Medicinrådet

Bilag til Medicinrådets anbefaling axicabtagene cilouleucel til behandling af diffust storcellet B-cellelymfom

Vers. 2.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. axicabtagene ciloleucel (axi-cel)
2. Forhandlingsnotat fra Amgros vedr. axicabtagene ciloleucel (axi-cel)
3. Ansøgers endelige ansøgning vedr. axicabtagene ciloleucel (axi-cel)

August 23rd, 2024

Gilead response to *DMC regarding the reassessment of Yescarta in 3L+ DLBCL*

Gilead appreciates that the Medicines Council has conducted a re-assessment of Yescarta in 3L+ DLBCL which was approved by the European Comission more than six years ago.

We have identified three topics raised in the report that we would like to offer our insights into. First, we will address the DMC comment on the importance of consistent and speedy delivery of Yescarta (axi-cel).

Manufacturing

We present data on Nordic manufacturing timelines based on all patients registered in the KiteKonnect portal in 2024: [redacted] patients for Yescarta and [redacted] for Tecartus. Table 1 shows median timelines from apheresis to QP (Qualified Person) release, FP (Final Product) delivery, and infusion, respectively, from January 1, 2024, through July 31, 2024. During this period, Denmark has the lowest median time from apheresis to patient infusion with Yescarta in the Nordics: [redacted] days. In Denmark it takes a median of [redacted] days from FP delivery until the patient is actually infused with Yescarta. It is of importance to highlight that only the time from QP release to FP delivery is in the control of Kite. Once the product is delivered, the hospital clinic has responsibility and control over the steps and time to infusion. We are in continued dialogue with the Danish Qualified Treatment Centers (QTCs) around best practice examples on how European QTCs operate to further reduce the time to infusion for their patients.

Table 1 - Median timelines (days) from apheresis since January 1st, 2024

Country	Apheresis – QP release	Apheresis – FP delivery	Apheresis – infusion
Denmark	[redacted]	[redacted]	[redacted]
Sweden	[redacted]	[redacted]	[redacted]
Norway	[redacted]	[redacted]	[redacted]
Finland	[redacted]	[redacted]	[redacted]

Gilead/Kite is continuously working on further reducing our manufacturing timelines, for example [redacted]

Age of patients treated with CAR T-cell therapy

The DMC appraisal of the economic value of Yescarta (axi-cel) in 3L DLBCL is profoundly impacted by the assumption of the patients' age. The QALY gain of Yescarta (axi-cel) is driven by survival and the potential for cure. Using the DMC assumption for average age leads to **underestimation of the survival gain**, and by extension the incremental QALYs gained are underestimated.

While the median age for a Danish DLBCL patient is established in registry studies, such as the one DMC refers to, it should be noted that the median age (71) includes frail patients with poor performance status, comorbidities or high tumor burden, making them ineligible to receive CAR T-cell therapy. UK real world evidence for 490 patients with 3L DLBCL treated with CAR T from January 2020 to June 2022 had a median age of 62 years[1]. In the Nordic context, there is data available demonstrating the treatment patterns of Yescarta (axi-cel). Starting 1st January 2023 and including the first half of 2024, [redacted] patients

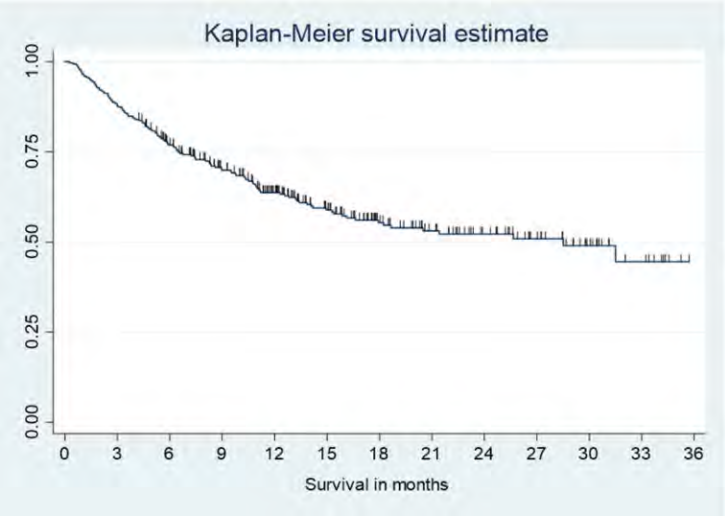
were treated with Yescarta (axi-cel) in the Nordics. Among the [redacted] patients treated in 2L DLBCL, the mean age was [redacted], while the mean age was [redacted] years among the [redacted] patients treated in 3L DLBCL. Danish patients had averages lower than the rest of the Nordics countries, both in 2L and 3L+. In fact, the [redacted] Danish patients treated (in any line) had a mean age of [redacted]. As such, the Gilead assumption of 56 years based on ZUMA-1 is much closer to the real-world data and clinical practice than the 71 years used in the health economic model by DMC.

Therefore, the DMC assumption of a *mean* age of a CAR T eligible patient being 71 years is not clinically relevant and is approximately a decade too high.

Comparative effectiveness

Gilead has had an ongoing dialogue with DMC to make CAR T-cell therapy available to Danish patients. Since 2018 in the reassessment processes, we have been seeking advice to provide the most suitable evidence package. We are confident that the long-term (>60 months) trial follow-up and large independent RWE studies would provide a robust basis for decision-making. Finding a comparator in a late line of treatment is challenging as treatment practices vary, change over time and over geographies. Gilead has, however, provided over the years, both SCHOLAR-1 and now most recently, the CORAL-EXT-1 and 2 as comparator studies in accordance with guidance provided by DMC (reference: letter dated 3rd of April 2023). That said, it is also reasonable to consider the newly published Danish registry data on DLBCL. Careful consideration should be made to the differences in the relevant treatment populations, and the generalizability of the study results. As the report states, this may create some uncertainty around the incremental benefit of Yescarta (axi-cel).

Gilead underlines, that uncertainty is not a one-way street. Uncertainty also means that the real-world benefit may be greater than demonstrated in the trial setting. As shown in the NICE re-appraisal (TA872) of Yescarta (axi-cel) in 3L DLBCL, the real world results from the SACT dataset showed a median OS of 28.5 months[2], versus the median 17.4 months OS in ZUMA-1, see figure to the left.



Furthermore, unpublished real-world evidence from Sweden also show considerably better efficacy results in 3L+ DLBCL compared to the ZUMA-1 study. We suggest that the DMC reach out to professor Mats Jerkeman at Lund University to see the real world Yescarta (axi-cel) experiences from Sweden.

We look forward to your decision and to help 3L+ DLBCL patients gain access to axi-cel.

References

1. Boyle, S. *et al.* Improved outcomes of large B-cell lymphoma patients treated with CD19 CAR T in the UK over time. *Br. J. Haematol.* **204**, 507–513 (2024).

2. NICE. Axicabtagene ciloleucel for treating diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma after 2 or more systemic therapies (CDF Review of TA559). https://www.nice.org.uk/guidance/ta872/documents/1 (2022).

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26.08.2024

MGK/CAF

Forhandlingsnotat

Dato for behandling i Medicinrådet	25.09.2024
Leverandør	Gilead
Lægemiddel	Yescarta (axicabtagene ciloleucel)
Ansøgt indikation	Behandling af voksne patienter med recidiveret eller refraktært (r/r) DLBCL og primært mediastinalt storcellet B-celle lymfom (PMBCL) efter to eller flere andre systemiske behandlinger.
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse (Advanced Therapy Medicinal Product (ATMP)) (CAR-T behandling) – engangsbehandling

Prisinformation

Amgros har forhandlet følgende pris på Yescarta (axicabtagene ciloleucel):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	AIP (DKK)*	Nuværende SAIP (DKK)	Nuværende rabatprocent ifht. AIP	Forhandlet SAIP (DKK)	Forhandlet rabatprocent ift. AIP
Yescarta	1 behandling CAR-T (genmodificerede hvide blodlegemer)	2.386.320	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]						

Prisen er betinget af Medicinrådets anbefaling, Det betyder, at hvis Medicinrådet ikke anbefaler Yescarta, indkøbes lægemidlet til nuværende SAIP.

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[redacted]

[redacted]

I Medicinrådets vurdering af Yescarta til DLBCL i 2. linje, estimeredes nedenstående antal nye patienter.

Tabel 2: Medicinrådets estimat af antal nye patiente pr. år (Yescarta 2. linje DLBCL)

År 1*	År 2	År 3	År 4	År 5
12	21	27	30	30

[redacted]

Konkurrencesituationen

Yescarta er indiceret til behandling af voksne patienter med diffust storcellet B-celle lymfom (DLBCL) og high-grade B-cellelymfom (HGBL), der recidiverer inden for 12 måneder efter gennemførsel af, eller er refraktær til, førstelinje kemo-immunterapi (2. linje).
Yescarta er indiceret til behandling af voksne patienter med recidiveret eller refraktært (r/r) DLBCL og primært mediastinalt storcellet B-celle lymfom (PMBCL) efter to eller flere andre systemiske behandlinger (3.linje).X

Der er i dag ingen behandlingsvejledning indenfor DLBCL. I september 2023 blev Yescarta anbefalet til DLBCL 2. linje behandling. Der er flere lægemidler på vej igennem EMA og Medicinrådet. I de kommende måneder vurderes fire lægemidler i Medicinrådet, som kan påvirke konkurrencesituationen på området:

- Glofitamab (Columvi) (bispecifikt antistof) er netop blevet vurderet i Medicinrådet til 3. linje behandling af DLBCL. Medicinrådet anbefalede ikke Glofitamab på Rådsmødet den 28.08.2024. [redacted]
- Epcoritamab (Tepkinly) (bispecifikt antistof) vurderes på nuværende tidspunkt i Medicinrådet til 3. linje behandling af DLBCL. Der forventes beslutning om anbefaling 27.11.2024.
- Lisocabtagene maraleucel (Breyanzi) (CAR-T) vurderes på nuværende tidspunkt i Medicinrådet både til DLBCL 2. linje og 3. linje. Der forventes beslutning om anbefaling 29.01.2025.
- Loncastuximab tesirine (Zynlonta) (monoklonalt antistof komb. med et antitoksin) er under vurdering i Medicinrådet til 3. linje behandling af DLBCL. En forventet dato for Medicinrådets anbefaling er endnu ikke fastlagt.

[redacted]

Minjuvi blev i september 2022 vurderet af Medicinrådet i kombination med lenalidomid til behandling af voksne patienter med kræfttypen recidiverende eller refraktær DLBCL, som ikke kan tåle autolog stamcelletransplantation. Minjuvi er ikke anbefalet af Medicinrådet.
Polivy blev i februar 2021 vurderet af Medicinrådet i kombination med bendamustin og rituximab til behandling af voksne patienter med recidiverende/refraktært DLBCL, der ikke er kandidater til hæmatopoietisk stamcelletransplantation. Polivy blev ikke anbefalet af Medicinrådet.

[redacted]

Tabel 3 viser lægemiddeludgifter i relation til andre lægemidler.

Tabel 3: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke	Lægemiddeludgift pr. behandling (SAIP, DKK)
Yescarta	1 behandling CAR-T (genmodificerede hvide blodlegemer)	[redacted]
Kymriah	1 behandling CAR-T (genmodificerede hvide blodlegemer)	[redacted]

[redacted]

Status fra andre lande

Tabel 4: Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet	[redacted]	Link til anbefaling
Sverige	Anbefalet	[redacted]	Link til anbefaling
England	Anbefalet	[redacted]	Link til anbefaling

Konklusion

[redacted]

Application for the assessment of axicabtagene ciloleucel (Yescarta®) for treatment of diffuse large B-cell lymphoma

Color scheme for text highlighting	
Color of highlighted text	Definition of highlighted text
	Confidential information

Contact information

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Tables and Figures

Abbreviations

Abbreviation	Definition
1L	First line
2L	Second line
3L+	Third line and later line of treatment
AE	Adverse event
Allo-SCT	Allogeneic stem cell transplantation
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
Axi-cel / AC	Axicabtagene ciloleucel
BEAM	Carmustine, etoposide, cytarabine and melphalan
BSA	Body surface area
BSC	Best supportive care
CAR	Chimeric antigen receptors
CEOP	Cyclophosphamide, vincristine, epirubicin, and prednisone
CHOP	Cyclophosphamide, vincristine, doxorubicin, and prednisone
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CRS	Cytokine release syndrome
CRu	Complete response unconfirmed
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CVP	Cyclophosphamide, vincristine, and prednisone
D	Day
DCO	Data cut off
DHAP	Cisplatin, cytarabine, and dexamethasone
DKK	Danish Kroner
DLBCL	Diffuse large B-cell lymphoma
DMA	Danish Medicines Agency
DMC	Danish Medicines Council
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSS	Disease-specific survival
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EMC	Electronic Medicines Compendium
EQ-5D	European Quality of Life Five Dimension Five Level Scale
FAS	Full analysis set
FL	Follicular lymphoma
FSW	Fine stratification weight
GDP	Gemcitabine, dexamethasone, and cisplatin
GemOx	Gemcitabine and oxaliplatin
GI	Gastrointestinal
HGBCL	High-grade B-cell lymphoma
HHG	Hypogammaglobulinemia
HSUV	Health state utility value
HR	Hazard ratio
HRQoL	Health-related quality of life
ICE	Ifosfamide, carboplatin, and etoposide
ICER	Incremental cost-effectiveness ratio

IEC	Independent Ethics Committee
IL	Interleukin
IPI	International Prognosis Index
IPD	Individual patient level data
IRB	Institutional Review Board
IRRC	Independent Radiological Review Committee
ITT	Intention-to-treat
IV	Intravenous
IVIG	Intravenous immunoglobulin
IWG	International Working Group
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
MAIC	Matching-adjusted indirect comparisons
MCM	Mixture cure models
N/A	Not applicable / not available
NE	Not estimable
NHL	Non–Hodgkin's lymphoma
NICE	The National Institute for Health and Care Excellence
NK	Natural killer
NR	Not reached
NSHL	Nodular sclerosing Hodgkin lymphoma
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression free survival
PMBCL	Primary mediastinal large B-cell lymphoma
PR	Partial response
R-CHOEP	Rituximab, cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-DHAOx	Rituximab, dexamethasone, cytarabine, and oxaliplatin
R-DHAP	Rituximab, cisplatin, cytarabine, and dexamethasone
R-GDP	Rituximab, gemcitabine, dexamethasone, and cisplatin
R-GemOX	Rituximab, gemcitabine, and oxaliplatin
R-ICE	Rituximab, ifosfamide, carboplatine, and etoposide
R-mini-CHOP	Rituximab and reduced dose CHOP
r/r	Relapsed or refractory
RCT	Randomised controlled trial
RNA	Ribonucleic acid
SACT	Systemic anti-cancer treatment
scFv	Single-chain variable region fragment
SCIG	Subcutaneous immunoglobulin
SCT	Stem cell transplantation
SD/sd	Stable disease/Standard deviation
SF-36	Short Form Survey - 36
SLR	Systematic literature review
SMR	Standard mortality ratio
SMRW	Standardised mortality ratio weight
SoC	Standard of care
SPM	Standard parametric model
TEAE	Treatment-Emergent Adverse Event
TFL	Transformed follicular lymphoma
Tisa-cel	Tisagenlecleucel
TTP	Time to progression
UK	United Kingdom
ULN	Upper limit of normal
VAS	Visual Analogue Scale

1. Regulatory information on the pharmaceutical

Overview of the pharmaceutical	
Proprietary name	Yescarta®
Generic name	Axicabtagene ciloleucel (axi-cel)
Therapeutic indication as defined by EMA	Axi-cel is indicated for the treatment of adult patients with relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy (1).
Marketing authorization holder in Denmark	Kite Pharma EU B.V.
ATC code	L01XX70
Combination therapy and/or co-medication	Pre-treatment (lymphodepleting chemotherapy): A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous should be administered on the 5th, 4th, and 3rd day before infusion of axi-cel (1). Pre-medication: Paracetamol 500-1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before axi-cel infusion is recommended (1). At least 1 dose of tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion (1).
Date of EC approval	23/08/2018 (1)
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	Orphan drug designation for treatment of DLBCL on the 16th of December 2014 (EU/3/14/1393) (2). Orphan drug designation for the treatment of PMBCL on the 9th of October 2015 (EU/3/15/1553) (3).
Other therapeutic indications approved by EMA	Axi-cel is indicated for the treatment of adult patients with DLBCL and high-grade B-cell lymphoma (HGBCL) that relapses within 12 months from completion of, or is refractory to, first line (1L) chemoimmunotherapy (1). Axi-cel is indicated for the treatment of adult patients with r/r follicular lymphoma (FL) after three or more lines of systemic therapy (1).
Other indications that have been evaluated by the DMC (yes/no)	Yes. Axi-cel is indicated for the treatment of adult patients with DLBCL and HGBCL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy (4).
Dispensing group	BEGR
Packaging – types, sizes/number of units and concentrations	Yescarta® (axicabtagene ciloleucel) 68 ml of dispersion for infusion, 1 infusion bag (5).

Abbreviations: 1L = first line; axi-cel = axicabtagene ciloleucel; CRS = cytokine release syndrome; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; HGBCL = grade B-cell lymphoma; PMBCL = primary mediastinal large B-cell lymphoma; r/r = relapsed or refractory.

Sources: European Medicines Agency, 2023 (1); European Medicines Agency, 2022 (2); European Medicines Agency, 2015 (3); Danish Medicines Council, 2023 (4); Danish Medicines Agency, 2023 (5).

