congress searches, clinical trial registry searches, HTAs, and other relevant regulatory reports, see Table 96 and Table 97.

Table 95. Bibliographic databases included in the literature search for health economic inputs

Database	Platform	Relevant period for the search	Date of search completion
Embase	Ovid®	1974 to 2024	12.9.2023 (re-run on 16.04.2024)
Medline		1946 to present	
Cochrane Library		1991 to 2024	

Table 96. Other sources included in the literature search for health economic inputs

Source name	Location/source	Search strategy	Date of search
Lancet Global Burden of Disease Resource Centre	https://www.thelancet.com/gbd	Keywords: acute lymphoblastic leukemia	12.9.2023 (re-run on 16.04.2024)
Our World in Data Burden of Disease:	https://ourworldindata.org/burden-of-disease		

Source name	Location/source	Search strategy	Date of search
Local treatment guidelines: US, Canada, UK, Germany, France, Italy, Spain, Portugal, Australia, China, Japan	N/A		
National Comprehensive Cancer Network (NCCN)	https://www.nccn.org/guidelines/category_1		
National Institute for Health and Care Excellence (NICE)	https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/nice-guidelines		
IHME Global Burden of Disease	https://www.healthdata.org/gbd		
WHO Global Health Observatory	https://www.who.int/gho/mortality_burden_disease/en/		

Table 97. Conference material included in the literature search for health economic inputs

Conference	Source of abstracts	Search strategy	Words/ terms searched	Date of search
American Society of Clinical Oncology (ASCO) Annual meeting	https://www.asco.org/	2018 to 2023 indexed in Ovid, covered through electronic searches 2024: congress had not happened at the time of data collection (April 2024)	N/A	12.9.2023 (re-run on 16.04.2024)
American Society of Hematology (ASH) meetings	Meetings - Hematology.org	2018 to 2023 indexed in Ovid, covered through electronic searches 2024: congress had not happened at the time of data collection (April 2024)		
European Hematology	EHA Meetings	2018 to 2022: indexed in Ovid, covered through electronic searches		

Conference	Source of abstracts	Search strategy	Words/ terms searched	Date of search
Association (EHA) meetings		2023: a PDF booklet was available and screened 2024: congress had not happened at the time of data collection (April 2024)		
European Society for Blood and Marrow Transplantation (EBMT) events	Annual Meeting & Educational Events | EBMT	2018 to 2022: indexed in Ovid, covered through electronic searches 2023: a PDF booklet was available and screened 2024: congress had not happened at the time of data collection (April 2024)		
European Society for Medical Oncology (ESMO)	https://oncologypro.esmo.org/meeting-resources	2018 to 2023: indexed in Ovid, covered through electronic searches 2024: congress had not happened at the time of data collection (April 2024)		
Society for Immunotherapy of Cancer (SITC)	SITC Cancer Immunotherapy CONNECT - Society for Immunotherapy of Cancer (SITC)	2018 to 2023: indexed in Ovid, covered through electronic searches 2024: congress had not happened at the time of data collection (April 2024)		
International Society of Pediatric Oncology, Asia Continental Branch (SIOP Asia)	Event | SIOP	2023: a PDF booklet was available and screened; other year abstracts not available 2024: congress had not happened at the time of data collection (April 2024)		
Nordic Society of Paediatric Haematology (NOPHO) annual meeting	Home - NOPHO	2023: a PDF booklet was available and screened; other year abstracts not available		

Conference	Source of abstracts	Search strategy	Words/ terms searched	Date of search
		2024: congress had not happened at the time of data collection (April 2024)		
The Professional Society for Health Economics and Outcomes Research (ISPOR) and ISPOR Europe	https://www.ispor.org/	2018 to 2023: indexed in Ovid, covered through electronic searches 2024: congress had not happened at the time of data collection (April 2024)		

J.1.2 Search strategies

The search strategy includes a mixture of Medical Subject Headings (MeSH)/Emtree terms and free text terms for population, study design, and outcomes of interest (e.g., economic, cost-effectiveness, incremental cost-effectiveness ratio [ICER], cost/resource use and HSUVs), see Table 98 - Table 103.

Table 98. Search strategy for Embase for health economic inputs (original SLR)

No.	Query	Results
#1	exp acute lymphoblastic leukaemia/ or acute lymphoblastic leukaemia*.mp.	72311
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	90458
#3	1 or 2	92445
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or philadelphia chromosome-negative/ or exp b lymphocyte/ or exp b-cell/ or exp b-precursor/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	412458
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or	2590733

No.	Query	Results
	utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	402873
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	154036
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	33198
#9	quality of life/ and ec.fs.	61290
#10	quality of life/ and (health adj3 status).ti,ab,kw.	20157
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	6834
#12	or/5-11	2841165
#13	3 and 4 and 12	1858
#14	(animal$ not human$).sh,hw.	4857623
#15	13 not 14	1797
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review")	263
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	709372

No.	Query	Results
#18	16 not 17	243
#19	15 not 18	1554
#20	case study/ or case report.tw.	631908
#21	19 not 20	1514
#22	limit 21 to english language	1498
#23	conference abstract.pt.	4877774
#24	limit 23 to yr="2021 -Current"	732780
#25	23 not 24	4144994
#26	22 not 25	825
#27	remove duplicates from 26	789
#28	limit 27 to yr="2012 -Current"	696

Table 99. Search strategy for Embase for health economic inputs (SLR update)