2. Summary table

Summary	
Therapeutic indication relevant for the assessment	Axi-cel is indicated for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy (1).
Dosage regiment and administration:	Treatment consists of a single dose for infusion containing a dispersion for infusion of autologous T cells genetically modified to express an anti-CD19 chimeric antigen receptor (CAR) in one infusion bag. The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (within a range of $1 \times 10^6 - 2 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above (1).
Choice of comparator	Salvage therapy for 3L DLBCL including stem cell transplant. Salvage therapy includes: Rituximab, cisplatin, cytarabine, and dexamethasone (R-DHAP), rituximab, ifosfamide, carboplatin, and etoposide (R-ICE), and rituximab, gemcitabine, dexamethasone, and cisplatin (R-GDP), rituximab, gemcitabine and oxaliplatin (R-GemOX), rituximab and gemcitabine (R-Gemcitabine), rituximab and bendamustine (R-Bendamustine).
Prognosis with current treatment (comparator)	Among patients with r/r DLBCL, the median overall survival (OS) was 4.4 months from failure of second line (2L) treatment with 1-year OS of 23% (6). Patients who received transplant (autologous or allogeneic) following third line (3L) treatment had a median OS of 11.1 months, and patients who were not transplanted had a median OS of 3.3 months (6).
Type of evidence for the clinical evaluation	Matching-adjusted indirect comparison (MAIC). Results from the MAICs led to stronger treatment effects, which aligns with the observed population differences that generally suggested a more severe population in ZUMA-1.
Most important efficacy endpoints (Difference/gain compared to comparator)	ORR • ZUMA-1, 101 patients who received axi-cel: 83% (n = 84; 95% confidence interval [CI], 74-90) (7) • CORAL EXT 1 & 2, 170 patient who received salvage therapy: 31% (8) • CORAL EXT 1 & 2, 205 patients in intention-to-treat population: 30% (8) Median OS • ZUMA-1, 101 patients who received axi-cel: 25.8 months (95% CI, 12.8-NE); 5-year OS rate = 42.6% (95% CI, 32.8-51.9) (7) • CORAL EXT 1 & 2, 170 patient who received salvage therapy: 5.36 months (95% CI, 4.34–6.37) (8) • CORAL EXT 1 & 2, 205 patients in intention-to-treat population: 5.13 months (95% CI, 3.88–6.21) (8)
Most important serious adverse events for the intervention and comparator	In ZUMA-1, encephalopathy, lung infection, and pyrexia were the most serious adverse events, experienced by 19%, 7%, and 7% of patients, respectively (9). CORAL EXT 1: infections, with a similar rate of infection as a result of neutropenia (16%) in both arms (10). CORAL EXT 2: fatal outcomes were observed in six patients in the rituximab group and three patients in the observation group (11).
Impact on health-related quality of life	Clinical documentation: EQ-5D-5L was used in ZUMA-1 to assess impact on health-related quality-of-life. Health economic model: The health economic model demonstrates an improvement in health-related quality of life.
Type of economic analysis that is submitted	Cost-utility analysis Partitioned survival model

Summary	
Data sources used to model the clinical effects	ZUMA-1 and CORAL EXT 1 & 2 were used to inform the partitioned survival model.
Data sources used to model the health-related quality of life	Health-related quality of life measured with EQ-5D-5L in study ZUMA-1. Danish population weights were used to estimate health-state utility values.
Life years gained	[redacted]
QALYs gained	[redacted]
Incremental costs	[redacted]
ICER (DKK/QALY)	[redacted]
Uncertainty associated with the ICER estimate	Deterministic: The parameters with largest impact on the ICER are the mean age of the patient population and the health state utility value of progressed disease. Scenario: The parameters with largest impact on the ICER are changing the time horizon to 20 years, the comparator progression assumption, and the duration of IVIG therapy.
Number of eligible patients in Denmark	An estimated 14 patients are candidates in 3L+, of which, 7 are eligible and receive axi-cel.
Budget impact (in year 5)	[redacted]

Abbreviations: 2L = second line; 3L = third line; axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CI = confidence interval; DLBCL = diffuse large B-cell lymphoma; ICER = incremental cost-effectiveness ratio; IVIG = intravenous immunoglobulin; MAIC = matching-adjusted indirect comparison; N/A = not applicable; ORR= objective response rate; OS = overall survival; PMBCL = primary mediastinal large B-cell lymphoma; R-DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; R-GDP = rituximab, gemcitabine, dexamethasone, and cisplatin; R-ICE = rituximab, ifosfamide, carboplatine, and etoposide; r/r = relapsed or refractory.

Sources: European Medicines Agency, 2023 (1); Van Den Este et al., 2016 (6); Neelapu et al., 2023 (7); Maziarz et al., 2022 (8); ZUMA-1 clinical strudy report (CSR), 2018, table 14.3.2.4.0.1 (9).

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

3.1 The medical condition

3.1.1 Pathophysiology

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers of the immune system, originating primarily in B-cells (approximately 90% of NHL cases (12)) and, to a lesser extent, in T-cells and natural killer cells. NHL can be broadly divided into two prognostic groups: indolent lymphomas and aggressive lymphomas (13). While the former type progresses slowly, it is often not curable at advanced clinical stages (13). Conversely, aggressive lymphomas progress more rapidly, but may be cured with intensive combination chemotherapy regimens (13). Aggressive subtypes of B-cell NHL include, amongst others, DLBCL and PMBCL (PMBCL is considered a rare subtype of DLBCL hence when referring to DLBCL this includes both DLBCL and PMBCL) (14). Both are considered as rare cancers. FL, although indolent, can undergo a histologic transformation into a high-grade lymphoma and patients with FL transformed into DLBCL (hereafter referred to as transformed

follicular lymphoma (TFL)) are included in the DLBCL population described in this dossier (15).

3.1.2 Pathogenesis

DLBCL is a heterogeneous disease with a wide range of molecular abnormalities contributing to its pathogenesis (16, 17). DLBCL cells are significantly enriched in NF-κB target genes and NF-κB activity has been shown to play a crucial role in disease pathogenesis. Both DLBCL and PMBCL tumours depend upon constitutional activation of the NF-κB pathway for their survival (17). In addition to an elevated proliferation of tumour cells and varied expression of various cell surface markers, two distinct immunophenotypes distinguish DLBCL (18):

- Presence of medium to large sized lymphoid cells distorting or altering normal tissue architecture
- Presence of B cell markers (CD20, CD19, CD79a, CD22, B Cell transcription factor PAX5)

PMBCL arises in the mediastinal region from transformed thymic B cells, expressing several genetic alterations. It is characterised by the presence of fibrous connective tissue bands dividing the tumour into compartments.

3.1.3 Clinical presentation of DLBCL and PMBCL

Most patients with DLBCL present with a rapidly growing mass involving one or more lymph nodes, although extra-nodal disease is also common, being observed in approximately 40% of patients at presentation (19). Between 33-50% of all DLBCL patients experience so called 'B symptoms', which include night sweats, fever, and weight loss (19, 20).

Despite PMBCL and DLBCL cells sharing similar morphology and immunophenotype (20, 21), the two diseases have largely different clinical presentations. Unlike DLBCL, which often involves multiple sites within the body (mediastinal involvement in 20% of the patients (20)), PMBCL arises from the thymus and usually presents as a bulky tumour (70-80% of patients with PMBCL present with a bulky tumour compared to 10–15% of patients with DLBCL) located within the mediastinum, which compresses on the surrounding organs, including the airways and superior vena cava. This gives rise to symptoms such as cough, chest pain, dyspnoea, hoarse voice, dysphagia, and oedema of the face, neck and/or arms (20, 21). B symptoms may also be present, although they are less common in PMBCL (<20% of the patients) than in DLBCL (20). In PMBCL extra-nodal disease is uncommon at initial presentation, but more frequent at relapse (20).

Furthermore, the male to female ratio is 1:2-1:3 in patients with PMBCL compared to 1:1 or slight male predominance in patients with DLBCL. The median age at diagnosis is 35 among PMBCL patients (20) compared to 71 among DLBCL patients (22). An estimated 70-80% of patients with PMBCL are diagnosed at stage I-II while 30-50% of patients with DLBCL are diagnosed at stages I-II. In patients with PMBCL, 2% have bone marrow involvement compared to 10-20% in patients with DLBCL (19-24).

3.1.4 Patient prognosis

Patients with r/r DLBCL have a poor prognosis. In 2021, the specialist committee of the Danish Medicines Council (DMC) assessed that patients who are refractory to treatment have a poorer prognosis than patients who experienced relapse (25).

The prognosis of DLBCL patients worsens with each relapse. In the CORAL trial, among patients with r/r DLBCL, the median OS was 4.4 months from failure of 2L treatment, with 1- and 2-year OS of 23% and 15.7%, respectively (6), which is substantially worse than the 49% 3-year OS (10) observed in this study at 2L. Although patients who received a transplant (autologous or allogeneic) following 3L treatment had a median OS of 11.1 months and 2-year OS of 33.9%, those who were not transplanted fared extremely poorly, with a median OS of just 3.3 months and a 2-year OS of 9.3% (6). Only a small subset of patients (14.8%) who achieved complete response (CR) following 3L therapy and were subsequently transplanted appeared to have a better prognosis, with a 1-year OS of 88.4% and median OS not reached at a median follow-up of 30.1 months (6), which suggests that transplantation in CR may be most beneficial.

As prognosis worsens with each relapse, there is an urgent need for new treatments for DLBCL or PMBCL patients who have consistently poor outcomes regardless of refractory subgroup, line of therapy, or disease stage (26).

3.1.5 Patients' functioning and health-related quality of life

Among patients with r/r DLBCL who have experienced two or more treatment failures, life expectancy is low, which subsequently impacts the HRQoL negatively. A recent analysis of health-related quality of life (HRQoL) in 441 patients with DLBCL revealed that patients with DLBCL consistently had poorer scores for global health status, physical, emotional, cognitive, and social functioning (27). Fatigue, diarrhoea, and dyspnoea were significantly worse in DLBCL patients receiving third line and later line of treatment (3L+) compared to 1L and 2L patients (27). Patients receiving 3L+ treatments also had significantly worse scores for global health status including physical, emotional, and social functioning (27).

3.2 Patient population

Approximately 450-500 cases of DLBCL are diagnosed annually in Denmark, and the incidence is increasing (28). The risk of developing DLBCL increases with age and the median age at the time of diagnosis is 67 years, as mentioned by the Danish Lymphoma Group (DLG) (22, 29, 30). Just over half of all new cases of DLBCL are seen in patients over 65 years of age, which in many contexts defines the threshold for younger versus older patients (29).

It is estimated that approximately 100 patients with DLBCL annually are refractory or experience relapse after two or more lines of systemic therapy in Denmark (background of the DMC's recommendation, p. 4) (14). According to Danish clinical experts, the patient numbers relevant for axi-cel in 3L will decrease following the recommendation of axi-cel in 2L (31). In Denmark, patients treated with axi-cel in 3L will include a fraction of patients who are refractory to 1L treatment with a high tumour burden and therefore are not able to wait for axi-cel production in 2L since no bridging (except for steroids) is allowed (31). These patients will receive chemotherapy to reduce tumour burden rendering them candidates for 3L axi-cel (31).

Incidence and prevalence data for the full DLBCL population was informed by the annual reports from the DLG (28) and is reported in Table 1. The DLG estimates 90% of the lymphomas in Denmark are NHLs, of those, 35% are categorised as DLBCL. These proportions were used to adapt the reported incidence in the annual report to Danish DLBCL incidence. The prevalence was informed by NORDCAN data on prevalence of NHL in Denmark

(32). These numbers were adapted with the proportion of DLBCL within NHL that was reported by the DLG.

Table 1 Incidence and prevalence in the past 5 years

Year	2018	2019	2020	2021	2022
Incidence in Denmark	450	454	476	523	506
Prevalence in Denmark	4 606	4 817	5 010	5 246	-
Global prevalence *	22 762 patients with relapsed or refractory DLBCL in Europe between 2019 - 2020				

* For small patient groups, also describe the worldwide prevalence.
Sources: DLG (28); NORDCAN (32); Kite Core Value Dossier [Data on file] (26)

Danish clinical experts were consulted to estimate the number of eligible patients for axi-cel in Denmark (31). With the recent introduction of axi-cel for 2L in Denmark, it is assumed that 50% fewer patients will be eligible to receive 3L axi-cel. The clinical experts expected of the remaining patients, 7 would be treated with axi-cel in 3L per year (31). Estimated patient numbers are presented in below.

Table 2 Estimated number of patients eligible for treatment assuming a positive recommendation in 3L in 2024 and patients treated with axi-cel in 2L DLBCL

Year	2024	2025	2026	2027	2028
Number of patients in Denmark who are eligible for treatment in the coming years	7	7	7	7	7

Abbreviations: 2L = Second line, 3L = Third line, DLBLC = Diffuse large B-cell lymphoma.

3.3 Current treatment options

There is no standard of care for 3L+ DLBCL in Denmark. According to the Danish clinical guidelines for 3L+ DLBCL, patients can be either considered for a clinical trial, allogeneic stem cell transplant, CAR T-cell therapy or radiotherapy (29). The choice of treatment is assessed for the individual patient and depends, among others, on the possibility of allogeneic stem cell transplantation (allo-SCT), performance status, comorbidity, previous treatments and age (14, 29).

The DMC has defined the best available treatment for adult patients with r/r DLBCL after two or more lines of systemic therapy, which include several different regimens: GDP (gemcitabine, dexamethasone, and cisplatin), CEOP (cyclophosphamide, vincristine, epirubicin, and prednisone), CHOP (cyclophosphamide, vincristine, doxorubicin, and prednisone), CVP (cyclophosphamide, vincristine, and prednisone), GemOx (gemcitabine and oxaliplatin), DHAP (cisplatin, cytarabine, and dexamethasone) and ICE (ifosfamide, carboplatin, and etoposide). Alternatively, the following single agent treatments can be considered: gemcitabine, pixantrone and bendamustine. The above mentioned treatments are sometimes combined with rituximab (14, 33).

3.4 The intervention

Table 3: Overview of the intervention (Axi-cel)

Overview of intervention	
Therapeutic indication relevant for the assessment	Axi-cel is indicated for the treatment of adult patients with r/r DLBCL and PMBCL, after two or more lines of systemic therapy (1).
Method of administration	Intravenous (IV)
Dosing	The target dose is 2×10^6 CAR-positive viable T cells per kg of body weight (within a range of $1 \times 10^6 - 2 \times 10^6$ cells/kg), with a maximum of 2×10^8 CAR-positive viable T cells for patients 100 kg and above.

Overview of intervention	
Dosing in the health economic model (including relative dose intensity)	N/A
Should the pharmaceutical be administered with other medicines?	No
Treatment duration / criteria for end of treatment	N/A
Necessary monitoring, both during administration and during the treatment period	Daily monitoring in the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Patients must be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No
Package size(s)	Yescarta® (axicabtagene ciloleucel) 68 ml of dispersion for infusion, 1 infusion bag

Abbreviations: CAR = chimeric antigen receptor; CRS = cytokine release syndrome; DLBCL = diffuse large B cell lymphoma; IV = intravenous; PMBCL = primary mediastina B cell lymphoma; r/r = relapsed or refractory.
Sources: European Medicines Agency, 2023 (1).

Axi-cel is a precision cancer treatment, individually manufactured for each patient using their own T-cells. Axi-cel belongs to the class of CAR T-cell therapies, which employ autologous human T-cells genetically engineered to express a novel cell surface receptor fragment antibody that identifies and binds cells expressing CD19 on their cell surface. As aggressive subtypes of B-cell NHL, such as DLBCL, PMBCL and TFL, express this antigen on their cell surface, axi-cel utilises it to effectively target the patient's immune system against them. However, CD19 is also expressed on the surface of normal B-cells meaning that axi-cel is not completely selective for tumour cells (26).

The engineered T-cell receptor complex is comprised of a single-chain variable region fragment (scFv) with specificity for CD-19, that is linked to an intracellular signalling part comprised of signalling domains from CD28 (a lymphocyte co-stimulatory receptor that plays an important role in optimising T-cell survival and function) and CD3ζ (a component of the T-cell receptor complex) molecules arranged in tandem (34). Following engagement of genetically engineered anti-CD-19 T-cells with CD-19 expressing target cells, CD3ζ activates signalling pathways leading to T-cell activation and proliferation and stimulating their effector functions (e.g., cytotoxicity). CD28 provides a co-stimulatory signal that enhances T-cell function, including stimulating interleukin (IL)-2 production. Both signalling molecules acting in tandem result in proliferation and activation of engineered CAR T-cells, which not only directly target CD19-expressing cells, but also secrete cytokines and other molecules that recruit additional immune cells, leading to apoptosis and necrosis of target cancer cells (26).

3.4.1 The intervention in relation to Danish clinical practice

Axi-cel is expected to be used for the treatment of adult patients with r/r DLBCL and PMBCL after two or more lines of systemic therapy. In Denmark, there is no established standard treatment for patients who are refractory to chemotherapy or relapse after

autologous stem cell transplantation, and the prognosis with traditional chemo-immunotherapy is poor (29). Thus, the current clinical practice will be altered to include a standard treatment for 3L+, if axi-cel is recommended. Axi-cel will not replace a specific treatment since there is no established standard of care for 3L+ DLBCL. Given axi-cel is now available for some 2L patients it is likely that fewer patients will need 3L+ treatment than previously. However, since no bridging (except for steroids) is allowed in 2L the 3L+ population will include a fraction of patients who are refractory to 1L treatment with a high tumour burden and therefore are not able to wait for axi-cel production in 2L since no bridging (except for steroids) is allowed. These patients will receive chemotherapy to reduce tumour burden rendering them candidates for 3L axi-cel (31).

3.5 Choice of comparator(s)

The use of DHAP, ICE, GDP, GemOx, gemcitabine and bendamustine (in combination with rituximab) as a salvage therapy is justified by its substantial representation (12.7% for DHAP/ICE/GDP; 4.2% for gemcitabine/GemOx and 3.2% for bendamustine) in recent Danish clinical practice based on a Danish real-world evidence study (35), particularly in the context of relapsed or refractory cases (3L). Considering that the CORAL EXT 1 & 2 MAIC includes ICE and DHAP in its comparative data, DHAP/ICE/GDP becomes a relevant choice for alignment. While the CORAL EXT 1 & 2 MAIC may not cover all included comparators in the real-world study (e.g., clinical trials and BSC when not specified), DHAP, ICE, GDP, GemOx, gemcitabine and bendamustine remains reasonable and justifiable as it allows for platinum-based chemotherapy and single agent treatments. This was further substantiated by Danish clinical experts who were consulted on the current salvage therapy for the patient population of interest, and confirmed that the R-ICE, R-GDP, R-DHAP, R-GemOx, R-Gem and R-Bendamustine regimens are relevant in Danish clinical practice for r/r DLBCL patients in the third line of treatment (31).

In addition, some patients may receive allogeneic or autologous stem cell transplant (4% each) after completing salvage therapy (35). The salvage therapies are described below.

Table 4 Overview of R-DHAP

Overview of comparator	
Generic name	Rituximab, dexamethasone, cytarabine, and cisplatin
ATC code	Rituximab: L01FA01 Dexamethasone: H02AB02 Cytarabine: L01BC01 Cisplatin: L01XA01
Mechanism of action	Rituximab is a monoclonal antibody designed to recognise and attach to a protein called CD20 present on the surface of B lymphocytes. When rituximab attaches to CD20, it causes the death of B lymphocytes. Dexamethasone is a highly potent and long-acting glucocorticoid. Cytarabine is a desoxycytidine analogue which, after *in vivo* activation, is intracellularly incorporated into DNA resulting in defective DNA synthesis. Cisplatin exerts its cytotoxic effect by losing one chloride ligand, binding to DNA to form intra-strand DNA adducts, and inhibiting DNA synthesis and cell growth.
Method of administration	IV for rituximab, cytarabine and cisplatin. Oral for dexamethasone.
Dosing	Rituximab: 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Dexamethasone: 20 mg to 40 mg once daily per oral

Overview of comparator	
	Cytarabine: Administration of 100-200 mg/m2 body surface area/day continuously or every 12 hours for 5-7 days Cisplatin: Given as IV infusion over 6-8 hours either 50-100 mg/m2 body surface area once every 3-4 weeks or 15-20 mg/m2 body surface area daily for 5 days every 3-4 weeks. Combination with other cytostatic agents may necessitate dose reduction
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m²/day and Dexamethasone: 40mg/day and Cytarabine: 2000mg/m²/day and Cisplatin: 100mg/m²/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Dexamethasone: Various dosage forms including tablets, vials and eye drops Cytarabine: Packages of 1 x 5 ml, 10 ml and 20 ml vials as well as 1 vial with powder for solution Cisplatin: Packages of 1 x 50 ml and 100 ml

Abbreviations: R- DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; DNA = deoxyribonucleic acid; IV = intravenous

Source: DMA, 2023 (36) (37); Roche, 2023 (38); Medicin.dk, 2023 (39); Medicin.dk, 2021 (40).

Table 5 Overview of R-GDP

Overview of comparator	
Generic name	Rituximab, gemcitabine, dexamethasone and cisplatin
ATC code	Rituximab: L01FA01 Gemcitabine: L01BC05 Dexamethasone: H02AB02 Cisplatin: L01XA01
Mechanism of action	Rituximab: see Table 4 Gemcitabine has cytotoxic effects due to an inhibition of DNA synthesis by two mechanisms of action of dFdCDP and dFdCTP Dexamethasone: see Table 4 Cisplatin: see Table 4
Method of administration	IV for rituximab, gemcitabine and cisplatin. Oral for dexamethasone.
Dosing	Rituximab: 375 mg/m² body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Gemcitabine: 1000 – 1250 mg/m2 of body surface area over 30 minutes once weekly for 7 weeks followed by a one-week break Dexamethasone: 20 mg to 40 mg once daily per oral Cisplatin: Given as IV infusion over 6-8 hours either 50-100 mg/m2 body surface area once every 3-4 weeks or 15-20 mg/m2 body surface area daily for 5 days every 3-4 weeks. Combination with other cytostatic agents may necessitate dose reduction
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m²/day and Gemcitabine: 1000mg/m²/day and Cisplatin: 100mg/m²/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity

Overview of comparator	
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Gemcitabine: Packages of 1x 25 ml, 50 ml, 120 ml, 140 ml, 160 ml, 180 ml, 200 ml and 220 ml vials. Also available in packages of 5 x 5 ml Dexamethasone: Various dosage forms including tablets, vials and eye drops Cisplatin: Packages of 1 x 50 ml and 100 ml

Abbreviations: R- GDP = rituximab, gemcitabine, dexamethasone, and cisplatin; DNA = deoxyribonucleic acid; IV = intravenous

Source: Medicinpriser.dk, 2023 (36); Roche, 2023 (38); EMC, 2022 (41); DMA, 2021 (37); DMC, 2021 (25); Medicin.dk, 2023 (39).

Table 6 Overview of R-ICE

Overview of comparator	
Generic name	Rituximab, ifosfamide, carboplatin and etoposide
ATC code	Rituximab: L01FA01 Ifosfamide: L01AA06 Carboplatin: L01XA02 Etoposide: L01CBCB01
Mechanism of action	Rituximab: see Table 4 Ifosfamide is a cytotoxic alkylating agent which interacts with DNA-DNA cross linking. This activity manifests itself by blocking the late S and early G2 phases of the cell cycle Carboplatin interferes with DNA crosslinks between different and within individual DNA strands in cells that are exposed to the compound Etoposide's main effect occurs to be the late S and early G2 part of the cell cycle in mammalian cells. The composition of microtubules is not affected. The dominant macromolecular effect of etoposide appears to be rupture of the double strand by interaction with DNA topoisomerase II or by the formation of free radicals
Method of administration	IV for rituximab, ifosfamide, carboplatin and etoposide
Dosing	Rituximab: 375 mg/m^2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Ifosfamide: 3.000 mg/m^2 on day 1 and day 2 Carboplatin: 550 mg/day Etoposide: 50 to 100 mg/m^2/day on days 1 to 5 or 100 to 120 mg/m^2 on days 1, 3 and 5 every 3 to 4 weeks in combination with other medicinal products indicated for the disease
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m^2/day and Ifosfamide: 5000mg/m^2/day and Carboplatin: 550mg/m^2/day and Etoposide: 100mg/m^2/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Ifosfamide: Package with 1 vial Carboplatin: Packages of 1 x 15 ml and 45 ml vials Etoposide: Packages of 1 x 5 ml, 20 ml and 25 ml vials and packages of 5 x 5 ml vials. Etoposide also comes in capsules

Abbreviations: R- ICE = rituximab, ifosfamide, carboplatin, and etoposide; IV = intravenous.
Source: Medicinpriser.dk, 2023 (36); Roche, 2023 (38); EMC, 2022 (41); DMC, 2021 (25); DMC, 2021 (42); DMC, 2022 (43)

Table 7 Overview of R-GemOx

Overview of comparator	
Generic name	Rituximab, gemcitabine, oxaliplatin
ATC code	Rituximab: L01FA01 Gemcitabine: L01BC05 Oxaliplatin: L01XA03
Mechanism of action	Rituximab: see Table 4 Gemcitabine: see Table 5 Oxaliplatin interacts with DNA to form both inter and intra-strand cross-links, resulting in the disruption of DNA synthesis leading to cytotoxic and anti-tumour effects
Method of administration	IV for rituximab gemcitabine and oxaliplatin
Dosing	Rituximab: 375 mg/m2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Gemcitabine: 1000 – 1250 mg/m2 of body surface area over 30 minutes once weekly for 7 weeks followed by a one-week break Oxaliplatin: 100 mg/m2 of body surface area every 2 weeks
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m²/day and Gemcitabine: 1000mg/m²/day and Oxaliplatin: 100mg/m²/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Gemcitabine: Packages of 1 x 25 ml, 50 ml, 120 ml, 140 ml, 160 ml, 180 ml, 200 ml and 220 ml vials. Also available in packages of 5 x 5 ml Oxaliplatin: Packages of 1 x 10 ml, 20 ml and 40 ml vials

Abbreviations: R-GemOx = rituximab, gemcitabine and oxaliplatin; IV = intravenous.
Sources: Medicinpriser.dk, 2023 (36); Roche, 2023 (38); EMC (44) (45)

Table 8 Overview of R-Gem

Overview of comparator	
Generic name	Rituximab, gemcitabine
ATC code	Rituximab: L01FA01 Gemcitabine: L01BC05
Mechanism of action	Rituximab: see Table 4 Gemcitabine: see Table 5
Method of administration	IV for rituximab and gemcitabine
Dosing	Rituximab: 375 mg/m2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Gemcitabine: 1000 – 1250 mg/m2 of body surface area over 30 minutes once weekly for 7 weeks followed by a one-week break
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m²/day and Gemcitabine: 1000mg/m²/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A

Overview of comparator	
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Gemcitabine: Packages of 1 x 25 ml, 50 ml, 120 ml, 140 ml, 160 ml, 180 ml, 200 ml and 220 ml vials. Also available in packages of 5 x 5 ml

Abbreviations: R-Gem = rituximab and gemcitabine; IV = intravenous.
Sources: Medicinpriser.dk, 2023 (36), EMC (45); Roche, 2023 (38)

Table 9 Overview of R-Bendamustine

Overview of comparator	
Generic name	Rituximab, bendamustine
ATC code	Rituximab: L01FA01 Bendamustine: L01AA09
Mechanism of action	Rituximab: see Table 4 Bendamustine's antineoplastic and cytocidal effect is based on a cross-linking of DNA single and double strands by alkylation. As a result, DNA matrix functions and DNA synthesis and repair are impaired
Method of administration	IV for rituximab and bendamustine
Dosing	Rituximab: 375 mg/m2 body surface area, administered on day 1 of each chemotherapy cycle for 8 cycles Bendamustine: 90 mg/m2 body surface area, administered on day 1 and 2 every 3 weeks
Dosing in the health economic model (including relative dose intensity)	Rituximab: 375mg/m^2/day and Bendamustine: 90 mg/m^2/day. Refer to Table 49
Should the pharmaceutical be administered with other medicines?	N/A
Treatment duration/ criteria for end of treatment	Until disease progression or unacceptable toxicity
Need for diagnostics or other tests (i.e. companion diagnostics)	No
Package size(s)	Rituximab: Packages of 1 or 2 vials Bendamustine: Packages of 5 x 4 ml, 10 ml, and 40 ml vials at 2.5mg/ml and 5 x 25 mg and 100mg vials

Abbreviations: R-bendamustine = rituximab and bendamustine; IV = intravenous.
Sources: Medicinpriser.dk, 2023 (36); EMC (46); Roche, 2023 (38)

3.6 Cost-effectiveness of the comparator(s)

R-DHAP, R-ICE, R-GDP, R-GemOx, R-gem and R-bendamustine and have not been previously assessed by the DMC for r/r DLBCL patients. According to the DMC methods guideline, if a comparator has not previously been assessed by the DMC, a comparison against placebo should be made, including cost-effectiveness (47). The comparison of axi-cel against placebo is not possible as there is no published clinical evidence of placebo's efficacy in r/r DLBCL patients (47).

3.7 Relevant efficacy outcomes

3.7.1 Definition of efficacy outcomes included in the application

Response rate (measured as objective response rate (ORR)), OS and progression free survival (PFS) are relevant efficacy outcomes included in this application. These outcomes

have been previously deemed relevant by the DMC to assess the efficacy of axi-cel in adult patients with r/r DLBCL after two or more lines of systemic therapies (14). In addition, CR, partial response (PR), stable disease (SD), progressive disease (PD), disease-specific survival (DSS), time to progression (TTP), duration of response (DOR) and event-free survival (EFS) are included as efficacy outcomes. The efficacy outcomes are defined in Table 10.

Table 10 Efficacy outcome measures relevant for the application

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
ORR	11 August 2021	ORR is defined as the percentage of participants achieving either a complete response or a partial response per the revised International Working Group (IWG) Response Criteria for Malignant Lymphoma (48).	Investigator assessment and central assessment.
CR	11 August 2021	CR is defined as complete disappearance of all detectable clinical evidence of disease and disease-related symptoms; all lymph nodes and nodal masses must have regressed to normal size; spleen and/or liver must be normal size, not be palpable, and no nodules; bone marrow aspirate and biopsy must show no evidence of disease.	Investigator assessment.
PR	11 August 2021	PR is defined as a ≥ 50% decrease in sum of the product of the diameters of up to 6 of the largest dominant nodes or nodal masses; no increase in size of nodes, liver or spleen and no new sites of disease; multiple splenic and hepatic nodules (if present) must regress by ≥ 50% in the sum of the product of the diameters; > 50% decrease in the greatest transverse diameter for single nodules.	Investigator assessment.
SD	11 August 2021	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.	Assessments of response made by the Independent Radiological Review Committee (IRRC) using IWG 2007 criteria (48).
PD	11 August 2021	PD is defined by at least one of the following: ≥ 50% increase from nadir in the sum of the products of at least 2 lymph nodes, or at least a 50% increase in the product of the diameters of a single lymph node; appearance of a new lesion > 1.5 cm in any axis; ≥ 50% increase in size of splenic or hepatic nodules; ≥ 50% increase in the longest diameter of any single previously identified node > 1 cm in its short axis.	Assessments of response made by the IRRC using IWG 2007 criteria (48).
OS	11 August 2021	OS is defined as the time from axi-cel infusion to the date of death. Participants who did not die by the analysis data cutoff date were censored at their last contact date.	Kaplan-Meier (KM) estimates were used for analyses.

Outcome measure	Time point*	Definition	How was the measure investigated/method of data collection
DSS	11 August 2021	DSS is defined as time from axi-cel infusion to death due to PD.	KM estimates were used for analyses.
PFS	11 August 2021	PFS is defined as the time from the axi-cel infusion date to the date of PD per the revised IWG Response Criteria for Malignant Lymphoma (48) or death from any cause. Participants not meeting the criteria for progression by the analysis data cutoff date were censored at their last evaluable disease assessment date.	Investigator assessment and central assessment. KM estimates were used for analyses.
TTP	11 August 2021	TTP is defined as time from axi-cel infusion to PD.	KM estimates were used for analyses.
Time to next therapy	11 August 2021	Time to next therapy is defined as time from axi-cel infusion to initiation of new anticancer therapy, including CAR T-cell retreatment and excluding stem cell transplantation, or death from any cause.	KM estimates were used for analyses.
DOR	11 August 2021	Among participants who experience an objective response, DOR was defined as the date of their first objective response to disease progression per the revised IWG Response Criteria for Malignant Lymphoma or death regardless of cause.	Investigator assessment and central assessment. KM estimates were used for analyses.
EFS	11 August 2021	Time from axi-cel infusion until PD, initiation of new anticancer therapy, excluding stem cell transplantation, or any-cause death.	KM estimates were used for analyses.

Abbreviations: Axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CR = complete response; DOR = duration of response; DSS = disease-specific survival; EFS = event-free survival; IRRC = Independent Radiological Review Committee; IWG = International Working Group; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression free survival; PR = partial response; SD = stable disease; TTP = time to progression.
Notes: * Time point for data collection used in analysis (follow up time for time-to-event measures)
Sources: Clinicaltrials.gov, 2022 (49); Kite Pharma Inc., 2018 (9); Neelapu et al.; 2023 (7).

Validity of outcomes

OS is considered an important clinical endpoint in clinical trials within oncology. For many years it has been considered the gold-standard endpoint for establishing clinical benefit. However, using OS can be associated with certain limitations as it may be affected by subsequent therapy (50). PFS is a commonly used endpoint within oncology trials. It is used to assess the time during which patients are alive without progressive disease. PFS is not affected by the impact of subsequent treatment in the same manner as OS, and therefore serves as a relevant supplement to OS (50). EFS is also not affected by the impact of subsequent treatment in the same manner as OS, and therefore serves as a relevant supplement to OS (50).

4. Health economic analysis

A cost-effectiveness analysis was conducted based on a Danish adaptation of an Excel-based cost-effectiveness model (CEM) [356 Gilead DLBCL yescarta DK ver3.0 12 Apr 2024]. The objective of the CEM is to assess the cost-effectiveness of axi-cel vs. salvage therapy

(named BSC in the Excel® model) in r/r DLBCL and PMBCL. The model outcomes include total and incremental costs and health outcomes expressed as quality-adjusted life years (QALYs) gained.

4.1 Model structure

A three-health state partitioned survival model (PartSA) is used to perform the cost-effectiveness analysis of axi-cel compared to salvage therapy (See Figure 1). This approach requires the use of OS and PFS curves, estimated independently, to predict the distribution of patients across the three health states: progression-free (PFS), progressed (PD), and death. A simplified representation of the model structure is shown in Figure 1.

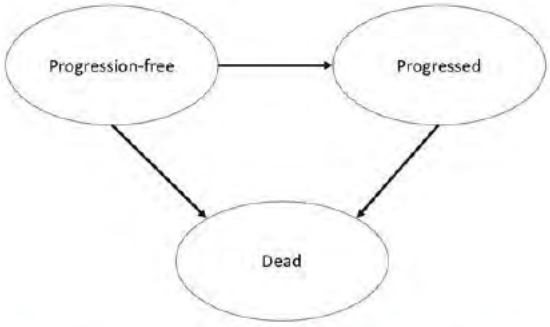


Figure 1: Illustration of the model structure of the partitioned survival model.

At any timepoint, the proportion of patients under the PFS curve is in the PF health state. The proportion of patients over the OS curve is in the death state. The remaining proportion of patients, neither in death nor PFS state, is in the PD health state.

Due to the independence of PFS and OS, illogical outcomes (PFS>OS) can be generated. Moreover, the structural relationship between health states is not preserved, and this can lead to differences between predicted and observed outcomes when extrapolating OS. This is accounted for in the model engines by not allowing PFS to exceed OS. Furthermore, as per National Institute for Health and Care Excellence (NICE) TSD 21 (51) all models were fitted in a relative survival framework, which takes into account background mortality in the estimation of long-term survival estimates.

Lastly, the PartSA model incorporates both standard parametric models and mixture cure models (MCMs), refer to Section 8.1.1 for further description.

4.2 Model features

Table 11 describes the model features.

Table 11 Features of the economic model

Model features	Description	Justification
Patient population	Adult patients with relapsed or refractory DLBCL and PMBCL after 2 or more lines of systematic therapy	Patient population according to EMA label (1).
Perspective	Limited societal perspective	According to DMC guidelines (47).
Time horizon	Lifetime (44 years)	To capture all health benefits and costs in line with DMC guidelines (47).

Model features	Description	Justification
		The mean age in the ZUMA-1 was 56.2 years (8). Considering the Danish median age for DLBCL at diagnosis of 67 years, 44 years was considered reasonable (29).
Cycle length	One month	As median OS in the BSC (salvage therapy) arm is expected to be approximately six months, a cycle length of one month is used to capture all relevant changes in the modelled cohort.
Half-cycle correction	Yes	
Discount rate	3.5%	According to DMC's methods guide (47).
Intervention	Axi-cel (Yescarta®)	
Comparator(s)	Salvage therapy	According to Danish treatment guideline no universal standard of care is considered (29). DHAP/ICE/GDP, GemOx/Gem-mono and bendamustine (in combination with rituximab) is justified as a salvage therapy based on a recent Danish clinical real-world study (35), where DHAP/ICE/GDP constitutes 12.7% of index-line treatments for relapsed or refractory cases (3L), GemOx/Gem mono constitutes 4.2% and bendamustine 3.2%. This is followed by SCT for eligible patients, refer to Section 8.3 for further description. The included regimens have been included in the previous DMC assessment (14). Note: salvage therapy is named "BSC" in the economic model.
Outcomes	OS, PFS	

Abbreviations: DLBCL = diffuse large B-cell lymphoma; PMBCL = primary mediastinal B-cell lymphoma, EMA= European Medicines Agency, DMC= Danish Medicines Council, OS= overall survival, BSC= best supportive care, R-DHAP= rituximab-dexamethasone, high-dose cytarabine, and cisplatin, R-ICE= rituximab, ifosfamide, carboplatin, and etoposide., R-GDP= rituximab, gemcitabine, dexamethasone, and cisplatin, PFS= progression-free survival.
Note: in the model, salvage therapy is named "BSC".

5. Overview of literature

5.1 Literature used for the clinical assessment

The clinical SLR was conducted on 14 July 2023 and 22 September 2023, the full details of which are provided in Appendix H. The aim of the SLR was to gather comprehensive clinical information (efficacy, safety, discontinuation and tolerability) about axi-cel and rituximab-based standard of care therapies for the management of patients with 3L DLBCL and PMBCL, and tisa-cel in 3L DLBCL. In summary, 170 publications were identified, which included 27 unique studies. From these, 3 studies (ZUMA-1 (7), CORAL EXT 1 (52) & 2 (6)) were most appropriate to describe the efficacy of axi-cel for 3L DLBCL patients. For the salvage therapy comparator, CORAL EXT 1 & 2 were the most appropriate as both studies included patients who received 3L DLBCL salvage therapies after relapsing in ASCT or did not receive ASCT after 2L treatment.

Table 12 Relevant literature included in the assessment of efficacy and safety

Reference (Full citation incl. reference number)*	Trial name*	NCT identifier	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Used in comparison of*
Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023 May 11;141(19):2307-2315. (7)doi: 10.1182/blood.2022018893. PMID: 36821768 (7)	ZUMA-1	NCT02348216	Start: 21/04/15 Completion: 10/09/20 Data cut-off: 11/08/21 Future data cut-offs: N/A	Axi-cel (single arm study) for patients with r/r DLBCL (diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma) after two or more lines of systemic therapy.
Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017 Feb;52(2):216-221. doi: 10.1038/bmt.2016.213. Epub 2016 Sep 19. PMID: 27643872 (52)	CORAL EXT 1	NCT00137995	Start: June 2003 Completion: October 2008 Data cut-off: N/A Future data cut-offs: N/A	Salvage therapy (maintenance or observation) (single arm study) for patients with r/r DLBCL after three lines of systemic therapy.
Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016 Jan;51(1):51-7. doi: 10.1038/bmt.2015.213. Epub 2015 Sep 14. PMID: 26367239 (6)	CORAL EXT 2	NCT00137995	Start: June 2003 Completion: October 2008 Data cut-off: N/A Future data cut-offs: N/A	Salvage therapy (grouped by major categories: ICE-type, DHAP-type, gemcitabine-containing, dexamethasone-BEAM-like, CHOP-like, cyclophosphamide, doxorubicin, vincristine, prednisone or acute lymphoblastic leukemia-type protocols, and a heterogeneous group of miscellaneous treatments (including lenalidomide, vincristine, bleomycin, fludarabine, bendamustine, in monotherapy or in various combinations) (single

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*
				arm study) for patients with r/r DLBCL after two lines of systemic therapy.