No.	Query	Results
#1	exp acute lymphoblastic leukaemia/ or acute lymphoblastic leukaemia*.mp.	76496
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	95145
#3	1 or 2	97145
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or philadelphia chromosome-negative/ or exp b lymphocyte/ or exp b-cell/ or exp b-precursor/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	431722
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health care financing/ or health economics.mp. or health economics/ or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or budget/ or	2708628

No.	Query	Results
	pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or health care planning/ or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	416313
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	161374
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	34803
#9	quality of life/ and ec.fs.	65487
#10	quality of life/ and (health adj3 status).ti,ab,kw.	21169
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	7056
#12	or/5-11	2970313
#13	3 and 4 and 12	2249
#14	(animal$ not human$).sh,hw.	4944482
#15	13 not 14	2185
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review")	290

No.	Query	Results
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	754979
#18	16 not 17	267
#19	15 not 18	1918
#20	case study/ or case report.tw.	662875
#21	19 not 20	1869
#22	limit 21 to english language	1852
#23	conference abstract.pt.	5108624
#24	limit 23 to yr="2021 -Current"	943440
#25	23 not 24	4165184
#26	22 not 25	1176
#27	remove duplicates from 26	1139
#28	limit 27 to yr="2012 -Current"	1046
#29	limit 28 to yr="2023 -Current"	229
#30	22 and 23	1249
#31	limit 30 to yr="2018 -2020"	447
#32	29 or 31	676

Table 100. Search strategy for Medline for health economic inputs (original SLR)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	35987
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	46118
#3	1 or 2	48213
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-	296427

No.	Query	Results
	lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health economics.mp. or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or resource management.mp. or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	1574813
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	263605
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	94463
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	15741
#9	quality of life/ and ec.fs.	10876
#10	quality of life/ and (health adj3 status).ti,ab,kw.	11650

No.	Query	Results
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	17002
#12	or/5-11	1721036
#13	3 and 4 and 12	414
#14	(animal$ not human$).sh,hw.	5110083
#15	13 not 14	405
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review") [Limit not valid in Ovid MEDLINE(R); records were retained]	86
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	448312
#18	16 not 17	85
#19	15 not 18	320
#20	case study/ or case report.tw.	2416634
#21	19 not 20	305
#22	limit 21 to english language	300
#23	congress.pt.	67343
#24	limit 23 to yr="2021 -Current"	688
#25	23 not 24	66655
#26	22 not 25	300
#27	remove duplicates from 26	299
#28	limit 27 to yr="2012 -Current"	241

Table 101. Search strategy for Medline for health economic inputs (SLR update)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	36726
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	47260

No.	Query	Results
#3	1 or 2	49414
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	303507
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health economics.mp. or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or resource management.mp. or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	1640974
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	270751
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	99081
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	16455

No.	Query	Results
#9	quality of life/ and ec.fs.	10883
#10	quality of life/ and (health adj3 status).ti,ab,kw.	12097
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	17562
#12	or/5-11	1792420
#13	3 and 4 and 12	436
#14	(animal$ not human$).sh,hw.	5167748
#15	13 not 14	427
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review") [Limit not valid in Ovid MEDLINE(R); records were retained]	90
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	480230
#18	16 not 17	89
#19	15 not 18	338
#20	case study/ or case report.tw.	2458426
#21	19 not 20	323
#22	limit 21 to english language	318
#23	congress.pt.	67546
#24	limit 23 to yr="2021 -Current"	891
#25	23 not 24	66655
#26	22 not 25	318
#27	remove duplicates from 26	317
#28	limit 27 to yr="2012 -Current"	259
#29	limit 28 to yr="2023 -Current"	41

Table 102. Search strategy for Cochrane for health economic inputs (original SLR)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	1665
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	3243
#3	1 or 2	3401
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	9021
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health economics.mp. or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or resource management.mp. or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	168760
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	55756
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or	38946

No.	Query	Results
	european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	3845
#9	quality of life/ and ec.fs.	3107
#10	quality of life/ and (health adj3 status).ti,ab,kw.	2099
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	4147
#12	or/5-11	199191
#13	3 and 4 and 12	83
#14	(animal$ not human$).sh,hw.	2783
#15	13 not 14	83
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review") [Limit not valid in DARE,CLEED,CLHTA,CLCMR,ACP Journal Club,CCTR,CDSR; records were retained]	0
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	26506
#18	16 not 17	0
#19	15 not 18	83
#20	(case study or case report).tw.	5316
#21	19 not 20	83
#22	limit 21 to english language [Limit not valid in DARE,CLCMR,ACP Journal Club,CDSR; records were retained]	83
#23	conference abstract.pt.	0
#24	limit 23 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	0
#25	23 not 24	0
#26	22 not 25	83

No.	Query	Results
#27	remove duplicates from 26	81
#28	limit 27 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	73

Table 103. Search strategy for Cochrane for health economic inputs (SLR update)