Abbreviations: axi-cel = axicabtagene ciloleucel; CHOP = cyclophosphamide, vincristine, doxorubicin, and prednisone; DBCL = diffuse large B-cell lymphoma; BEAM = carmustine, etoposide, cytarabine and melphalan; DHAP = cisplatin, cytarabine, and dexamethasone; ICE = ifosfamide, carboplatin, and etoposide; N/A = not applicable; r/r = relapsed or refractory; R-DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; R-ICE = rituximab, ifosfamide, carboplatine, and etoposide.
Notes: * If there are several publications connected to a trial, include all publications used.
Source: ClinicalTrials.gov, 2023 (49); ClinicalTrials.gov, 2019 (53); Neelapu et al., 2023 (7); Van Den Este et al., 2017 (52); Van Den Este et al., 2016 (7).

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

The HRQoL SLR was conducted together with the clinical SLR and follow the same methodology described in Appendix H. The SLR was conducted on 14 July 2023 and 22 September 2023, and aimed to address the following: to gather comprehensive clinical information (efficacy, safety, discontinuation and tolerability) about axi-cel and rituximab-based standard of care therapies for the management of patients with 3L DLBCL and PMBCL, and tisa-cel in 3L DLBCL. In summary, 170 publications were identified, which included 27 unique studies. From these, 2 studies (Schuster et al., 2019 (54) & ZUMA-1 (7)) were deemed most relevant to provide HRQoL values for axi-cel and the salvage therapy comparators. Listed in the table below, the NoMA assessment of Kymriah® (also based on the JULIET trial) as well as the NICE TA306, which wasn't captured in the SLR (TA306 is from 2014, but considered reasonable to include for utility input for scenario analyses).

Table 13 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
Schuster SJ, Bishop MR, Tam CS, et al. Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma. N Engl J Med. 2019 Jan 3;380(1):45-56. doi: 10.1056/NEJMoa1804980. Epub 2018 Dec 1. PMID: 30501490	SF-36 scores	Appendix F
Found in Norwegian Medicines Agency. Kymriah® assessment 2019 (page 67 / 142) (55, 56).	PF and PD HSUV (EQ-5D)	Section 10 and 10.3

Reference (Full citation incl. reference number)	Health state/Disutility	Reference to where in the application the data is described/applied
Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023 May 11;141(19):2307-2315 (7)	PF and PD HSUV (EQ-5D)	Section 10
NICE TA306/TA178 (NICE TA306, ERG report, table 27)(57)	PF and PD HSUV	Section 10 and 10.3

Abbreviations: PF= progression-free, PD= progressed disease, HSUV= health-state utility value, EQ-5D= EuroQol-5 dimension

5.3 Literature used for inputs for the health economic model

No economic SLR was made to provide inputs for the health economic model, as the SLR was not expected to bring further information. Previous assumptions that have been used in past submission dossiers were still deemed relevant for this dossier and are listed in the table below.

Table 14 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
Dental and Pharmaceutical Benefits Agency. Assessment of Pixuvri® Pixantrone 2016 (58) Danish Medicines Council. Yescarta® 2019 (section: Questions for Key Opinion Leaders in Denmark regarding the treatment of B-cell lymphoma with CAR-T therapy Axicabtagene ciloleucel (Axi-cel)) (14)	HCRU	The average resource utilisation for the PF state and PD state is largely based on an estimate for similar patients in 2016, based on TLV's Pixuvri® assessment (58) Based on the Swedish Pixuvri® assessment, the resource utilization in the model is derived from a prior application of Pixuvri® to NICE (TA306) (57) and has been validated through an expert opinion from a clinical expert in Sweden. These estimations have subsequently been validated by a clinical expert in Denmark (reported in the Yescarta® assessment from 2019) (14).	Section 11.4
European Medicines Agency. Summary of product characteristics for Yescarta 2023 (1) Rigshospitalet. CAR-T - behandling med: Region Hovedstaden (59)	Hospitalisation days for axi-cel administration	Based on SmPC	Section 11.1, Section 11.2 and Section 11.3
Norwegian Medicines Agency. Kymriah® assessment 2019 (Tabel 15) (69)	Days per cycle for salvage therapy	Based on previous DMC / NoMA assessments	Section 11.2

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Danish Medicines Council. Yescarta® assessment 2019 (page 12 of Amgros' assessment, table 5) (14)			
Region Midtjylland. R-ICE Medicinsk kræftbehandling (blodsygdomme): AUH (60)			
Region Midtjylland. R-DHAP Medicinsk kræftbehandling (blodsygdomme): AUH (61)			
Herlev Hospital. Gemcitabin, behandling med. Region Hovedstaden (62)			
Herlev Hospital. Gemcitabin og Oxaliplatin, behandling med. Region Hovedstaden (63)			
Kunskapsbanken (Cancercentrum) Gemcitabin – Oxaliplatin (GemOX) (64)			
Pettengell R, Długosz-Danecka M, Andorsky D, Belada D, Georgiev P, Quick D, et al. Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a phase 3, randomized, multicentre trial (PIX306). British journal of haematology. 2020;188(2):240-8 (65)			
Danske Multidisciplinære Cancer Grupper, Kvalitetsudviklingsprogram RK. Kliniske retningslinjer. Kræft. Diffust storcellet B-celle lymfom.: Dansk Lymfomgruppe; 2022 (29)			
Danish Medicines Council. Minjuvi® 2022 (66)			
Danish Medicines Council. Polivy® 2021 (50)			
NHS South East London Cancer Network (Collins LLPG. NSSG chemotherapy protocol. NHS; 2022) (67)			
Hong JY, Yoon DH, Suh C, Kim WS, Kim SJ, Jo JC, et al. Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a multicenter retrospective analysis. Ann Hematol. 2018 (68)			

Reference (Full citation incl. reference number)	Input/estimate	Method of identification	Reference to where in the application the data is described/applied
Kite Pharma Inc. 24-month follow-up analysis of ZUMA-1 Cohorts 1 and 2. Addendum to Module 5.3.5.1 ZUMA-1 Clinical Study Report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1). Data on file. 2 November 2018.(9)).	Multiplier for leukapheresis cost, for conditioning chemotherapy costs and re-treatment.		Section 8.3
	SCT proportion observed in ZUMA-1		Section 8.3
AL-Mashhadi AL, Jakobsen LH, Brown P, Gang AO, Thorsteinsson AL, Rasoul K, et al. Real-world outcomes following third or subsequent lines of therapy: A Danish population-based study on 189 patients with relapsed/refractory large B-cell lymphomas. British Journal of Haematology. 2023.(35).	SCT proportion applied for comparator arm	Real-world outcomes following third or subsequent lines of therapy: A Danish population-based study on 189 patients with relapsed/refractory large B-cell lymphomas (Al-Mashhadi et al). (35).	Section 8.3
Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016;51(1):51-7.(6)	SCT proportion applied for comparator arm	CORAL MAIC reported proportion. Comparing with the CORAL EXT 1 & 2 data, 29% of patients eventually underwent SCT (ASCT 21.2%, allogeneic SCT 7.5%), providing a broader context for the range of potential outcomes (6).	Section 8.3
Kite Pharma Inc. 24-month follow-up analysis of ZUMA-1 Cohorts 1 and 2. Addendum to Module 5.3.5.1 ZUMA-1 Clinical Study Report: KTE-C19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of KTE-C19 in subjects with refractory aggressive non-Hodgkin lymphoma (ZUMA-1). Data on file. 2 November 2018.(9)). Kite Pharma I. Clinical study report: kte-c19-101 a phase 1/2 multicenter study evaluating the safety and efficacy of kte-c19 in subjects with refractory aggressive non hodgkin lymphoma (ZUMA). 2017.(81))	Proportion with HGG and CRS + proportion treated with IVIG (including frequency of dose and average duration of treatment)	Reported in the clinical study report.	Section 11.5
Universitetshospital A. Immunglobulin (Privigen®): Region Midtjylland (69)	IVIG treatment	Based on Privigen®	Section 11.5

6. Efficacy

6.1 Efficacy of axi-cel compared to R-DHAP, R-ICE, R-GDP, R-GemOx, R-Gemcitabine and R-Bendamustine for patients with relapsed or refractory diffuse large B-cell lymphoma

6.1.1 Relevant studies

The ZUMA-1 study (NCT02348216) describes the efficacy of axi-cel in patients with r/r DLBCL with a 5-year follow-up. The CORAL EXT 1 & 2 studies (NCT00137995) describe the efficacy of R-DHAP, R-ICE, R-GDP, R-GemOx, R-Gemcitabine and R-Bendamustine, which is considered salvage therapy.

The CORAL EXT 1 & 2 are extension studies of the CORAL study (NCT00137995) in which patients received either R-ICE or R-DHAP (53). The extension studies include patients who relapsed after ASCT either before or after randomisation between rituximab and observation (CORAL EXT 1) and in patients not proceeding to planned transplantation according to the protocol because of an event leading to withdrawal between cycle 1 and scheduled ASCT (CORAL EXT 2). The ZUMA-1 and CORAL EXT 1 & 2 studies are presented in Table 15.

Table 15 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 period
ZUMA-1 (NCT02348216) Neelapu SS, Jacobson CA, Ghobadi A, et al. Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Blood. 2023 May 11;141(19):2307-2315. doi: 10.1182/blood.2022018893. PMID: 36821768 (7) Caron Jacobson, Frederick L. Locke, Armin Ghobadi, et al; Long-Term (≥4 Year and ≥5 Year) Overall Survival (OS) By 12- and 24-Month Event-Free Survival (EFS): An Updated Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma (LBCL). Blood 2021; 138 (Supplement 1): 1764. doi: https://doi.org/10.1182/blood-2021-148078 (70) Vadgama S, Mann J, Bashir Z, et al. Predicting Survival for Chimeric Antigen Receptor T-Cell Therapy: A Validation of Survival Models Using Follow-Up Data From ZUMA-1. Value Health. 2022 Jun;25(6):1010-1017. doi: 10.1016/j.jval.2021.10.015. Epub 2022 Jan 31. PMID: 35667774 (71) Oluwole OO, Bouabdallah K, Muñoz J, et al. Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Br J Haematol. 2021 Aug;194(4):690-700. doi: 10.1111/bjh.17527. Epub 2021 Jul 22. PMID: 34296427; PMCID: PMC8457222 (72) Locke FL, Ghobadi A, Jacobson CA, et al. Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Lancet Oncol. 2019 Jan;20(1):31-42. doi: 10.1016/S1470-2045(18)30864-7. Epub 2018 Dec 2. PMID: 30518502; PMCID: PMC6733402 (73) Neelapu SS, Locke FL, Bartlett NL, et al. Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. N Engl J Med. 2017 Dec 28;377(26):2531-2544. doi: 10.1056/NEJMoa1707447. Epub 2017 Dec 10. PMID: 29226797; PMCID: PMC5882485 (74)	Multicentre, single group assignment, open label, phase I/II	First subject enrolled in Phase 1: 21 April 2015. Data cutoff date 11 August 2021.	Patients with r/r DLBCL, PMBCL, or TFL	Axi-cel, IV, 2 x 10^6 anti-CD19 CAR T cells/kg	N/A	ORR (11 August 2021) OS (11 August 2021) PFS (11 August 2021) EFS (11 August 2021) DSS (11 August 2021) TTP (11 August 2021) Time to next therapy (11 August 2021)

Trial name, NCT-number (reference)	Study design	Study duration	Patient population	Intervention	Comparator	Outcomes and follow-up period
CORAL EXT 1 and CORAL EXT 2 (NCT00137995) Van Den Neste E, Schmitz N, Mounier N, et al. Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Bone Marrow Transplant. 2017 Feb;52(2):216-221. doi: 10.1038/bmt.2016.213. Epub 2016 Sep 19. PMID: 27643872. (52) Van Den Neste E, Schmitz N, Mounier N, et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016 Jan;51(1):51-7. doi: 10.1038/bmt.2015.213. Epub 2015 Sep 14. PMID: 26367239. (6)	Observational follow-up studies of an unblinded, randomised study comparing the two chemotherapy regimens R-DHAP and R-ICE	CORAL EXT 1: July 2003 - June 2008 CORAL EXT 2: July 2003 – June 2008	CORAL EXT 1: Patients included in the CORAL study (53) who relapsed after ASCT either before or after randomisation between rituximab and observation. CORAL EXT 2: Patients not proceeding to planned transplantation according to the protocol because of an event leading to withdrawal between cycle 1 and scheduled ASCT.	Salvage therapy	N/A	CORAL EXT 1: • OS (date of relapse after ASCT until death) • Overall response rate including CR/CR unconfirmed (CRu) and PR CORAL EXT 2 • OS (time from the date the patient was declared as having failed CORAL induction until death) • Overall response rate including CR/CRu and PR

Abbreviations: ASCT = autologous stem cell transplantation; axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptors; CR = complete response; CRu = complete response unconfirmed; DLBCL = diffuse large B-cell lymphoma; DSS = disease-specific survival; EFS = event-free survival; IV = intraveneous; N/A = not applicable; ORR = objective response rate; OS = overall survival; PFS = progression free survival; PMBCL = primary mediastinal B-cell lymphoma; PR = partial response; R-DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; R-ICE = rituximab, ifosfamide, carboplatine, and etoposide; r/r = relapsed or refractory; TFL = transformed follicular lymphoma; TTP = time to next therapy.
Sources: Clinicaltrials.gov, 2022 (49); Kite Pharma Inc., 2018 (9); Neelapu et al., 2023 (7); Van Den Neste et al., 2016 (6); Van Den Neste et al., 2017 (52).

6.1.2 Comparability of studies

Two trials were included in the evidence base: ZUMA-1, assessing axi-cel; and CORAL EXT 1 & 2, assessing historical treatments following the trial phase comparing R-ICE to R-DHAP. These two studies represent the complete set of evidence used in the comparative analyses of efficacy. The comparative analyses are based on an analysis done by Maziarz et al. (2022) (8). Maziarz et al. (2022) compared tisagenlecleucel (tisa-cel) (JULIET; NCT02445248) to salvage therapy from the CORAL EXT 1 & 2 trials (NCT00137995) using IPD data (8). Table 16 presents some of the basics of study designs and locations. Overall, the geographies and study design were comparable.

Table 16 Comparison of study designs

Study	Intervention	Study design	Blinding	Setting
ZUMA-1	Axi-cel	Phase I/II trial	Open label	Phase I: US, Canada, Europe; Phase II: US, Israel
CORAL EXT 1 & 2	Salvage therapy	Phase III interventional trial	Open label	US, Israel, Europe, Australia

Source: Kite Pharma Inc., 2022 (75).

Table 17 presents and compares the inclusion criteria for each study. The inclusion/exclusion criteria were very similar across the studies, and only minor differences were observed. Both studies included adults, however CORAL EXT 1 & 2 had a maximum age of 65, while ZUMA-1 did not have an age criterium for axi-cel treatment. This difference was mitigated by the fact that the lines of treatment used in the analyses were post-trial – meaning that patients were older by the time they were included in the analysis. While CORAL EXT 1 & 2 allowed the inclusion of Eastern Cooperative Oncology Group (ECOG) performance score of 2, these patients were excluded from the analyses in Maziarz et al. (2022) (8). The application of the JULIET criteria to the CORAL EXT 1 & 2 trials resulted in a population that is similar to the ZUMA-1 trial.

Table 17 Inclusion criteria across trials

Inclusion criteria	ZUMA-1	CORAL EXT 1 & 2
Demographics		
Adults aged 18 or more	✓	X
Adults aged 18-65	X	✓
Men and women eligible	✓	✓
Histologically confirmed large B cell lymphoma including the following types		
Diffuse large B-cell lymphoma	✓	✓
Primary mediastinal B-cell lymphoma	✓	unspecified
Transformed follicular lymphoma	✓	unspecified
High grade B-cell lymphoma	✓	unspecified
Other criteria		
R/r disease after at least 1 line of treatment with combination chemoimmunotherapy	X	✓
R/r disease after at least 2 lines of treatment with combination chemoimmunotherapy	✓	X
ECOG performance status of 0 or 1	✓	X
ECOG performance status of 0 - 2	X	✓
No known history or suspicion of CNS involvement by lymphoma	✓	✓
Not pregnant or breastfeeding	✓	✓
Adequate organ function	✓	✓
No prior CAR-T therapy	✓	✓
No prior allo-SCT	✓	✓

Abbreviations: allo-SCT = allogeneic stem cell transplantation; CAR = chimeric antigen receptor; CNS = central nervous system; ECOG = Eastern Cooperative Oncology Group; r/r = relapsed or refractory.
Source: Kite Pharma Inc., 2022 (75).

Another aspect of trial design is variable definitions. OS was defined as time from index date to death or censoring date for patients not experiencing a death event (death due to any reason). In CORAL EXT 1 & 2, the index date was the start of therapy for the full analysis set (FAS) population. In the intention-to-treat (ITT) population, the index date for CORAL EXT 1 & 2 follow-up ITT was defined as the date of the selected index treatment initiation, if known, or the date of relapse from last line if the initiation date of the index treatment was missing. In ZUMA-1, the index date for the FAS analysis set was the date of axi-cel infusion, while the index date for the ITT analysis set was the leukapheresis date. This emulates the methods used in Maziarz et al. (2022) (8) and informs the comparative analysis for this submission. Date of censoring was the last follow-up date. So, for OS, the key difference was in the delay between choice and administration of treatment. For ZUMA-1, there is a vein-to-vein time between leukapheresis and axi-cel infusion, but in CORAL EXT 1 & 2 there is no such delay. As we used leukapheresis as an index date for the ITT population and infusion as the index date for the FAS population, this difference was negligible. ORR was measured in both the ZUMA-1 and CORAL EXT 1 & 2 trials, but the criteria used were different. CORAL EXT 1 & 2 trials used the 1999 IWG response criteria (76), while ZUMA-1 used the revised 2007 IWG criteria (48). This is of minimal concern given that the more important difference between the two criteria is how complete response is assessed rather than how ORR is measured. For both studies, patients with unknown response or without an index treatment were considered non-responders.

Overall, there was acceptable agreement in study design between ZUMA-1 and CORAL EXT 1 & 2. Differences in study design cannot be mitigated by MAICs themselves, therefore having acceptable alignment between the studies was critical.

6.1.2.1 Comparability of patients across studies

Table 18 presents the baseline characteristics of patients included in ZUMA-1 and CORAL EXT 1 & 2. Results of CORAL EXT 1 & 2 are presented together, although by two datasets. These are defined by the two analysis populations from CORAL EXT 1 & 2, FAS (N=145) and ITT (N=205) that are based on population weighting (standardised mortality ratio weight (SMRW)). The weighting procedure is described briefly in section 7.1.2.1 and more detailed in appendix C.1.3.1. Calculation of effective sample size (ESS) is described in appendix C.1.3.