No.	Query	Results
#1	exp leukemia, lymphoblastic, acute/ or acute lymphoblastic leukaemia*.mp.	1781
#2	exp acute lymphoblastic leukemia/ or acute lymphoblastic leukemia*.mp.	3350
#3	1 or 2	3504
#4	(philadelphia and chromosome).mp. or philadelphia chromosome/ or exp b lymphocyte/ or exp Precursor B-Cell Lymphoblastic Leukemia-Lymphoma/ or exp Lymphoma, B-Cell/ or (b lymphocyte* or b-lymphocyte* or b cell* or b-cell* or b precursor* or b-precursor* or b lineage* or b-lineage*).mp.	9527
#5	"health care cost"/ or "drug cost"/ or "hospital cost"/ or "hospitalization cost"/ or "nursing cost"/ or ((health or global) adj2 burden).mp. or ((direct or indirect or societ* or employe*) adj2 (resource* or benefit*)).mp. or exp caregiver burden/ or exp caregiver support/ or (caregiver* or carer*).mp. or economics/ or budget*.mp. or cost*.mp. or productivity/ or productivity.mp. or absenteeism.mp. or absenteeism/ or presenteeism.mp. or presenteeism/ or "length of stay"/ or Cost control/ or (fiscal or financ* or funding).mp. or financial management.mp. or financial management/ or health care utilization/ or health care utili*.mp. or health care financing.mp. or health economics.mp. or (burden adj2 (illness or disease$ or treatment*)).mp. or resource allocation/ or resource management.mp. or budget/ or pharmacoeconomics/ or pharmacoeconomic*.mp. or pay?r.mp. or health care planning.mp. or (resource adj2 (use* or utili?ation or allocat* or burden or health)).mp. or (economic adj5 (burden or impact)).mp. or cost of illness.mp. or "cost of illness"/ or cost control.mp. or "cost control"/ or Economics, Medical/	181207
#6	(cost-effectiveness or cost-utility or ((economic or pharmacoeconomic) adj1 (evaluation or assessment or analys?s or stud*))).mp. or Cost effectiveness analysis/ or Cost minimization analysis/ or Cost benefit analysis/ or Cost utility analysis/ or Budget impact/ or Cost consequence analysis/ or (Cost effectiveness analysis or Cost minimization analysis or Cost benefit analysis or Cost utility analysis or Budget impact or Cost consequence analysis or ICER or CMA or CEA or CBA or CUA or CCA).mp.	58893
#7	Quality-Adjusted Life Years/ or (quality adjusted or adjusted life year$).ti,ab,kw. or (qaly$ or qald$ or qale$ or qtime$).ti,ab,kw. or (illness state$1 or health state$1).ti,ab,kw. or (hui or hui1 or hui2 or	41158

No.	Query	Results
	hui3).ti,ab,kw. or (multiattribute$ or multi attribute$).ti,ab,kw. or (utility adj3 (score$1 or valu$ or health$ or cost$ or measur$ or disease$ or mean or gain or gains or index$)).ti,ab,kw. or utilities.ti,ab,kw. or (eq-5d or eq5d or eq-5 or eq5 or euro qual or euroqual or euro qual5d or euroqual5d or euro qol or euroqol or euro qol5d or euroqol5d or euro quol or euroquol or euro quol5d or euroquol5d or eur qol or eurqol or eur qol5d or eur qol5d or eur?qul or eur?qul5d or euro$ quality of life or european qol).ti,ab,kw. or (euro$ adj3 (5 d or 5d or 5 dimension$ or 5dimension$ or 5 domain$ or 5domain$)).ti,ab,kw. or (sf36$ or sf 36$ or sf thirtysix or sf thirty six).ti,ab,kw. or (time trade off$1 or time tradeoff$1 or tto or timetradeoff$1).ti,ab,kw.	
#8	quality of life/ and ((quality of life or qol) adj (score$1 or measure$1)).ti,ab,kw.	3697
#9	quality of life/ and ec.fs.	3351
#10	quality of life/ and (health adj3 status).ti,ab,kw.	2133
#11	(quality of life or qol).ti,ab,kw. and Cost-Benefit Analysis/	4921
#12	or/5-11	213003
#13	3 and 4 and 12	91
#14	(animal$ not human$).sh,hw.	3349
#15	13 not 14	91
#16	limit 15 to (editorial or erratum or letter or note or patent or reports or "conference review" or "review") [Limit not valid in DARE,CLEED,CLHTA,CLCMR,ACP Journal Club,CCTR,CDSR; records were retained]	0
#17	systematic review/ or "systematic review (topic)"/ or systematic review.mp. or meta-analysis/ or "meta analysis (topic)".mp. or meta-analysis.mp.	28650
#18	16 not 17	0
#19	15 not 18	91
#20	(case study or case report).tw.	5543
#21	19 not 20	91
#22	limit 21 to english language [Limit not valid in DARE,CLCMR,ACP Journal Club,CDSR; records were retained]	91
#23	conference abstract.pt.	0

No.	Query	Results
#24	limit 23 to yr="2021 -Current" [Limit not valid in DARE; records were retained]	0
#25	23 not 24	0
#26	22 not 25	91
#27	remove duplicates from 26	88
#28	limit 27 to yr="2012 -Current" [Limit not valid in DARE; records were retained]	80
#29	limit 28 to yr="2023 -Current" [Limit not valid in DARE; records were retained]	6

J.1.3 Systematic selection of studies

The study selection followed an identical approach as for the SLR of HRQoL inputs, see Appendix I.1.2.

The inclusion/exclusion criteria presented in Table 104. Given that only a small number of studies were included, the inclusion criteria were broadened to include mixed populations (i.e., patients with T-cell ALL and patients with B-cell ALL, or Ph- and Ph+) and this was classed as proxy evidence. The study selection process was reported in a PRISMA flow diagram, see Figure 37.