Table 18 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety (pre and post adjustment)

	ZUMA-1 (FAS)	ZUMA-1 (FAS, SMRW)	CORAL EXT 1 & 2 (FAS, SMRW)	ZUMA-1 (ITT)	ZUMA-1 (ITT, SMRW)	CORAL EXT 1 & 2 (ITT, SMRW)
	Axi-cel	Axi-cel	Salvage therapy	Axi-cel	Axi-cel	Salvage therapy
	N = 101	N = 101	N = 145	N = 111	N = 111	N = 205
Age at diagnosis – mean (standard deviation [sd])	56.3 years (12.1)	56.2 years (11.8)	54.1 years (11.5)	56.2 years (11.9)	57.2 years (12.2)	54.7 years (11.5)
Age at diagnosis > 60	33.7%	28.6%	28.6%	32.4%	36.9%	36.9%
Sex – Male	67.3%	63.5%	65.7%	69.4%	70.6%	54.7%
Ann Arbor disease stage_3-4	85.1%	75.9%	75.9%	84.7%	63.6%	63.6%
IPI ≥ 2	75.2%	77.4%	87.1%	76.6%	75.8%	89.7%
ECOG performance score 0-1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
LDH > ULN	57.0%	54.6%	27.7%	57.0%	54.6%	36.1%
Prior ASCT	24.8%	51.0%	51.0%	23.4%	43.8%	43.8%
Status of disease						
Relapsed after last	11.9%	47.5%	47.5%	11.7%	52.6%	52.6%
Refractory to all	22.8%	17.6%	17.6%	22.5%	16.1%	16.1%
Refractory to last, not all	65.3%	34.9%	34.9%	65.8%	41.3%	41.3%
Time to 2L from diagnosis						
< 12 months	76.2%	54.6%	54.6%	75.7%	59.5%	59.5%
12 to 24 months	14.9%	23.2%	23.2%	13.5%	23.6%	23.6%
> 24 months	8.9%	22.2%	22.2%	10.8%	16.9%	16.9%
Number of relapses – mean (sd)	1.5 (1.4)	2.1 (1.5)	1.5 (0.9)	1.5 (1.5)	2.1 (1.5)	1.4 (0.9)
Number of prior lines – mean (sd)	3.3 (1.5)	3.4 (1.2)	2.4 (0.7)	3.4 (1.5)	3.4 (1.3)	2.4 (0.7)

Abbreviations: 2L = second line; ASCT = autologous stem cell transplant; axi-cel = aqxicabtagene ciloleucel; CAR = chimeric antigen receptor; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; IPI = international prognostic index; ITT = intention-to-treat; LDH = lactase dehydrogenase; N/A = not applicable; sd = standard deviation; SMRW = standardised mortality ratio weight; ULN = upper limit of normal.
Source: Kite Pharma Inc., 2022; table 4 and 7 (75).

While there is some variation across the different cohorts, the general trends are consistent. Relative to CORAL EXT 1 & 2, ZUMA-1 has slightly older patients, more previous lines of treatment, and a higher proportion of patients with stage 3 or 4 disease. Nonetheless, there were a few important differences between the two trials. First, there were roughly 25% with prior ASCT in ZUMA-1 compared to around 50% in CORAL EXT 1 & 2. Second, there were much more patients that were refractory to the last line of therapy in ZUMA-1 (65.3% in the FAS population and 65.8% in the ITT population) than CORAL EXT 1 & 2 (34.9% in the FAS population and 41.3% in the ITT population), which was to be expected given that the ZUMA-1 trial focused on enrolled patients with chemotherapy-refractory disease. Differences between trials were addressed by conducting a MAIC. Taken together, these results suggested that there could be potential issues of alignment between the two studies, with some patients having high weights. MAICs are most effective when the differences are not too large. The differences turned out to not be critically problematic (75).

Generally, the ZUMA-1 weighted population was similar to the CORAL EXT 1 & 2 population. However, for the weighted FAS populations the following differences was observed: 77.4% had an IPI ≥ 2 in ZUMA-1 compared to 87.1% in CORAL EXT 1 & 2, 54.6% had LDH > ULN in ZUMA-1 compared to 27.7% in CORAL EXT 1 & 2, while the mean number of prior lines was 3.4 in ZUMA-1 compared to 2.4 in CORAL EXT 1 & 2. For the weighted ITT population some differences were observed: 70.6% males in ZUMA-1 compared to 54.7% in CORAL EXT 1 & 2, 75.8% had an IPI ≥ 2 in ZUMA-1 compared to 89.7% in CORAL EXT, 54.6% had LDH > ULN in ZUMA-1 compared to 36.1% in CORAL EXT 1 & 2, while the mean number of prior lines was 3.4 in ZUMA-1 compared to 2.4 in CORAL EXT 1 & 2.

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

It is expected that the study population from ZUMA-1 will match patients seen in Danish clinical practice for 3L DLBCL, as confirmed by the Danish clinical expert (31). The main difference is the reported median age at diagnosis for Danish patients, which is older than what is seen in the ZUMA-1 trial.

Table 19 Characteristics in the relevant Danish population and in the health economic model

	Value in Danish population (reference)	Value used in health economic model (reference if relevant)
Age	67 (median) (25)	56.2 (median) (7)

Notes: The value in the Danish population is based on the appendix to the DMC's recommendation of polatuzumab vedotin (p. 5) (25).

6.1.4 Efficacy – results per ZUMA-1

The outcomes from the ZUMA-1 study are presented in the sections below. The source of the primary data for ZUMA-1 study presented in this submission is Neelapu et al., 2023, which presents data from the FAS population (N = 101) (7). For completeness, data from the ITT population (N=111) (77) is presented as well, since both the FAS and ITT population are presented in the comparative analyses (Section 7).

6.1.4.1 Overall response rate (August 2021 data cut)

Patients treated with axi-cel had a median follow-up of 63.1 months (range 58.9-68.4) from infusion at the latest data cut (11 August 2021). The ORR was one of the primary

endpoints for the ZUMA-1 study (49). Table 20 presents response rates from the ZUMA-1 study. Among the FAS population who received axi-cel, the investigator-assessed ORR was 83% (n = 84; 95% CI, 74-90). This included 58% CRs (n = 59) and 25% PRs (n = 25). Among all treated patients, median DOR was 11.1 months (95% CI, 4.2-51.3). At data cutoff, 31 patients (31%) had an ongoing objective response, 30 (30%) had an ongoing CR, and 1 (1%) had an ongoing PR. Concordantly, the median duration of CR was 62.2 months, whereas the median duration of PR was 1.9 months (7). Similar results were observed in the ITT population.

Table 20 Summary of response outcomes

Parameters	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
ORR, [a] n (%, 95% CI)	84 (83, 74–90)	86 (77, 69–85)[Ω]
CR, [a] n (%, 95% CI)	59 (58, 48–68)	61 (55, N/A–N/A) [Ω]
PR, [a] n (%, 95% CI)	25 (25, 17–34)	25 (23, N/A–N/A) [Ω]
SD, [b] n (%, 95% CI)	10 (10, 5–17)	10 (9, N/A–N/A) [Ω]
PD, [b] n (%, 95% CI)	5 (5, 2–11)	5 (5, N/A–N/A) [Ω]
Not done	2 (2, 0–7)	10 (9, N/A–N/A) [Ω]
Median DOR, [c] months (95% CI)	11.1 (4.2–51.3)	11.1 (4.2–51.3)*
Median CR, [c] months (95% CI)	62.2 (12.9–not estimable (NE))	62.2 (12.9, NE)*
Median PR, [c] months (95% CI)	1.9 (1.3–2.1)	1.9 (1.3–2.1)*

Abbreviations: Axi-cel = axicabtagene ciloleucel; CAR = chimeric antigen receptor; CI = confidence interval; CR = complete response; DOR = duration of response; NE = not estimable; N/A = not applicable; ORR = objective response rate; PD = progressive disease; PR = partial response; SD = stable disease.
Notes: [a], per the revised IWG Response Criteria for Malignant Lymphoma (48); [b], Assessments of response made by the IRRC using IWG 2007 criteria (48); [c], based on the KM estimator. [Ω] Based on the 24-month data cut, as these estimates have not changed. *, Using investigator assessment per Cheson 2007 (48) among subjects with objective response.
Source: Neelapu et al., 2023 (7); Kite Pharma Inc., 2021 (77); Kite Pharma Inc., 2018 (9).

6.1.4.2 Overall survival (August 2021 data cut)

OS is a secondary outcome in the ZUMA-1 study (49). Table 21 presents OS outcomes based on the August 11 2021 data cut. Median OS in the FAS population who received treatment was 25.8 months (95% CI, 12.8-NE), while the ITT population had a median OS of 17.4 months (95% CI, 11.6-49.5). The Kaplan-Meier curve for OS is presented in Figure 2 for the FAS population and in Figure 3 for the ITT population. The 5-year OS rate was 42.6% (95% CI, 32.8-51.9) for the FAS population.

Table 21 Summary of overall survival outcomes (August 2021 data cut))

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median OS, months (95% CI)	25.8 (12.8–NE)	17.4 (11.6–49.5)
5-year OS rate, % (95% CI)	42.6% (32.8–51.9)	N/A

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval; NE = not estimable; N/A = not applicable; OS = overall survival.
Source: Neelapu et al., 2023 (7); Kite Pharma Inc., 2021 (77).

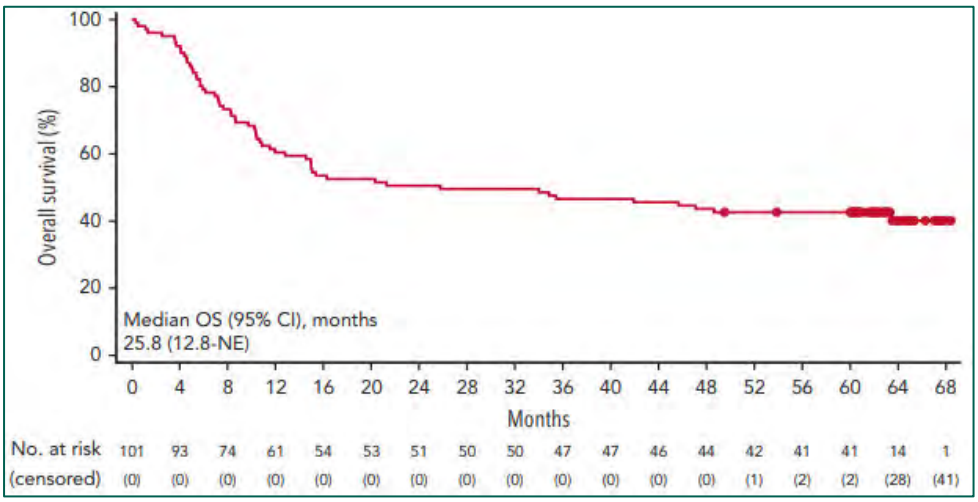


Figure 2 Kaplan-Meier survival curve of overall survival among 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval; NE = not estimable; OS = overall survival.
Notes: One patient's event time for OS was updated from month 42 to month 39 after data cutoff and is not reflected in this figure.
Source: Neelapu et al., 2023 (7).

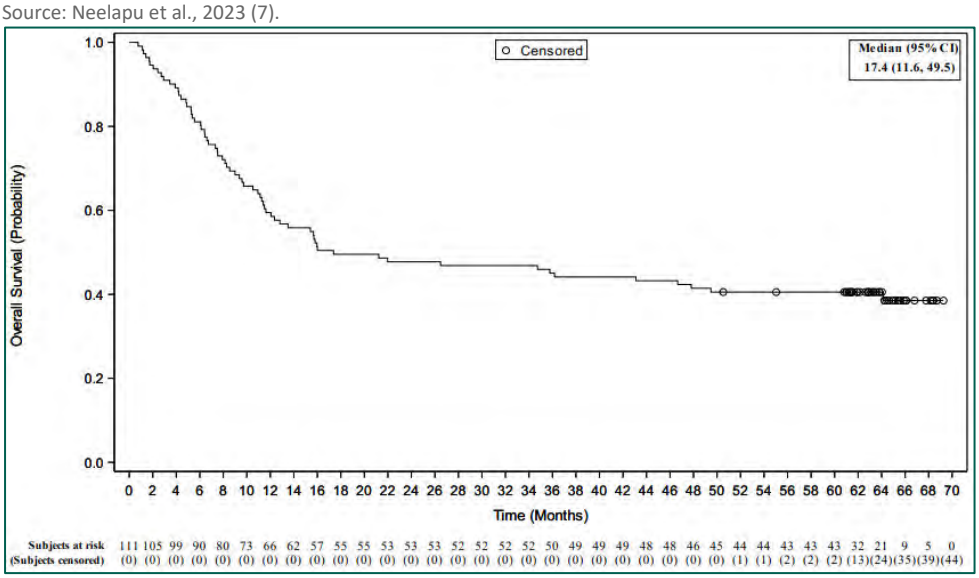


Figure 3 Kaplan-Meier survival curve of overall survival among the 111 patients in cohorts 1 and 2 of phase 2, ITT, August 2021 data cut

Abbreviations: CI = confidence interval.
Source: Kite Pharma Inc., 2021 (77).

6.1.4.3 Progression-free survival (August 2021 data cut)

PFS is a secondary outcome in the ZUMA-1 study (49). Table 22 presents PFS outcomes based on the August 11 2021 data cut. The median PFS was 5.9 months (95% CI, 3.3-15.0) among the FAS population who received treatment and 6.3 months (95% CI, 4.0-12.7) among the ITT population. The Kaplan-Meier curve for PFS is presented in Figure 4 for the FAS population and in Figure 5 for the ITT population. The 5-year PFS rate was 31.8% (95% CI, 22.9-41.1) for the FAS population.

Table 22 Summary of progression-free survival outcomes (August 2021 data cut)

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median PFS, months (95% CI)	5.9 (3.3–15.0)	6.3 (4.0–12.7)*
5-year PFS rate, % (95% CI)	31.8% (22.9–41.1)	N/A

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval; N/A = not applicable; PFS = progression-free survival.
Notes: *, Using investigator assessment per Cheson 2007 (48).
Source: Neelapu et al., 2023 (7); Kite Pharma Inc., 2021 (77).

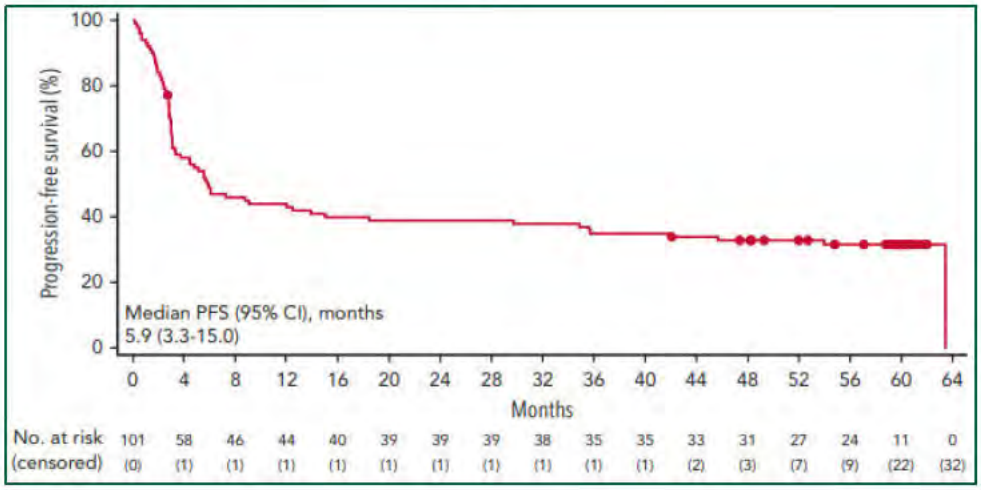


Figure 4 Kaplan-Meier survival curve of progression-free survival by investigator assessment among the 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval; PFS = progression-free survival.
Source: Neelapu et al., 2023 (7).

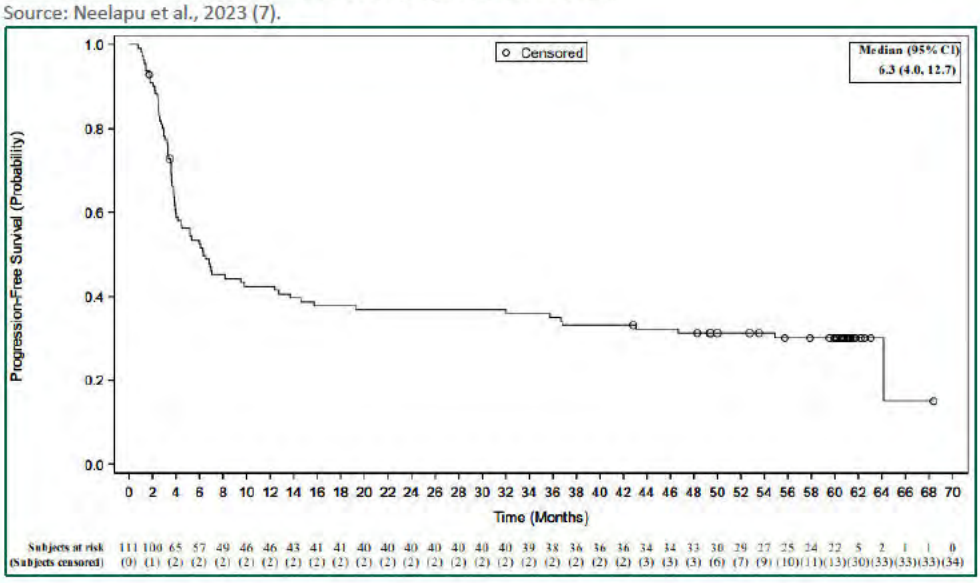


Figure 5 Kaplan-Meier survival curve of progression-free survival by investigator assessment among the 111 patients in cohorts 1 and 2 of phase 2, ITT, August 2021 data cut

Abbreviations: CI = confidence interval.
Source: Kite Pharma Inc., 2021 (77).

6.1.4.4 Event-free survival (August 2021 data cut)

EFS is an additional efficacy endpoint included in the 5-year follow up study (7). Table 23 presents EFS outcomes based on the August 11 2021 data cut. Median EFS was 5.7 months (95% CI, 3.1-13.9) among the FAS population. The Kaplan-Meier curve for EFS is presented in Figure 6. The estimated 5-year EFS rate was 30.3% (95% CI, 21.5-39.6) for the FAS population.

Table 23 Summary of event-free survival outcomes (August 2021 data cut)

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median EFS, months (95% CI)	5.7 (3.1–13.9)	N/A
5-year EFS rate, % (95% CI)	30.3% (21.5–39.6)	N/A

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval; EFS = event-free survival; N/A = not applicable.
Source: Neelapu et al., 2023 (7).

Figure 6 Kaplan-Meier survival curve of event-free survival by investigator assessment among the 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval; EFS = event-free survival.
Source: Neelapu et al., 2023 (7).

6.1.4.5 Disease-specific survival (August 2021 data cut)

DSS is an additional efficacy endpoint included in the 5-year follow up study (7). Table 24 presents DSS outcomes based on the August 11 2021 data cut. The median DSS was not yet reached (95% CI, 15.4 months-NE) at the august 2021 data cut for the FAS population. The Kaplan-Meier curve for DSS is presented in Figure 7. The 5-year DSS rate was 51.0% (95% CI, 40.4-60.6).

Table 24 Summary of disease-specific survival outcomes (August 2021 data cut)

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median DSS, months (95% CI)	Not reached (15.4–NE)	N/A
5-year DSS rate, % (95% CI)	51.0% (40.4–60.6)	N/A

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval; DSS = disease-specific survival; NE = not estimable; N/A = not applicable.
Source: Neelapu et al., 2023 (7).

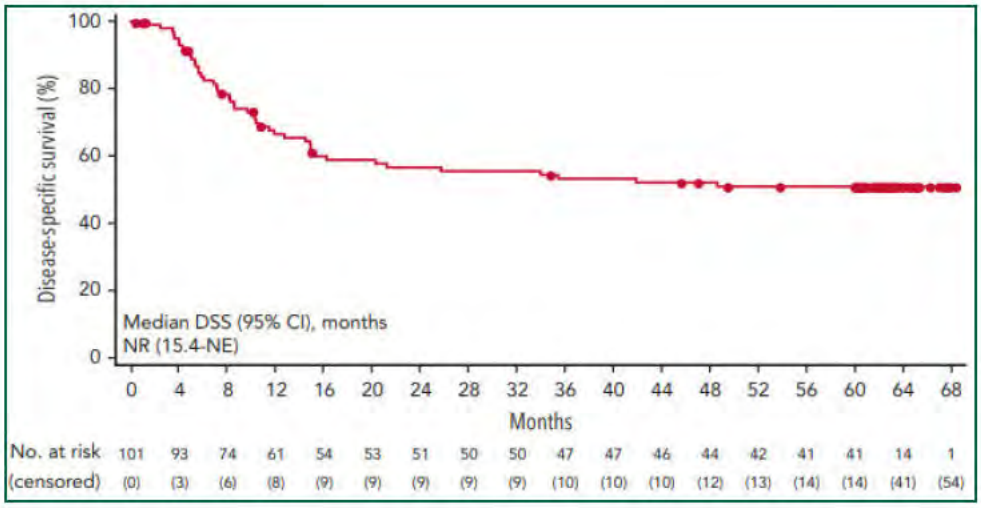


Figure 7 Kaplan-Meier survival curve of disease-specific survival among 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval; DSS = disease-specific survival; NE = not estimable; NR = not reached.
Source: Neelapu et al., 2023 (7).

6.1.4.6 Time to progression outcomes (August 2021 data cut)

TTP is an additional efficacy endpoint included in the 5-year follow up study (7). Table 25 presents TTP outcomes based on the August 11 2021 data cut. The median TTP was 6.1 months (95% CI, 4.4-29.7) for the FAS population. The Kaplan-Meier curve for TTP is presented in Figure 8.

Table 25 Summary of time to progression outcomes (August 2021 data cut)

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median TTP, months (95% CI)	6.1 (4.4–29.7)	N/A

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval; N/A = not applicable; TTP = time to progression.
Source: Neelapu et al., 2023 (7)

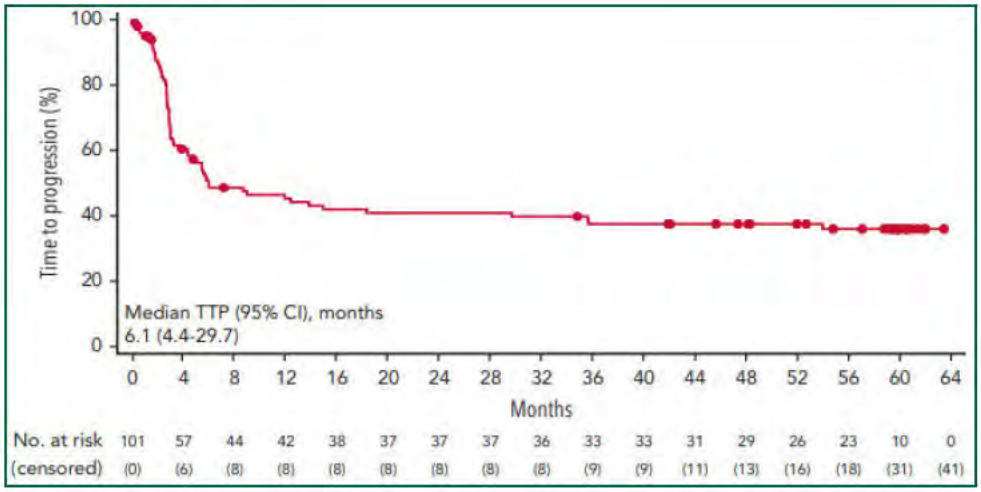


Figure 8 Kaplan-Meier survival curve of time to progression by investigator assessment among the 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval; TTP = time to progression.

Source: Neelapu et al., 2023 (7).

6.1.4.7 Time to next therapy outcomes (August 2021 data cut)

Time to next therapy is an additional efficacy endpoint included in the 5-year follow up study (7). Table 26 presents median time to next therapy outcomes based on the August 11 2021 data cut. The median time to next therapy was 8.7 months (95% CI, 6.9-34.9) among the FAS population who received treatment. The Kaplan-Meier curve for time to next therapy is presented in Figure 9.

Table 26 Summary of time to next therapy outcomes (August 2021 data cut)

Estimate	Axi-cel, N = 101 (FAS)	Axi-cel, N = 111 (ITT)
Median time to next therapy, months (95% CI)	8.7 (6.9–34.9)	9.0 (7.3–22.0)

Abbreviations: CAR = chimeric antigen receptor; CI = confidence interval.
Source: Neelapu et al., 2023 (7); Kite Pharma Inc., 2021 (77)..

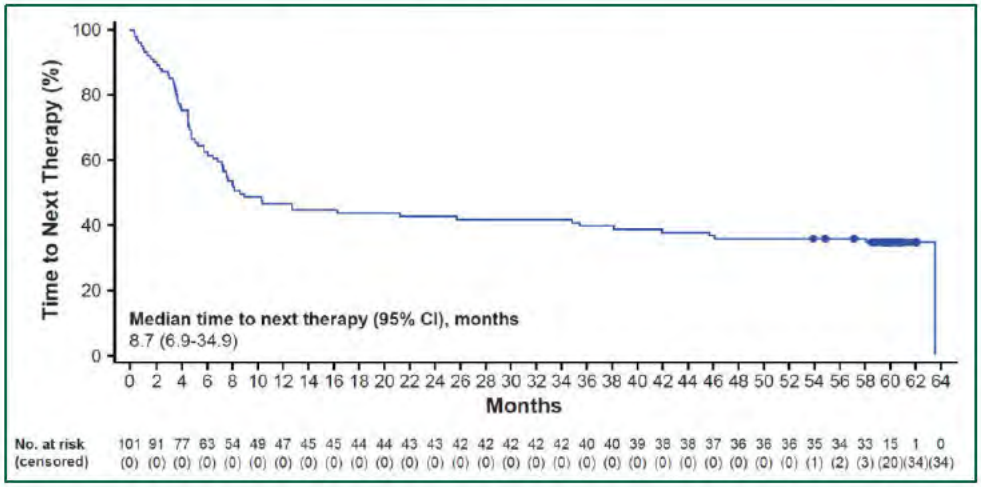


Figure 9 Kaplan-Meier survival curve of median time to next therapy among the 101 patients treated with axi-cel in cohorts 1 and 2 of phase 2, FAS, August 2021 data cut

Abbreviations: CI = confidence interval
Source: Supplementary material of Neelapu et al., 2023 (7)

6.1.5 Efficacy – results per CORAL EXT 1 & 2 (pooled)

Evidence for the key outcomes from the CORAL EXT 1 & 2 are presented the sections below. The results are presented pooled based on Maziarz et al. (2022) as individual patient data were not available. In Maziarz et al. (2022) the results are presented for the treated (FAS) and the enrolled (ITT) study populations (8).

6.1.5.1 Overall response rate

ORR was one of the primary endpoints for the CORAL EXT 1 & 2 studies (6, 52). Table 27 presents response rates pooled for the CORAL EXT 1 & 2 studies for the FAS and ITT population, respectively. Among the 170 patients in the FAS population, the investigator-assessed overall response rate was 31%. Among the 205 patients in the ITT population, the investigator-assessed overall response rate was 30% (8).

Table 27 Overall response rates (CORAL EXT 1 & 2)

Parameters	FAS population (salvage therapy) N = 170	ITT population (salvage therapy) N = 205
Overall response rate,[a] %	31	30

Abbreviations: FAS = full analysis set; ITT = intention-to-treat.
Notes: [a], per the 1999 IWG response criteria (76), Cru was included under CR.
Source: Mazairz et al., 2022, table 3 and table 5 (8).

6.1.5.2 Overall survival

OS was one of the primary endpoints in the CORAL EXT 1 & 2 studies (8). Table 28 presents Kaplan-Meier estimates for the median OS in the FAS and ITT population, respectively. The median OS in the 170 patients in the FAS population was 5.36 months (95% CI, 4.34–6.37), while the median OS in the 205 patients in the ITT population was 5.13 months (95% CI, 3.88–6.21).

Table 28 Summary of Kaplan-Meier estimates of overall survival

Kaplan-Meier estimates	FAS population (salvage therapy) N = 170	ITT population (salvage therapy) N = 205
Median OS, months (95% CI)	5.36 (4.34–6.37)	5.13 (3.88–6.21)

Abbreviations: CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat; OS = overall survival.
Source: Mazairz et al., 2022 (8).

Pooled survival curves for CORAL EXT 1 & 2 are not available.

7. Comparative analyses of efficacy

7.1.1 Differences in definitions of outcomes between studies

As described in section 6.1.2, for OS, the key difference was in the delay between choice and administration of treatment. For ZUMA-1, there is a vein-to-vein time between leukapheresis and axi-cel infusion, but in CORAL EXT 1 & 2 there is no such delay. As we used leukapheresis as an index date for the ITT population and infusion as the index date for the FAS population, this difference was negligible. For ORR, CORAL EXT 1 & 2 trials used the 1999 IWG response criteria (76), while ZUMA-1 used the revised 2007 IWG criteria (48). This is of minimal concern given that the more important difference between the two criteria is how complete response is assessed rather than how ORR is measured. For both studies, patients with unknown response or without an index treatment were considered non-responders.

7.1.2 Method of synthesis

As the ZUMA-1 study is a single-arm clinical trial, there is no direct head-to-head evidence to compare the clinical efficacy of axi-cel and salvage therapy. For this reason, an unanchored MAIC using CORAL EXT 1 & 2 has been conducted to assess the relative efficacy. An overview of the methods used is provided below. The full methods are available in Appendix C.

The evidence base was composed of individual patient level data (IPD) from the ZUMA-1 trial (74) and aggregate data extracted from the CORAL EXT 1 & 2 trials. The data used from ZUMA-1 were from the 48-month DCO (August 11, 2020) on Cohorts 1 & 2, as this

was the latest data at the time the MAIC was conducted. However, as the results from the latest ZUMA-1 data-cut (60-month DCO) are very similar, results using this DCO would likely be very similar.

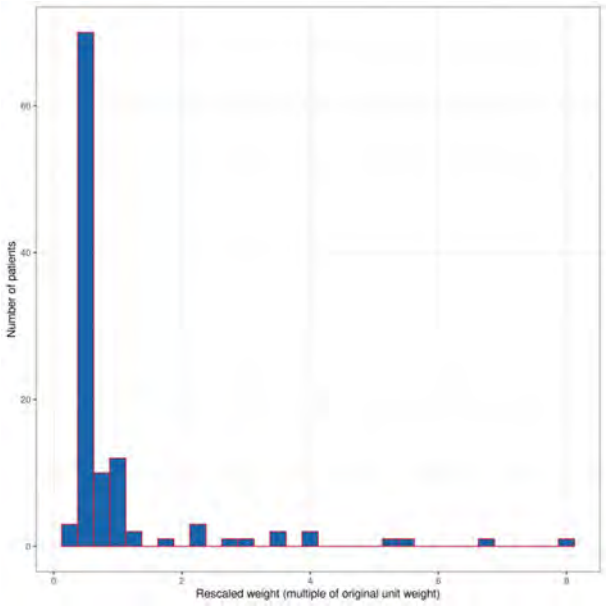
7.1.2.1 Estimating weights for ZUMA-1

A logistic propensity score model was used to estimate weights for the IPD such that the weighted mean baseline characteristics of interest for the ZUMA-1 trial matches those reported from CORAL EXT 1 & 2. As the MAIC is unanchored, both prognostic factors and effect modifiers were included in the model.

The variables included in the model were: Age at diagnosis, Ann Arbor disease stage, disease status, time from diagnosis to 2nd line, and whether patients had received prior ASCT. The choice of variables included in the model is described in detail in Appendix C.

The distribution of the weights obtained from the model are shown in Figure 8. The reweighting led to an effective sample size (ESS) of 44.58 for the ITT population and 41.93 for the FAS population. The reduction from the total sample size is less than 60%, which is in line with the values reported in the NICE DSU TSD 18 (78).

Figure 10 Distribution of weights obtained from the logistic model



Patient characteristics before and after matching adjustment are provided in in Appendix C.

7.1.2.2 Estimating relative treatment effects

Given the outcomes of interest, two forms of analyses were conducted. For the categorical outcome (ORR), a meta-analysis of the proportion for the evidence base were obtained using meta-analyses for proportions using the DerSimonian-Laird method and the proportion for axi-cel was obtained using a weighted mean.

For OS, the analyses were weighted Cox regressions, which modeled the IPD from ZUMA-1 simultaneously with the pseudo-IPD from CORAL EXT 1 & 2. The patients from ZUMA-1 were weighted according to the propensity weights, while all patients from CORAL EXT 1

& 2 were given a weight of 1. Cox regression relies on the assumption of proportional hazards, which was tested using the global test for proportionality based on Schoenfeld residuals.

7.1.3 Results from the comparative analysis

The global Schoenfeld test of the proportional hazard assumption produced p-values of 0.00013 and 0.00177 for the ITT and FAS population, respectively. This strongly indicates that the proportional hazard assumption is violated, which is also shown in the Schoenfeld residual plots (Figure 23 and Figure 24, Appendix D). Therefore, the hazard ratios produced by the Cox regression do not appropriately capture the ratio of hazards between axi-cel and salvage therapy over time and should be interpreted with caution.

Table 29 presents the unadjusted and adjusted survival estimates for OS of axi-cel vs salvage therapy as well as estimates for overall response rate based on the ZUMA-1 and CORAL EXT 1 & 2 trials. Further details are presented in the next sections.

Table 29 Results from the comparative analysis of axi-cel vs. salvage therapy for patients with r/r DLBCL; 48-month DCO

Population		Sample size		Median OS (95% CI)		Hazard ratio (95% CI)
		Axi-cel	CORAL EXT 1 & 2	Axi-cel	CORAL EXT 1 & 2	Axi-cel vs. salvage therapy
FAS	Unadjusted SMRW	101	145	25.8 months (14.6-NR)	4.34 months (3.48-5.39)	0.30 (0.22-0.42)
	Adjusted SMRW	63	145	NR (25.8-NR)	4.34 months (3.48-5.39)	0.24 (0.16-0.36)
ITT	Unadjusted SMRW	111	205	17.3 months (12.3-NR)	4.04 months (3.25-5.75)	0.38 (0.28-0.50)
	Adjusted SMRW	72	205	36.1 months (12.0-NR)	4.04 months (3.25-5.75)	0.31 (0.22-0.45)

Population		Sample size		ORR (95% CI)		Odds ratio (95% CI)
		Axi-cel	CORAL EXT 1 & 2	Axi-cel	CORAL EXT 1 & 2	Axi-cel vs. salvage therapy
FAS	Unadjusted SMRW	101	145	74.3% (64.4 – 82.2)	31.2% (24.4 – 38.8)	11.06 (6.07 – 20.16)
	Adjusted SMRW	63	145	80.9% (68.7 – 89.4)	20.7% (14.6 – 28.4)	15.26 (7.32 – 31.80)
ITT	Unadjusted SMRW	111	205	67.6% (57.9 – 76.0)	30.2% (24.1 – 37.1)	5.68 (3.43 – 9.40)
	Adjusted SMRW	72	205	76.4% (64.7 – 85.3)	26.8% (21.0 – 33.5)	9.05 (4.83 – 16.97)

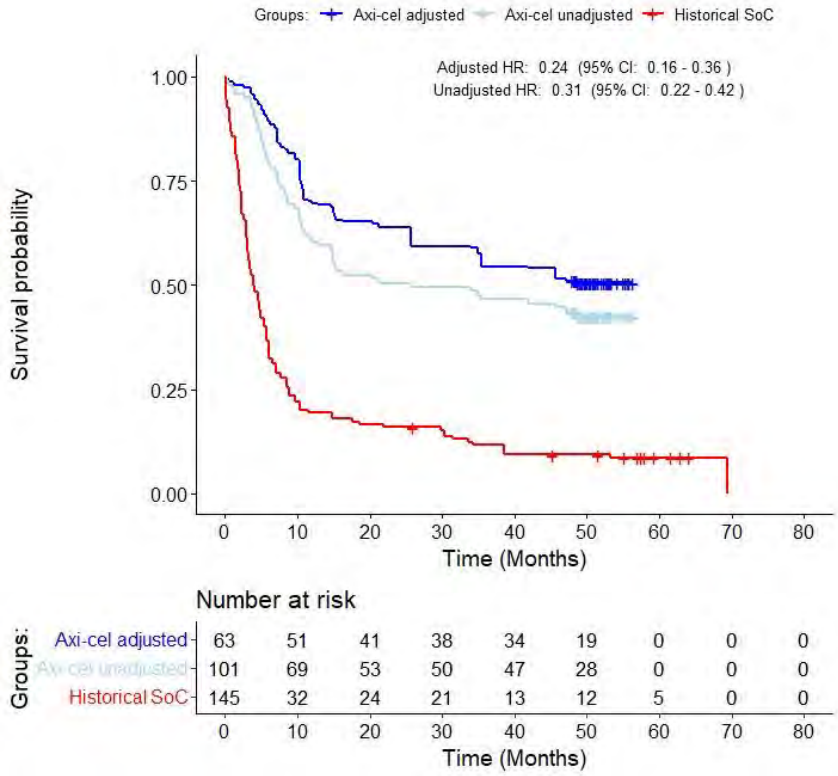
Abbreviations: Axi-cel = axicabtagene ciloleucel; CI = confidence interval; FAS = full analysis set; ITT = intention-to-treat; NR = not reached; ORR = overall response rate; OS = overall survival; SMRW = standardised mortality ratio weights, DCO= data cut-off.
Source: Kite Pharma Inc., 2022; table 8 and 10 (75).

7.1.4 Efficacy – overall survival

The median OS and hazard ratio (HR) for both the unadjusted and adjusted analyses are reported in Table 29 in section 7.1.3. Overall survival was notably shorter in the CORAL EXT 1 & 2 population than in the ZUMA-1 population. This trend is observed in the unadjusted analyses, as well as in all analyses that were adjusted for prognostic factors. The reweighting of ZUMA-1 patients led to stronger treatment effects (as shown by the longer median survival and the KM curves), which aligns with the observed population differences that generally suggested a more severe population in ZUMA-1.

Figure 11 presents the axi-cel adjusted, axi-cel unadjusted and the salvage therapy Kaplan-Meier curves for OS in the FAS population of the ZUMA-1 and CORAL EXT 1 & 2 studies. The survival curve for the adjusted axi-cel curve is shifted up but conserved the general shape of the unadjusted curve.