Table 104. Inclusion and exclusion criteria used for assessment of studies for health economic inputs

Clinical effectiveness	Inclusion criteria	Exclusion criteria	Changes, local adaption
Population	Patients (pediatric and adults) with newly diagnosed Ph- B-cell ALL	R/R disease T-ALL only Studies of mixed B- and T-ALL, without reporting subgroup results for B-ALL patients Studies reporting data from Ph+ patients or if results reported from a mixed Ph+ and Ph- population, without reporting	N/A

		subgroup results for Ph- patients	
Intervention	Any pharmacologic first-line therapy (irrespective of whether the therapy has received regulatory approval), including induction, consolidation, and maintenance treatment	Second-line or later therapy Studies of mixed lines of therapies without reporting subgroup results for first-line therapies	N/A
Comparators	Any first-line therapy, as reported	N/A	N/A
Outcomes	Economic burden of illness and economic evaluations: Direct medical costs Indirect medical costs Resource use/resource utilization ICER, budget impact, and other outcomes from economic models[b] Health state utility values	N/A	N/A
Study design/publication type	Any study type, including economic models and evaluations SLRs, meta-analyses, and indirect treatment comparisons	Animal/in vitro studies Case series and case reports General reviews, editorials, and letters	N/A
Language restrictions	English only	N/A	N/A

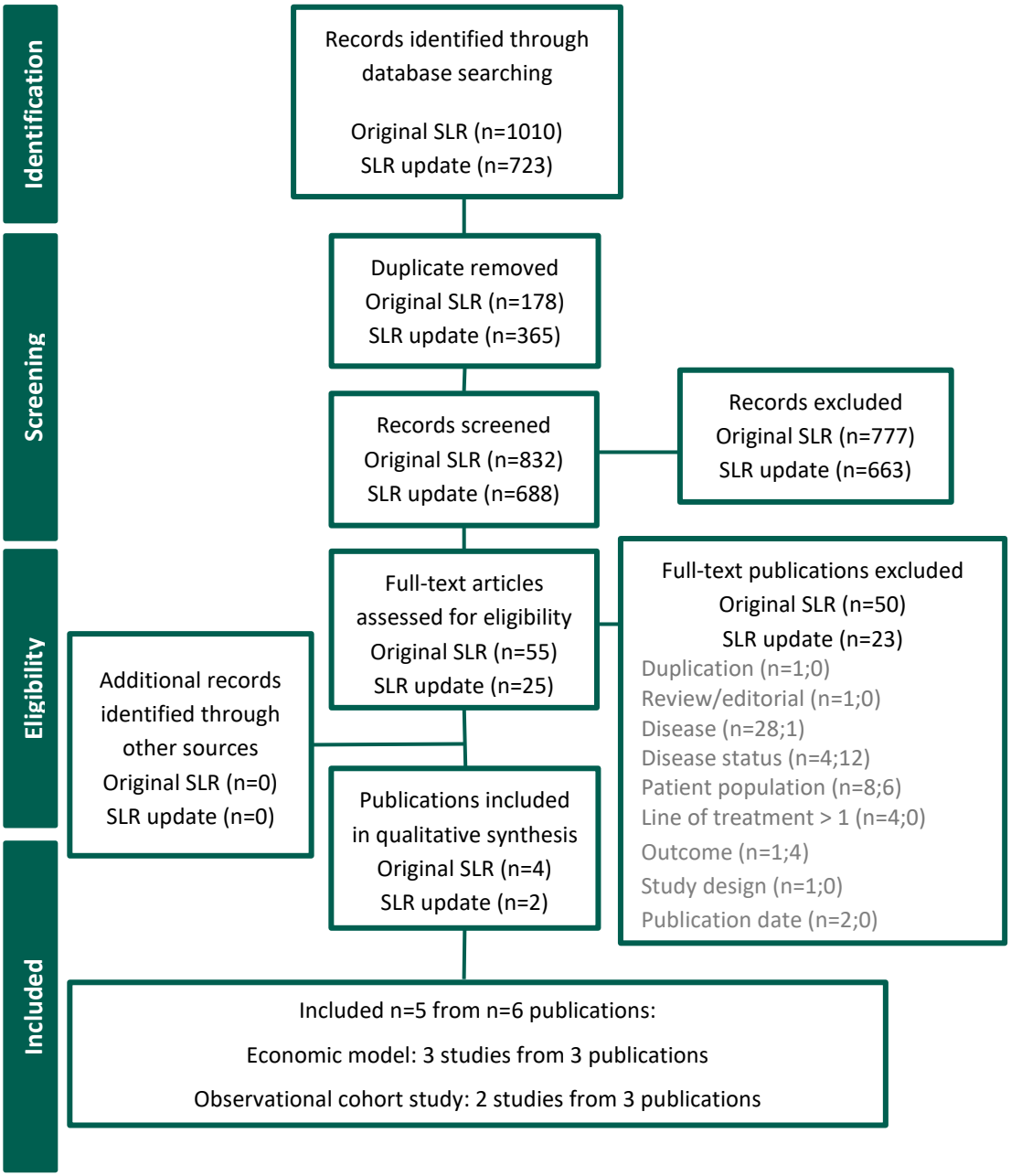

Figure 37. PRISMA diagram for health economic inputs

J.1.3.1 Strengths and weaknesses of the literature search and the selection

This review followed robust methodologies and standards from the DMC and the PRISMA statement, including an extensive literature search covering trial registries, conference abstracts, and treatment guidelines, hereby capturing various study designs, including RCTs, SATs, and observational evidence. The interventions/comparators of interest were any pharmacologic treatments (irrespective of whether the therapy has

received regulatory approval) used in the first line for induction, consolidation, or maintenance treatment. The interventions of interest may have been given as monotherapy or in combination with other treatments. Thus, the search strings did not include search terms specifically for the intervention and comparators, e.g. generic and trade names, of interest for this specific application. This approach enabled a more expansive search to identify all studies of interest to minimize overlooking relevant studies. However, a limitation of this approach is that it may result in a larger number of irrelevant results, which increases the effort required to screen the results.