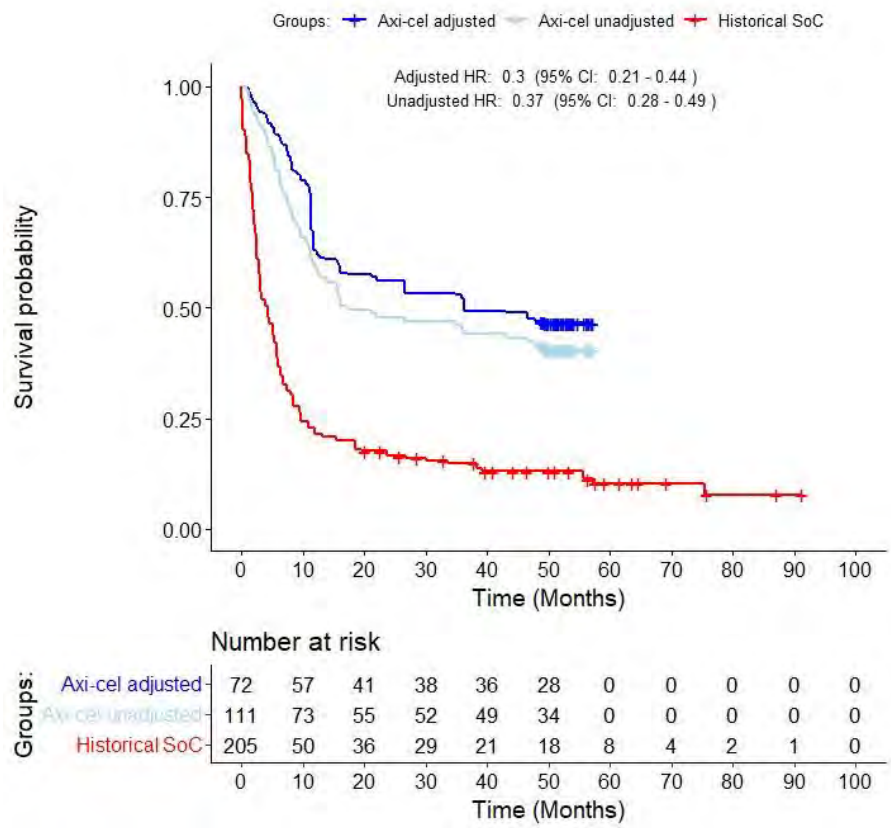
Figure 11 Kaplan-Meier plot of weighted overall survival ZUMA-1 data compared to CORAL EXT 1 & 2; FAS, SMRW, used variables



Abbreviations: Axi-cel = axicabtagene ciloleucel; HR = hazard ratio; SoC = standard of care.
Notes: In this case SoC is the same as salvage therapy.
Source: Kite Pharma Inc., 2022 (75).

Figure 12 presents the axi-cel adjusted, axi-cel unadjusted and the salvage therapy Kaplan-Meier curves for OS in the ITT population of the ZUMA-1 and CORAL EXT 1 & 2 trials. The survival curve for the adjusted axi-cel curve is shifted up but conserved the general shape of the unadjusted curve.

Figure 12 Kaplan-Meier plot of weighted overall survival ZUMA-1 data compared to CORAL EXT 1 & 2; ITT, SMRW, used variables



Abbreviations: Axi-cel = axicabtagene ciloleucel; HR = hazard ratio; SoC = standard of care.
Notes: In this case SoC is the same as salvage therapy.
Source: Kite Pharma Inc., 2022 (75).

7.1.5 Efficacy – overall response rate

Response outcomes for both the unadjusted and adjusted analyses are reported in Table 29 in section 7.1.3. Across all analyses, there was a trend of better response outcomes in ZUMA-1 patients. This was translated into statistically significant odds ratios across all analyses.

8. Modelling of efficacy in the health economic analysis

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

As previously mentioned, the ZUMA-1 study is a single-arm clinical trial. Therefore, no direct head-to-head evidence to compare the clinical efficacy of axi-cel and BSC was available in this indication. For this reason, a MAIC using CORAL EXT 1 & 2 has been conducted to enable an assessment of the relative efficacy.

A limitation of the CORAL EXT 1 & 2 MAIC data is that it does not contain PFS data; as a result, the PFS of CORAL EXT 1 & 2 MAIC was generated using the ratio of OS to PFS from ZUMA-1 as a conservative assumption. To assess the impact of this assumption, bookend scenario analyses are considered in which 100% of time alive in the salvage therapy (BSC) arm is spent in the progression-free state, or 100% of time alive in the salvage therapy

(BSC) arm is spent in the progressed state. The key efficacy inputs in the model are PFS and OS. The analysis utilized patient-level datasets from ZUMA-1 and CORAL EXT 1 & 2 MAIC (using the 48-month data cut-off (DCO) from ZUMA-1, 18 August 2020). An unadjusted comparison to the SCHOLAR-1 analysis is also available in the model.

8.1.1 Extrapolation of efficacy data

In this analysis, extrapolation of OS and PFS can be generated using single parametric curves or mixture cure models.

1) Standard parametric model: Standard parametric modelling estimates patient movement over a specified time-period through a variety of different distributions, including exponential, Weibull, lognormal, loglogistic, Gompertz, and generalized gamma. Parametric modelling can be selected for use for both treatment arms, specifically OS for salvage therapy and OS and PFS for axi-cel.

2) Mixture cure model: Mixture cure models represent a flexible approach to modelling OS for axi-cel that can potentially account for more complex hazard functions.(79) Mixture cure models work on the assumption that observed survival in the trial population represents a blend of patients who are "cured" and "not cured", and the model will determine a cure fraction based on the observed trial data and exogenous mortality data obtained from published lifetables. The survival estimates for the overall population treated with a potentially curative intervention is the weighted average of the survival among the cured and non-cured patients. For OS the survival function is described as: $S(t) = S^*(t)[p + (1-p)S_u(t)]$

   Where *S(t)* denotes survival probability at time *t*, S^* is the survival in the general population associated with background mortality, S_u is the survival probability associated with the excess disease-related risk, and *p* denotes the cure fraction. For the models, S^* will be derived from the latest published lifetables for Denmark to reflect current all-cause mortality Parameterisation was performed by the R package `flexsurvcure` in r studio (80).

The model does also include flexible spline models. However, this option is not applicable when CORAL EXT 1 & 2 MAIC is used as the base case efficacy data.

The use of MCMs is statistically feasible regardless of the intervention used, as the model will determine a cure fraction based on the observed trial data. However, good practice dictates that it should only be used when a "cure" is clinically feasible. Furthermore, single parametric models poorly predicted long-term survival in axi-cel treated patients. Therefore, the use of MCMs can be justified in this case to model the long-term OS of axi-cel patients. While the rationale for curative potential is less obvious with salvage therapy, MCMs were also used in the base case for this arm, as visual fits were better. Modelling the proportion of patients receiving salvage therapy as cured can be seen as a conservative approach. Please refer to Table 82 in Appendix D with estimated cure fractions.

The selection of base case parametric functions for OS and PFS for axi-cel and salvage therapy were informed by: Goodness-of-fit statistics (i.e., Akaike information criterion [AIC] and Bayesian information criterion [BIC]) and visual inspection to assess the concordance between predicted and observed PFS and OS curves. Finally clinical plausibility of long-term extrapolations was evaluated based on smoothed hazard plots and clinical

plausibility. Survival estimates were corrected for all-cause mortality in the Danish general population.

For both OS and PFS, MCMs are used for the base case analysis. The ITT population is used in the base case. In a scenario analysis, the use of the FAS population will be explored. Refer to Appendix D for full description on extrapolation method applied in this analysis.

8.1.1.1 Extrapolation of overall survival (OS)

Patient-level data from ITT population ZUMA-1 / CORAL EXT 1 & 2 MAIC was analysed with a mixture cure model (base case for axi-cel OS and salvage therapy OS). Table 30 summarises assumptions and extrapolation methods for OS. For scenario analysis, the use of standard parametric model (both AC and salvage therapy) will be explored using the Log-logistic distribution.

Table 30 Summary of assumptions associated with extrapolation of overall survival (OS)

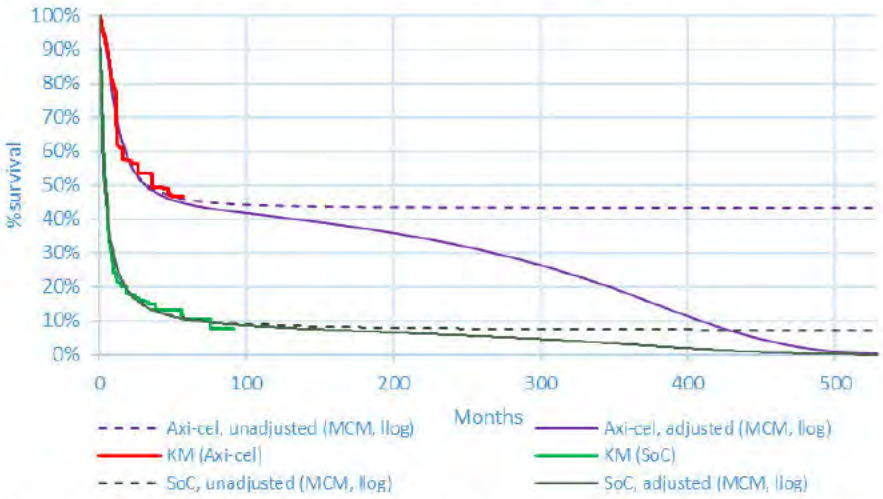
Method/approach	Description/assumption
Data input	Axi-cel: IPD data from the ZUMA-1 study – ITT population in base case (48-month DCO). Salvage therapy: CORAL EXT 1 & 2 MAIC analysis.
Model	The extrapolation of OS can be generated using single parametric curves or mixture cure models. The considered parametric distributions include Exponential, Weibull, Lognormal, Loglogistic, Gompertz, and Generalized Gamma.
Assumption of proportional hazards between intervention and comparator	No assumption on proportional hazards. Independent fits were used, as the proportional hazards assumption was clearly violated (see section D.1.3)
Function with best AIC fit	Axi-cel: SPM: Generalised gamma, MCM: Log-logistic Salvage therapy: SPM: Log-logistic, MCM: Log-logistic
Function with best BIC fit	Axi-cel: SPM: Gompertz, MCM: Log-logistic Salvage therapy: SPM: log-logistic, MCM: log-logistic
Function with best visual fit	Axi-cel: MCM visual fits were generally better than visual fits from standard parametric models. All fitted MCMs produced very similar visual fits Salvage therapy: MCM visual fits were generally better than visual fits from standard parametric survival models. All fitted MCMs produced very similar visual fits.
Function with best fit according to evaluation of smoothed hazard assumptions	Axi-cel: MCM hazard profiles were generally closer to the smoothed hazard for the observed data than the standard parametric model hazard profiles. Of the fitted MCMs, the log-logistic and log-normal produce the best visual fit for hazard profiles Salvage therapy: All hazard profiles were relatively similar to the smoothed hazard for the observed data. For the MCMs, the log-logistic, log-normal, and generalized gamma models produced the best visual fits.
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility.
Function with the best fit according to external evidence	Axi-cel: N/A Salvage therapy: N/A
Selected parametric function in base case analysis	Axi-cel: MCM with Loglogistic distribution Salvage therapy: MCM with Loglogistic distribution
Adjustment of background mortality with	Yes

Method/approach	Description/assumption
data from Statistics Denmark	
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	Yes. A logistic regression is used to predict the proportion of individuals who are 'cured' (who experience long-term remission), and parametric survival modelling is used to estimate survival in those who are not cured. Based on these two curves, and the expected proportion of patients who are cured, an average survival curve can be predicted by weighting the 'cured' and non-cured survival curved. Thus, in the MCMs the "cure point" is the point where all non-cured individuals are dead, and only background mortality is contributing to decreases in modelled survival.

Abbreviation: Axi-cel = axicabtagene ciloleucel, IPD= individual patient data, OS = overall survival, BSC = best supportive care, SPM= standard parametric model, MCM= mixture cure model.
Source: Kite Pharma, Inc. Survival analysis ZUMA-1 vs CORAL EXT 1 & 2 MAIC (2023) (81)

The observed and predicted survival for the base case (MCM, log-logistic distribution for both axi-cel and salvage therapy) are presented in Figure 13. As the mixture cure models predict a proportion of patients that are cured and have a hazard of 0, predicted survival is shown both before and after adjustment for background mortality.

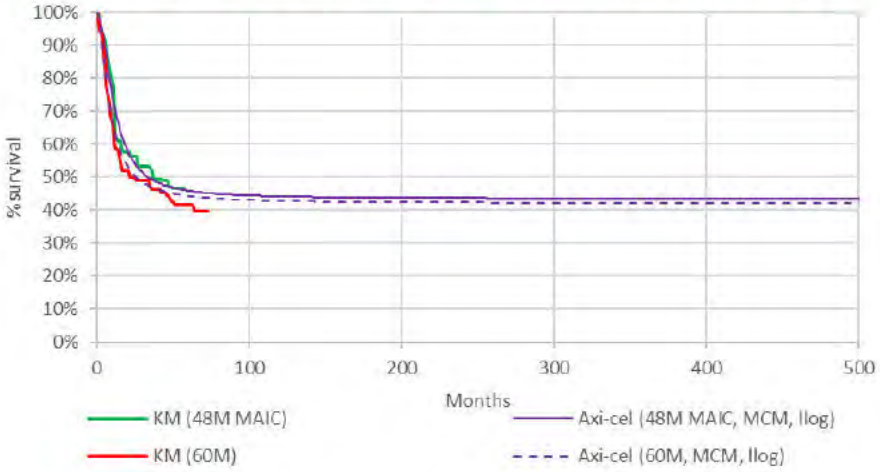
Figure 13. Observed and predicted OS for axi-cel and salvage therapy base case



Abbreviations: OS= overall survival, MCM= mixture cure model, SoC= standard of care (salvage therapy), KM= Kaplan-Meier

The MAIC against CORAL EXT 1 & 2 is done using the 48-month DCO from ZUMA-1, rather than the more recent 60-month DCO. However, OS results from the two data-cuts are very similar, with a median OS of 25.8 months for patients treated with axi-cel at both data-cuts. The observed and modelled OS for the unadjusted ZUMA-1 60-month DCO as well as the KM and modelled OS from the 48-month DCO MAIC are shown in Figure 14. As re-weighting to match the CORAL EXT 1 & 2 population led to improved OS in ZUMA-1, the KM curves from the MAIC are slightly better; however modelled OS between the two data-cuts is very similar and the cure fractions converge.

Figure 14. KM and modelled OS for ZUMA-1 (unadjusted 60-month DCO and MAIC 48-month DCO)



Abbreviations: OS= overall survival, DCO= data cut-off, KM= Kaplan-Meier

8.1.1.2 Extrapolation of progression-free survival

Patient-level data from ITT population ZUMA-1 was analysed with a MCM (base case for axi-cel PFS) – PFS was not included in the MAIC against CORAL EXT 1 & 2, as PFS was not reported in the CORAL EXT 1 & 2; as the reweighting done in the MAIC let to improved OS estimates, using unadjusted PFS is a conservative approach. Since PFS data was not available for salvage therapy, it was assumed in the base case for salvage therapy, that the ratio between PFS and OS at each time point is the same in the salvage therapy arm as in the axi-cel arm; this is likely a conservative assumption as PFS is likely worse in the salvage therapy arm, in the absence of curative therapy. Table 31 summarises assumptions and extrapolation methods for PFS. In a scenario analysis, axi-cel PFS extrapolation using the Gompertz distribution will be explored.

Table 31 Summary of assumptions associated with extrapolation of progression-free survival (PFS)

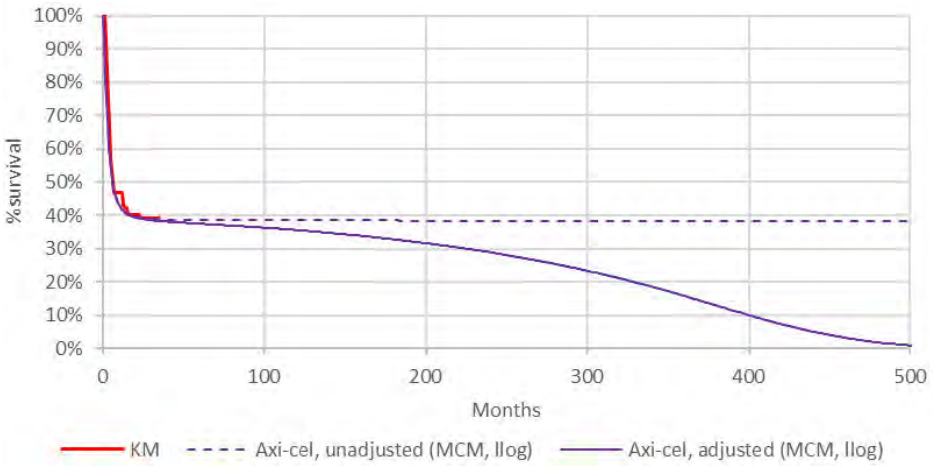
Method/approach	Description/assumption
Data input	Axi-cel: IPD data from the ZUMA-1 study – ITT population (24-month DCO). Salvage therapy: Since no PFS data was obtained from the CORAL EXT 1 & 2 MAIC to inform the salvage therapy arm, the PFS curves were inferred by using the ratio of OS to PFS from ZUMA-1.
Model	The extrapolation of PFS can be generated using single parametric curves or mixture cure models. The considered parametric distributions include Exponential, Weibull, Lognormal, Loglogistic, Gompertz, and Generalized Gamma.
Assumption of proportional hazards between intervention and comparator	No assumption on proportional hazards
Function with best AIC fit	Axi-cel: MCM using log-logistic Salvage therapy: N/A
Function with best BIC fit	Axi-cel: MCM using log-logistic Salvage therapy: N/A

Method/approach	Description/assumption
Function with best visual fit	Axi-cel: For the MCMs, all models generated very similar fits, with the log-logistic being slightly closer to the observed data in the beginning of the curve. Salvage therapy: N/A
Function with best fit according to evaluation of smoothed hazard assumptions	Axi-cel: Smooth hazard pots were not available for PFS Salvage therapy: N/A
Validation of selected extrapolated curves (external evidence)	Clinical experts' opinions on clinical plausibility
Function with the best fit according to external evidence	Axi-cel: N/A Salvage therapy: N/A
Selected parametric function in base case analysis	Axi-cel: N/A Salvage therapy: N/A
Adjustment of background mortality with data from Statistics Denmark	All models are adjusted for background mortality with data from statistics Denmark
Adjustment for treatment switching/cross-over	No
Assumptions of waning effect	No
Assumptions of cure point	For the mixture cure models, a cure point is calculated based on the observed data. For the SPM models, the model allows for definition of a cure-point, after which patients that are not progressed are considered cured.

Abbreviations: Axi-cel = axicabtagene ciloleucel, IPD= individual patient data, BSC= best supportive care, N/A = not applicable, OS= overall survival, PFS= progression-free survival, SPM= standard parametric model, DCO= data cut-off.
Sorce: Kite Pharma, Inc. Survival analysis ZUMA-1 vs CORAL EXT 1 & 2 MAIC (2023) (81)

The observed and predicted progression free survival for the base case (MCM, log-logistic distribution for both axi-cel) are presented in Figure 15. As the mixture cure models predict a proportion of patients that are cured and have a hazard of 0, predicted progression free survival is shown both before and after adjustment for background mortality.

Figure 15. Observed and predicted PFS for axi-cel, base case



Abbreviations: PFS= progression-free survival, KM= Kaplan-Meier, MCM= mixture cure model

8.1.2 Calculation of transition probabilities

Not applicable.

8.2 Presentation of efficacy data from [additional documentation]

Not applicable.