One limitation may be associated with the search being restricted to publications from 2012 onwards. However, the rationale for limiting searches to the last 12 years was to capture evidence from the most relevant and currently used therapies and therefore minimize inappropriate comparisons. While having strict inclusion and exclusion criteria is a methodologic strength in this review, the review may have missed some potentially relevant evidence for adults from studies reporting mixed populations (B/T ALL populations; Ph-/Ph+ populations).

Despite attempts to reduce the risk of bias in this review by using robust and accepted systematic review methods, as with all systematic reviews, the results are limited by the quantity and quality of the evidence from the included studies. Some included RCTs were only available as abstracts, and therefore were not assessed for risk of bias, because they lacked the detail of a journal manuscript. Risk of bias in the included RCTs varied; however, only 2 RCTs were rated as having a high risk of bias owing to the open-label design.

J.1.4 Excluded full text references

Table 105. Overview of the excluded full-text references with reasons (Original SLR)

Author	Year	Title	Journal	Citation	Final reviewer decision
Almajed	2022	Cost-effectiveness evidence on approved cancer drugs in Ireland: the limits of data availability and implications for public accountability	European Journal of Health Economics	23(3):375-431.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Anonymous	2016	Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: An economic analysis	Ontario Health Technology Assessment Series	16(8):1-83.	I2 – Include (SLR, Meta-analysis, ITC; all study types)
Athale	2022	Healthcare utilization and costs associated with acute lymphoblastic leukemia in children with and without Down syndrome	Pediatric Blood & Cancer	69:e29829.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Baba Moussa	2022	EE263 Cost-Effectiveness Analyses (CEAs) of CAR-T Therapies Over the Past Four Years: What's New?	Value in Health	25(12 Supplement):S105.	E5 – Disease (e.g. not ALL, not B-cell)
Baraka	2017	Detection of minimal residual disease in childhood B-acute lymphoblastic leukemia by 4-color flowcytometry	International Journal of Hematology	105(6):784-91.	E11 – Outcome (i.e. no economic outcomes mentioned)
Barakat	2022	Is hypoalbuminemia a risk factor for high-dose methotrexate toxicity in children with acute lymphoblastic leukemia?	Journal of the Egyptian National Cancer Institute	34(1) (no pagination):	E11 – Outcome (i.e. no economic outcomes mentioned)
Barba	2022	Impact of Center Characteristics and Macroeconomic Factors on the Outcome of Adult Patients with Acute Lymphoblastic Leukemia Treated with Pediatric-Inspired Protocols	HemaSphere	6(Supplement 3):2985-6.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

Buldini	2018	Minimal residual disease by MFC in acute lymphoblastic leukemia in children	Haematologica	103:S1-S2.	E11 – Outcome (i.e. no economic outcomes mentioned)
Chakumatha	2022	Towards zero percent treatment abandonment of patients with common and curable childhood cancer types in Blantyre, Malawi	Pediatric Blood & Cancer	69:e29899.	E11 – Outcome (i.e. no economic outcomes mentioned)
Chen	2021	Cost-effectiveness and drug wastage of immunotherapeutic agents for hematologic malignancies: a systematic review	Expert Review of Pharmacoeconomics and Outcomes Research	21(5):923-41.	I2 – Include (SLR, Meta-analysis, ITC; all study types)
Chen	2022	Solving coagulation conundrums: comparing prophylaxis strategies in adult patients receiving PEG-asparaginase	Leukemia and Lymphoma	63(11):2663-70.	E11 – Outcome (i.e. no economic outcomes mentioned)
Cherla	2020	Cost-effectiveness of cancer drugs: Comparative analysis of the United States and England	EClinicalMedicine	29-30 (no pagination):	E6 – Disease status (i.e. R/R)
DuMontier	2019	Function, Survival, and Care Utilization Among Older Adults With Hematologic Malignancies	Journal of the American Geriatrics Society	67(5):889-97.	E5 – Disease (e.g. not ALL, not B-cell)
Goswami	2020	Quality-of-life issues and symptoms reported by patients living with haematological malignancy: a qualitative study	Therapeutic Advances in Hematology	11:	E5 – Disease (e.g. not ALL, not B-cell)
Gupta	2021	Efficacy of Single Low-Dose Rasburicase in Management of Tumor Lysis Syndrome in Leukemia and Lymphoma Patients	Clinical Lymphoma, Myeloma and Leukemia	21(1):e99-e104.	E5 – Disease (e.g. not ALL, not B-cell)

Gupta	2023	Racial and ethnic disparities in childhood and young adult acute lymphocytic leukaemia: secondary analyses of eight Children's Oncology Group cohort trials	The Lancet Haematology	10(2):e129-e41.	E11 – Outcome (i.e. no economic outcomes mentioned)
Halford	2021	A Systematic Review of Blinatumomab in the Treatment of Acute Lymphoblastic Leukemia: Engaging an Old Problem With New Solutions	Annals of Pharmacotherapy	55(10):1236-53.	E6 – Disease status (i.e. R/R)
Health Quality	2016	Minimal residual disease evaluation in childhood acute lymphoblastic leukemia: an economic analysis (Structured abstract)	E1 – Duplicate		
Heine	2021	Health Economic Aspects of Chimeric Antigen Receptor T-cell Therapies for Hematological Cancers: Present and Future	HemaSphere	5(2) (no pagination):	E6 – Disease status (i.e. R/R)
Hettle	2017	The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal	Health Technology Assessment (Winchester, England)	21:1-204.	E6 – Disease status (i.e. R/R)
Ho	2021	Economic Evidence on Potentially Curative Gene Therapy Products: A Systematic Literature Review	PharmacoEconomics	39(9):995-1019.	E6 – Disease status (i.e. R/R)
Jabbour	2023	Payer and Provider Solutions to Utilization Management Challenges in the Management of Rare Hematologic Cancers	American Journal of Managed Care	29(Suppl 4):S551-S60.	E2 – Review/editorial
Kako	2022	Decision Analysis for Unrelated Bone Marrow Transplantation or Immediate Cord Blood Transplantation for Patients with Philadelphia	Transplantation and Cellular Therapy	28(3):161.e1-.e10.	E6 – Disease status (i.e. R/R)

		Chromosome-Negative Acute Lymphoblastic Leukemia in First Complete Remission			
Kriegsmann	2019	Collection, Cryostorage, Transplantation, and Disposal of Hematopoietic Stem Cell Products	Biology of Blood and Marrow Transplantation	25(2):382-90.	E11 – Outcome (i.e. no economic outcomes mentioned)
Liao	2022	Association of Minimal Residual Disease by a Single-Tube 8-Color Flow Cytometric Analysis With Clinical Outcome in Adult B-Cell Acute Lymphoblastic Leukemia	Archives of pathology & laboratory medicine.	13:	E10 – Study design (e.g. trial protocols)
Luskin	2022	EXABS-132-ALL Approach to Acute Lymphoblastic Leukemia in The Elderly	Clinical Lymphoma, Myeloma and Leukemia	E2 – Review/editorial	
Mayerhoff	2019	Cost associated with hematopoietic stem cell transplantation: A retrospective claims data analysis in Germany	Journal of Comparative Effectiveness Research	8(2):121-31.	E11 – Outcome (i.e. no economic outcomes mentioned)
Nam		Cost-effectiveness of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia	Value in health	Vol.20:A111p.	E4 – Published before 2012 (FP) or before 2021 (abstracts)
Nam	2017	Cost-effectiveness of rituximab in addition to standard of care chemotherapy for adult patients with acute lymphoblastic leukemia	Haematologica	102:2017-05.	E4 – Published before 2012 (FP) or before 2021 (abstracts)
Ouchveridze	2022	Financial toxicity in hematological malignancies: a systematic review	Blood Cancer Journal	12(4) (no pagination):	I2 – Include (SLR, Meta-analysis, ITC; all study types)

Paganin	2014	Postinduction minimal residual disease monitoring by polymerase chain reaction in children with acute lymphoblastic leukemia	Journal of Clinical Oncology	32(31):3553-8.	E11 – Outcome (i.e. no economic outcomes mentioned)
Patkar	2012	Standardizing minimal residual disease by flow cytometry for precursor B lineage acute lymphoblastic leukemia in a developing country	Cytometry Part B, Clinical Cytometry	82:252-8.	E11 – Outcome (i.e. no economic outcomes mentioned)
Paula	2015	Comparison between qualitative and real-time polymerase chain reaction to evaluate minimal residual disease in children with acute lymphoblastic leukemia	Revista Brasileira de Hematologia e Hemoterapia	37:373-80.	E11 – Outcome (i.e. no economic outcomes mentioned)
Radhakrishnan	2021	Systematic Review of the Burden and Treatment Patterns of Adult and Adolescent Acute Lymphoblastic Leukemia in India: Comprehending the Challenges in an Emerging Economy	Clinical Lymphoma, Myeloma and Leukemia	21(1):e85-e98.	E11 – Outcome (i.e. no economic outcomes mentioned)
Ragoonanan	2022	A multicenter study of ICU resource utilization in pediatric, adolescent and young adult patients post CAR-T therapy	Frontiers in Oncology	12 (no pagination):	E6 – Disease status (i.e. R/R)
Tariq	2022	Efficacy of Furosemide in Methotrexate Clearance in Patients Treated with High Dose Methotrexate: A Cohort Study	Pakistan Journal of Medical and Health Sciences	16(4):485-7.	E5 – Disease (e.g. not ALL, not B-cell)
Totadri	2021	A single assessment of methotrexate levels at 42 hours permits safe administration and early discharge in children with lymphoblastic lymphoma and leukemia receiving high-dose methotrexate	Pediatric Hematology & Oncology	38:434-43.	E5 – Disease (e.g. not ALL, not B-cell)
Umaretiya	2021	Household material hardship and parental distress in a multicenter clinical trial for pediatric acute lymphoblastic leukemia	Journal of Clinical Oncology. Conference: Annual	39:	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

			Meeting of the American Society of Clinical Oncology, ASCO		
Vokinger	2021	Analysis of Launch and Postapproval Cancer Drug Pricing, Clinical Benefit, and Policy Implications in the US and Europe	JAMA Oncology	7:	E5 – Disease (e.g. not ALL, not B-cell)
Vu	2022	Health economic evidence for the use of molecular biomarker tests in hematological malignancies: A systematic review	European Journal of Haematology	108(6):469-85.	E5 – Disease (e.g. not ALL, not B-cell)
Wilson	2022	The expense of sending cerebrospinal fluid for analysis on all lumbar punctures in pediatric acute lymphoblastic leukemia patients	Pediatric Blood and Cancer	69(8) (no pagination):	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)
Yang	2023	Impact of Infection Patterns on the Outcomes of Patients with Hematological Malignancies in Southwest China: A 10-Year Retrospective Case-Control Study	Infection and Drug Resistance	16:3659-69.	E11 – Outcome (i.e. no economic outcomes mentioned)
Zhang	2018	Economic Burden of Veno-occlusive Disease in Patients With B-cell Acute Lymphoblastic Leukemia in the United States	Clinical Therapeutics	40(10):1711-9.e1.	E7 – LOT (i.e. not 1L, mixed LoT, no 1L subgroup)

Table 106. Overview of the excluded full-text references with reasons (SLR update)

Author	Year	Title	Journal	Citation	Final reviewer decision
Arjunji	2019	Assessment of Cost-Effectiveness Results from Icer Advanced Therapies Medicinal Products Reviews	Value in Health Regional Issues	19(Supplement):S75.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Batra	2023	Teleconsultation in pediatric acute lymphoblastic leukemia (ALL) - Its feasibility and impact	Pediatric Hematology Oncology Journal	8(4 Supplement):S15.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Borga	2019	Pbi71 Exploring Uncertainties and Solutions Allowing Patient Access to Car T-Cell Therapies: Learning Today How to Improve Tomorrow	Value in Health	22(Supplement 3):S430.	E5 – Disease (i.e. not ALL)
Caillon		Cost-Effectiveness of Blinatumomab in Pediatric Patients with High-Risk First-Relapse B-Cell Precursor Acute Lymphoblastic Leukemia in France	PharmacoEconomics - open	Vol.7:639-53p.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Clou	2018	Standardization of blinatumomab preparation for saving cost	European Journal of Oncology Pharmacy	1(3 Supplement 1):44.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Davitt	2023	Drivers of Differential Time to Diagnosis in Pediatric ALL Tied to Race and Ethnicity	Journal of Pediatric Hematology/Oncology	45(7):E879-E84.	E8 – Outcome
Duffy	2023	Evaluating Blinatumomab Treatment Adoption in Varied Resource Settings Using the RE-AIM Framework	Blood	142(Supplement 1):3713.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Guerra	2020	Risk Factors Associated with 30-Day Unplanned Readmissions for Adult Acute Lymphoblastic Leukemia (ALL)	Blood	136(Supplement 1):3-4.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)

Hall	2019	Minimizing drug waste and optimizing cost effectiveness of blinatumomab in a tertiary care center	Pediatric Blood and Cancer	66(Supplement 2):S30.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Jain	2023	Association of Age with Acuity and Severity of Illness at Initial Presentation in Children, Adolescents, and Young Adults with Leukemia	Blood	142(Supplement 1):3769.	E8 – Outcome
Janitz	2020	Exploring disparities among American indian children with cancer	Pediatric Blood and Cancer. Conference	67:	E8 – Outcome
Krakora	2019	Impact of Insurance Status on Survival Outcomes in Adults with Acute Lymphoblastic Leukemia (ALL): A Single Center Experience	Blood	134(Supplement 1):5071.	E8 – Outcome
Libanore	2023	HTA6 Balancing National Financial Stability with Commercial Expectations of Return on R&D Investment: A Review of Price Discounts for the Reimbursement of Oncology Drugs in Brazil	Value in Health	26(6 Supplement):S259-S60.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Mayerhoff	2018	Cost Associated with Hematopoietic Stem Cell Transplantation (Hsct) - a Retrospective Claims Data Analysis in Germany	Value in Health	21(Supplement 3):S36.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Mungle	2023	Comparative treatment costs of risk-stratified therapy for childhood acute lymphoblastic leukemia in India	Cancer Medicine	12(3):3499-508.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Pigneux	2019	Healthcare resource utilization (HRU) associated with minimal residual disease (MRD) status in adults with B-cell precursor (BCP) acute lymphoblastic leukemia (ALL)	HemaSphere	3(Supplement 1):1012.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Rompola	2018	Pediatric intensive care admissions in children with acute lymphoblastic leukemia	HemaSphere	2(Supplement 2):544.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)

Rompola	2020	Intensive care admissions for children with acute lymphoblastic leukaemia: A 13 years single centre experience	British Journal of Haematology	189(Supplement 1):133.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Salcedo	2019	Pcn126 Lifetime Costs for Diffuse Large B-Cell Lymphoma and B-Cell Acute Lymphoblastic Leukemia: A Literature Review to Inform Potential Financial Impact of Curative Therapies	Value in Health	22(Supplement 2):S79-S80.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Shah	2019	Thirty Day Resource Utilization after Chimeric Antigen Receptor (CAR) T Cell Infusion for Hematologic Malignancies	Biology of Blood and Marrow Transplantation	25(3 Supplement):S38-S9.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Wakase	2018	Costs of Hematopoietic Stem Cell Transplantation (Hsct) in Patients with Acute Lymphoblastic Leukemia (All), Diffuse Large B-Cell Lymphoma (Dlbcl) and Follicular Lymphoma (Fl) - a Retrospective Analysis of Japanese Claims Data	Value in Health	21(Supplement 3):S36.	E4 – Patient population (i.e. R/R, not Ph-, not B-cell)
Yingying	2019	Comparison between Hypercvad and CALLG2008 Protocol in Adult Patients with Newly Diagnosed Acute Lymphoblastic Leukemia:a Single Center Study	Blood	134(Supplement 1):5122.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)
Zhang	2019	Pcn120 Economic Burden for Patients with Newly Diagnosed Acute Lymphoblastic Leukemia (All) in Complete Remission (Cr)	Value in Health	22(Supplement 2):S78.	I3 – Include (Proxy data; i.e., T-cell and B-cell ALL, Ph−/+)

J.1.5 Quality assessment and generalizability of estimates

Quality assessment was performed in a double-blind manner for the 1 study that performed economic evaluations and was published as full text, using the NICE checklist [125]. In the first part of the assessment (applicability), the evidence was classed as partially applicable and useful to inform the decision-making of the NICE public health advisory committee. The second part of the assessment was on study limitations, with the study assessed as having “potentially serious

limitations," as the study failed to meet 1 or more quality criteria, which could change the conclusions about cost-effectiveness. The other identified economic models were published as abstracts only, and therefore not appropriate to assess, as per protocol.

J.1.6 Targeted literature search for health economic inputs

Due to the SLR for health economic inputs resulted in sparse evidence targeted for the patient population in question, data from grey literature of relevance for a Danish setting was used in the health economic model. This includes grey literature searches for utility values, cost data and additional information on assumptions to be integrated into the health economic model. The sources included in the targeted literature search are listed in Table 107 below. For sources used to derive utility decrements of AEs, see Table 41 in section 10.3.3.1.

Table 107. Sources included in the targeted literature search

Source name/ database	Location/source	Search strategy	Date of search
NICE	www.nice.org.uk	Grey literature search	21.01.2025
DMC	https://medicinraadet.dk/	Grey literature search	21.01.2025
Medicinpriser	https://www.medicinpriser.dk/	Grey literature search	21.01.2025
DRG tarrifs	https://sundhedsdatastyrelsen.dk/data-og-registre/sundhedsoekonomi/drg-takster	Grey literature search	21.01.2025
Statistikbanken	https://www.dst.dk/en	Grey literature search	21.01.2025

Appendix K. Additional materials

K.1 Current treatment options for ALL patients in Denmark

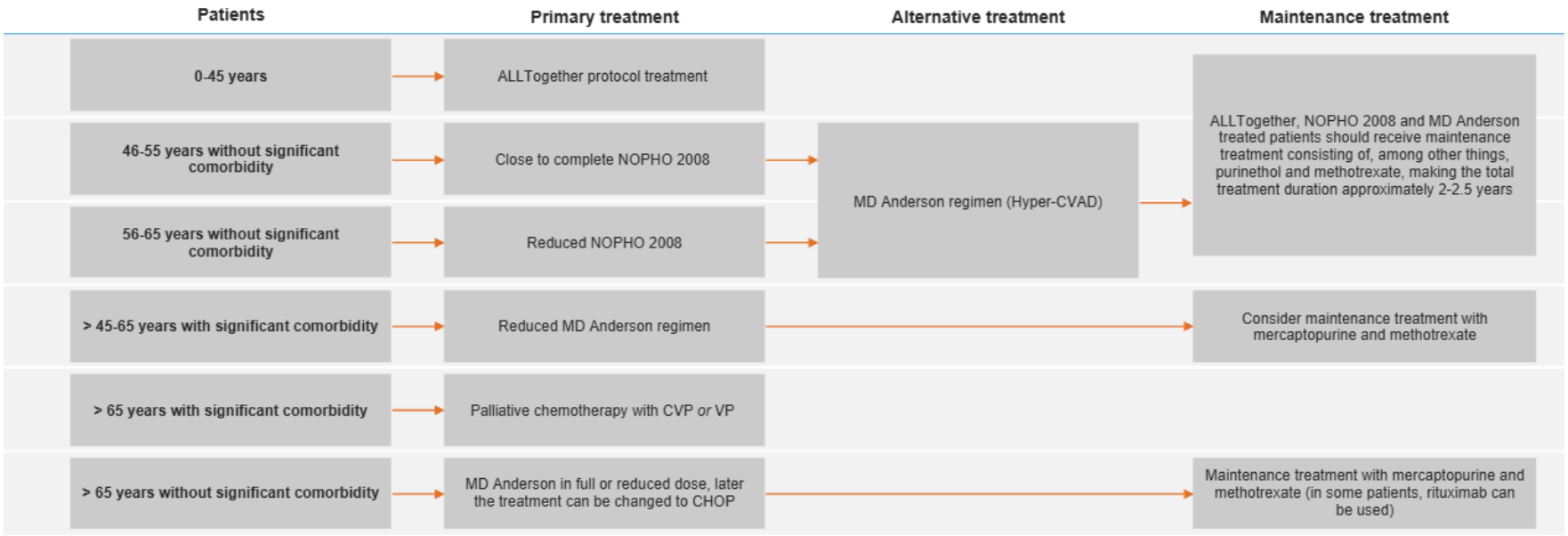

Figure 38. Treatment overview of Philadelphia Chromosome Negative Patients in Denmark

Abbreviations: ALL, acute lymphoblastic leukemia; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisolone; CVP, cyclophosphamide, vincristine, and prednisolone; DMC, Danish Medicine Council; MD Anderson (hyper-CVAD), chemotherapy with cyclophosphamide, vincristine, doxorubicin, dexamethasone, methotrexate, and cytarabine; NOPHO – Nordic Society of Paediatric Haematology and Oncology; SCT, stem cell transplantation; VP, vincristine and prednisolone.
Source: [5,51,52]

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