8.3 Modelling effects of subsequent treatments

Re-treatment

Nine of 101 subjects (8.9%) were retreated with axi-cel in ZUMA-1 (estimate is derived from the 2017 CSR DCO) (82). [redacted] Of the nine patients who underwent conditioning chemotherapy for retreatment, all nine went on to receive retreatment; there is therefore no requirement to apply a cost multiplier for a proportion who underwent conditioning chemotherapy but did not progress to retreatment. [redacted]

Subsequent SCT

Two subjects of 101 (2%) underwent allogeneic SCT while in response after axi-cel retreatment in Phase 2 of ZUMA-1 (9); no subjects underwent autologous SCT after responding to axi-cel treatment. The cost of allogeneic SCT is therefore applied to 2% of patients in the axi-cel arm of the model (note: only transplants received while in remission after axi-cel are included. Therefore: mITT population). However, it is unlikely that SCT post CAR-T treatment will be offered in clinical practice. For the BSC arm, it would be conservative to assume that no patients in the salvage therapy arm undergo allogeneic or autologous SCT. The use of SCT in the current treatment landscape is informed by a recent Danish real-world evidence study by Al-Mashhadi et al. (35). Based on this publication, 4% received high-dose therapy/autologous SCT and 4% received allogeneic SCT in the third line. This rate can be supported by NoMA's Yescarta® assessment (10% of patients in the salvage therapy arm will undergo allogeneic SCT based on Norwegian clinical experts) (NoMA

Yescarta® page 28 / 121) (83). Furthermore, comparing with the CORAL EXT 1 & 2 data, 29% of patients eventually underwent SCT (ASCT 21.2%, allogeneic SCT 7.5%), providing a broader context for the range of potential outcomes (6).
Therefore, the weighted cost of allogeneic SCT or autologous SCT is therefore applied to 8% of patients in the comparator arm (4% allo-SCT/4% auto-SCT) for the base case. Additionally, two scenarios explore the impact of two extremes with 29% (ASCT 21.2%, allogeneic SCT 7.5%) observed from the comparative data, and with 0% (6).

8.4 Other assumptions regarding efficacy in the model

Long-term progression-free

In the base case, a mixture cure model is used, meaning that a proportion of patients are modelled as being cured, thus the cancer-specific mortality asymptotically approaches zero. Therefore, modelled survival is adjusted for general population mortality derived from lifetables (as visualized in Figure 13).
If standard parametric survival models are used, it is still expected that patients who are progression-free in the long-term will no longer experience cancer-specific mortality, quality of life, or costs. Functionality is therefore included in the model such that separate time points may be defined, beyond which:

- Mortality derived from general population life tables is applied in the PF state.
  - This time point is set to 60 months by default when parametric survival models are used.
  - Where this point is not defined, general population life tables are used where the monthly mortality estimated by the modelled extrapolation falls below that estimated based on life tables.
  - In either case, at the point where life tables are used in the PF state, the greater of extrapolated mortality or general population mortality is assumed in the PD state until the point at which the OS and PFS curves meet; after this, it is assumed that all modelled individuals remaining alive are progression-free.
- General population utility values are applied in the progression-free state.
  - This time point is 24 months in the model base case.
- No cancer specific costs are applied in the progression-free state.
  - This time point is 24 months in the model base case.

As those who are in long-term remission following DLBCL may be expected to have higher mortality and worse QoL than the general population, functionality is included such that multipliers may be applied to general population life tables and utility values. In the absence of data, these multipliers are set to be 1.09. For both mixture cure and standard parametric models, this SMR of 1.09 was applied to patients in both treatment arms who were alive after 60 months to address the uncertainty of excess mortality for long-term survivors. A scenario analysis explores the impact of a SMR equal to 1, indicating that observed mortality is in line with expected mortality. Table 32 and Table 33 presents other model assumptions applied in the MCM and SPM model, respectively.

Table 32 Other model assumptions applied – MCM model (base case)

Assumption	Rationale	Base case value
Standardised mortality ratio	Patients who recover have an increased risk of mortality compared to the general population. The SMR of 1.09 is applied to all patients alive after 60 months for both arms	SMR of 1.09 used for all patients after 60 months

Assumption	Rationale	Base case value
Cut-off after which general population mortality is used (axi-cel)	The cutoff functions as a hard-coded "cure point" beyond which all living patients are considered cured. Under the mixture cure models, no such hard-coded cure point is needed, as general population mortality is automatically applied when all non-cured patients are dead.	999 months
Cut-off after which general population mortality is used (salvage therapy / BSC)	The cutoff functions as a hard-coded "cure point" beyond which all living patients are considered cured. Under the mixture cure models, no such hard-coded cure point is needed, as general population mortality is automatically applied when all non-cured patients are dead.	999 months
Set OS to PFS at defined time point	Suggested by ERG in initial NICE submission for UK	Convergence at 999 months

Abbreviations: ERG= Evidence Review Group, NICE= National Institute for Health and Care Excellence, OS= overall survival, PFS= progression-free survival, SMR= standardised mortality ratio.

Table 33 Other model assumptions applied - SPM model

Assumption	Rationale	Base case value
Standardised mortality ratio	Patients who recover have an increased risk of mortality compared to the general population. The SMR of 1.09 is applied to all patients alive after 60 months for both arms	SMR of 1.09 used for all patients after 60 months
Cut-off after which general population mortality is used (axi-cel)	To function as a hard-coded "cure point" beyond which all living patients are considered cured	60 months
Cut-off after which general population mortality is used (salvage therapy / BSC)	To function as a hard-coded "cure point" beyond which all living patients are considered cured	60 months
Set OS to PFS at defined time point	Suggested by ERG in initial NICE submission for UK	Convergence at 999 months

Abbreviations: ERG= Evidence Review Group, NICE= National Institute for Health and Care Excellence, OS= overall survival, PFS= progression-free survival, SMR= standardised mortality ratio.

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

Table 34 and Table 35 presents the estimates in the model for the modelled average OS and PFS, respectively. The modelled estimates are undiscounted, without half-cycle correction and adjusted for background mortality of the Danish population, as requested by the DMC. The individual results of ZUMA-1 are only provided for the FAS population.

Table 34 Estimates in the model - OS

	Modelled average OS (reference in Excel)	Modelled median OS (reference in Excel)	Observed median OS from ZUMA-1
Axi-cel	[redacted]	[redacted]	[redacted]
Salvage therapy	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel = axicabtagene ciloleucel; OS = overall survival.

Table 35 Estimates in the model - PFS

	Modelled average PFS (reference in Excel)	Modelled median PFS (reference in Excel)	Observed median from ZUMA-1 and pooled CORAL EXT 1 & 2
Axi-cel	[redacted]	[redacted]	[redacted]
Salvage therapy	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel = axicabtagene ciloleucel; PFS = Progression-free survival.

Table 36 presents the modelled average treatment length and time in the model health states.

Table 36 Overview of modelled average treatment length and time in model health state, undiscounted and not adjusted for half cycle correction

Treatment	Treatment length [years]	PF [years]	PD [years]
Axi-cel	[redacted]	[redacted]	[redacted]
Salvage therapy	[redacted]	[redacted]	[redacted]

Abbreviations: Axi-cel = axicabtagene ciloleucel; PF= progression-free, PD= progressed disease.

9. Safety

9.1 Safety data from the clinical documentation

In ZUMA-1, the safety population includes all subjects treated with any dose of axi-cel in phase 1 (N = 7) and 2 (N = 101). In ZUMA-1, all AEs reported are treatment-emergent AEs (TEAEs) hence, the term AE will be used to indicate TEAE. TEAEs are defined as AEs with an onset on or after the first dose of conditioning chemotherapy. TEAEs that occurred on or after the day of axi-cel infusion were summarised in safety analyses. The latest safety data available is from the 24-month data cut-off (11 August 2018). At the time of this analysis, all subjects had had the opportunity to be followed for a minimum of 24 months or until death, with a median follow-up of 27.1 months (9). This data is presented in Table 37.

No information on safety was available for the CORAL EXT 1 & 2 studies. However, information on some safety events was available for the CORAL 1 (median follow-up time of 27 months) and CORAL 2 (median follow-up time of 44 months) study. This information is presented in Table 37 based on publications by Gisselbrecht et al. (10, 11). A comparative analyses of safety events presented in Table 37 was not feasible due to limited data.

Table 37 Overview of safety events in ZUMA-1 (24-month data cut), CORAL 1 (3-year follow-up), and CORAL 2 (4-year follow-up)

	Axi-cel (N=108) (ZUMA-1)	R-ICE (N=197) (CORAL 1)	R-DHAP (N=191) (CORAL 1)	Rituximab (N=116) (CORAL 2)	Observation (N=119) (CORAL 2)
Number of adverse events, n	N/A	N/A	N/A	162	99
Number and proportion of patients with ≥1 adverse events, n (%)	108 (100)	N/A	N/A	N/A	N/A
Number of serious adverse events*, n	N/A	90	120	N/A	N/A

	Axi-cel (N=108) (ZUMA-1)	R-ICE (N=197) (CORAL 1)	R-DHAP (N=191) (CORAL 1)	Rituximab (N=116) (CORAL 2)	Observation (N=119) (CORAL 2)
Number and proportion of patients with ≥ 1 serious adverse events*, n (%)	60 (56)	58 (29)	68 (36)	N/A	N/A
Number of Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 3 events, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 CTCAE grade ≥ 3 events§, n (%)	106 (98)	N/A	N/A	N/A	N/A
Number of adverse reactions, n	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients with ≥ 1 adverse reactions, n (%)	107 (99)	N/A	N/A	N/A	N/A
Number and proportion of patients who had a dose reduction, n (%)	N/A	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment regardless of reason, n (%)	10 (9)	N/A	N/A	N/A	N/A
Number and proportion of patients who discontinue treatment due to adverse events, n (%)	5 (5)	N/A	N/A	N/A	N/A

Abbreviations: Axi-cel = axicabtagene ciloleucel; CTCAE = Common Terminology Criteria for Adverse Events; N/A = not available; R-DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; R-ICE = rituximab, ifosfamide, carboplatine, and etoposide.

*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

§ CTCAE v. 5.0 must be used if available.

Sources: Gisselbrecht et al., 2010 (CORAL 1) (10); Gisselbrecht et al., 2012 (CORAL 2) (11); ZUMA-1 CSR, 2018, table 29 and 14.1.2 (9).

In Table 38, the frequency of all serious adverse events with frequency of ≥ 5% recorded in ZUMA-1 are reported.

Frequency of all serious adverse events with frequency of ≥5% recorded in CORAL 1 & 2 or CORAL EXT 1 & 2, is not available. For CORAL 1 the following information is available: the most common serious adverse events were infections, with a similar rate of infection as a result of neutropenia (16%) in both arms (10). For CORAL 2, the following information is available: fatal outcomes were observed in six patients in the rituximab group and three patients in the observation group (11).

Table 38 Serious adverse events* in ZUMA-1 (24-month DCO)

Adverse events, n (%)	Axi-cel (N=108)
	Number of patients with adverse events

Encephalopathy	20 (19)
Lung infection	8 (7)
Pyrexia	8 (7)
Febrile neutropenia	6 (6)
Pneumonia	6 (6)
B-cell lymphoma	5 (5)
Confusional state	5 (5)

Abbreviations: Axi-cel = axicabtagene ciloleucel, DCO= data cut-off.
*A serious adverse event is an event or reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.
Source: ZUMA-1 CSR, 2018, table 14.3.2.4.0.1 (9).

The incidences of AEs associated with axi-cel in the model were based on data from the ZUMA-1 trial (cohort 1 and 2 combined, primary analysis DCO: Jan 2017 (82)). In the economic model, only grade 3 or higher adverse events occurring in ≥10% of subjects in ZUMA-1 were included (with the exception of cytokine release syndrome which does not have the ≥10% cut-off). The model separately considers AEs related to "conditioning chemotherapy" (modelling comparator purpose) and AEs relating to axi-cel treatment (as reported in Table 51 and Table 50, respectively, of the clinical study report (Jan 2017 DC) (82)). The Jan 2017 DCO was used for modelling AEs, since the latest DCO Aug 2018 did not report the tables: "Subject Incidence of Conditioning Chemotherapy-related AEs Occurring in ≥ 10% of Subjects in Phase 2 Cohort 1 and 2 Combined" and the "Subject Incidence of Grade 3 or Higher Axicabtagene Ciloleucel-related AEs Occurring in ≥ 10% of Subjects in Phase 2 Cohorts 1 and 2 Combined" for conditioning chemotherapy and axi-cel, respectively.

The following AEs are modelled in the base case:

- grade ≥3 axi-cel-related AEs occurring in ≥10% of subjects in ZUMA-1 (82)
- grade ≥3 conditioning chemotherapy-related AEs occurring in ≥10% of subjects in ZUMA-1 (82)
- grade ≥3 treatment-emergent cytokine release syndrome (CRS) occurring in ZUMA-1 (13% of subjects). Note that the latest DCO (August 2018) reports a lower incidence of 11%, hence it is considered as a conservative approach to model the 13% incidence of CRS instead of 11% (9). However, the model allows for a scenario using the 11% incidence.
- any grade treatment-emergent hypogammaglobulinemia occurring in ZUMA-1 (11% of subjects (according to CSR with 2017 DCO (82)), and 16% of subjects (according to the latest DCO 2018 (9)). Although the latest data shows a slightly higher incidence of hypogammaglobulinemia, the older data is employed to maintain alignment across safety data. However, the model allows for a scenario using the 16% incidence.

It should be noted that only CRS and hypogammaglobulinemia are associated with costs in the model. The remaining AEs included in the model are solely utilized for disutility decrements. In the base case, AE disutility decrements are not applied, considering that the ZUMA-1 trial is considered to encompass the impact of reported AEs. This choice makes the utilization of the older data cut-off for AE rates, even though not influencing cost, a reasonable choice for the base case analysis.

Cohorts 4 and 6 are reported in the model. However, none of the analyses are carried out using cohort 4 and 6 (these are simply presented as alternative strategies for preventing adverse events, however, they have considerably shorter follow-up and should not be considered for scenario analyses).

Table 39 presents the AEs used in the model, as reported in the ZUMA-1 CSR DCO Jan 2017 (82).

Table 39 Adverse events used in the health economic model

Adverse events	Axi-cel	Salvage therapy		
	Frequency used in economic model for intervention	**Frequency used in economic model for comparator**	**Source**	**Justification**
Adverse event, n (%)	95 (95)	95 (95)	ZUMA-1 CSR (DCO JAN 2017) (82)	Grade ≥3 AEs with ≥ 10% incidence (82)
Axi-cel related AE	64 (63)	N/A	Same as above	Same as above
Cytokine release syndrome	13 (13)	N/A	Same as above	Same as above
Encephalopathy	21 (21)	N/A	Same as above	Same as above
Febrile neutropenia	17 (17)	N/A	Same as above	Same as above
Hypotension	11 (11)	N/A	Same as above	Same as above
Neutropenia	13 (13)	N/A	Same as above	Same as above
Pyrexia	12 (12)	N/A	Same as above	Same as above
Conditioning chemotherapy-related AE		86 (85)	Same as above	Same as above
Anaemia	N/A	41 (41)	Same as above	Same as above
Febrile neutropenia	N/A	29 (29)	Same as above	Same as above
Hypophosphataemia	N/A	11 (11)	Same as above	Same as above
Leukopenia	N/A	17 (17)	Same as above	Same as above
Lymphocyte count decreased	N/A	19 (19)	Same as above	Same as above
Neutropenia	N/A	35 (35)	Same as above	Same as above
Neutrophil count decreased	N/A	28 (28)	Same as above	Same as above
Platelet count decreased	N/A	13 (13)	Same as above	Same as above
Thrombocytopenia	N/A	23 (13)	Same as above	Same as above
White blood cell count decreased	N/A	27 (27)	Same as above	Same as above
Other			Same as above	
Hypogammaglobulinemia (grade 1/2)	11 (11)	N/A	Same as above	Grade 1 or 2 AE (did not present as a grade 3 or 4 in any patients)

Abbreviations: AE = adverse event; Axi-cel = axicabtagene ciloleucel; CSR = clinical study report; DCO = Data cut-off, N/A= not available

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

Not applicable as safety data is from the ZUMA-1 trial are both for the axi-cel treatment arm and the conditioning chemotherapy arm in the ZUMA-1 CSR.

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

The health state utility values (HSUVs) used in the model base case were taken from the ZUMA-1 trial (safety population) (84). As per the Danish guidelines, the model uses utilities with DK tariffs, using the value set informed by Jensen et al (85). For scenario analysis, the UK weighted HSUVs from ZUMA-1, HSUVs from the JULIET trial (55) (found in the NoMA Kymriah® assessment, page 67/142) (54), and an additional source of utility data (NICE TA of bevacizumab, sorafenib, sunitinib and temsirolimus in advanced/metastatic renal cell carcinoma) were included (57, 86) (NICE TA306, ERG report, Table 27). The HSUVs are applied in both axi-cel arm and salvage therapy arm.

The AE disutilities were sourced from previous NICE appraisals and published literature. Age-specific general population utility values were taken from the DMC's appendix: "Aldersjustering for sundheds-relateret livskvalitet". Table 40 summarizes the included HRQoL instruments.

Table 40 Overview of included HRQoL instruments

Measuring instrument	Source	Utilization
EQ-5D-5L	ZUMA-1 (84)	To inform the PF and PD HSUVs

Abbreviations: EQ-5D-5L= EuroQol-5 Dimension 5-levels, HRQoL= health-related quality of life, PF= progression-free, PD= progressed disease, HSUV= health state utility value.

10.1 Presentation of the health-related quality of life

10.1.1 Study design and measuring instrument

In ZUMA-1, HRQoL was collected using the EQ-5D-5L. This aligns with the DMC guidelines (EQ-5D-5L is the preferred instrument for measuring life quality) (47). The data used to inform the utility analysis came from the safety management study (SMS) cohort 3 (NCT02348216; DCO: August 11, 2017) (84). The study sample consists of 34 patients who received axi-cel. The SMS was designed to investigate ways to further improve safety of axi-cel therapy in R/R-LBCL. The utility values for the PF health state included values for patients who were in complete remission, partial remission, and stable disease. The utility value for the PD health state included patients with progressive or relapsed disease.

Patients experienced a decrease in utility scores from screening to week 4, most likely because of a disutility associated with the timing of the transient toxicities associated with CAR-T therapy. By month 3 and month 6, the patient utilities had increased back to beyond their original levels showing that patient HRQL was improved by axi-cel therapy (refer to Table 46).

10.1.2 Data collection

Utility values were measured at screening, week 4, month 3 and month 6 post axi-cel infusion. Complete case analysis was undertaken i.e., patients with both disease status and corresponding EQ-5D-5L data were included in the analysis, regardless of the time point and intrapatient correlation. Patients without complete EQ-5D-5L or disease status were excluded from the analysis as multiple imputation was not undertaken. No further

information can be provided. Information on the pattern of missing data and completion from the ZUMA-1 trial is not available and thus cannot fully be reported (84).

Table 41 Pattern of missing data and completion, EQ-5D-5L data (DK)

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/at screening	33	N/A	N/A	N/A
Week 4	33	6 (18.2%)	N/A	N/A
Month 3	33	13 (39.4%)	N/A	N/A
Month 6	33	26 (78.8%)	N/A	N/A

Abbreviations: EQ-5D-5L= EuroQol-5 Dimension 5-levels, HRQoL= health-related quality of life, N/A= not available.
Source: ZUMA-1 safety management study (SMS) cohort 3 (NCT02348216; data cut-off: August 11, 2017) (84)

10.1.3 HRQoL Results

There were 49 complete observations in the PF health state and 5 complete observations in the PD health state. The mean EQ-5D-5L (DK) in the PF health state was 0.794 and 0.707 in the PD health state (84). EQ-5D-5L results by time point (mean change from baseline) is reported in Table 42 as well as illustrated in Figure 16 EQ-5D-5L (DK weighted) mean change from baseline for axi-cel, ZUMA-1.

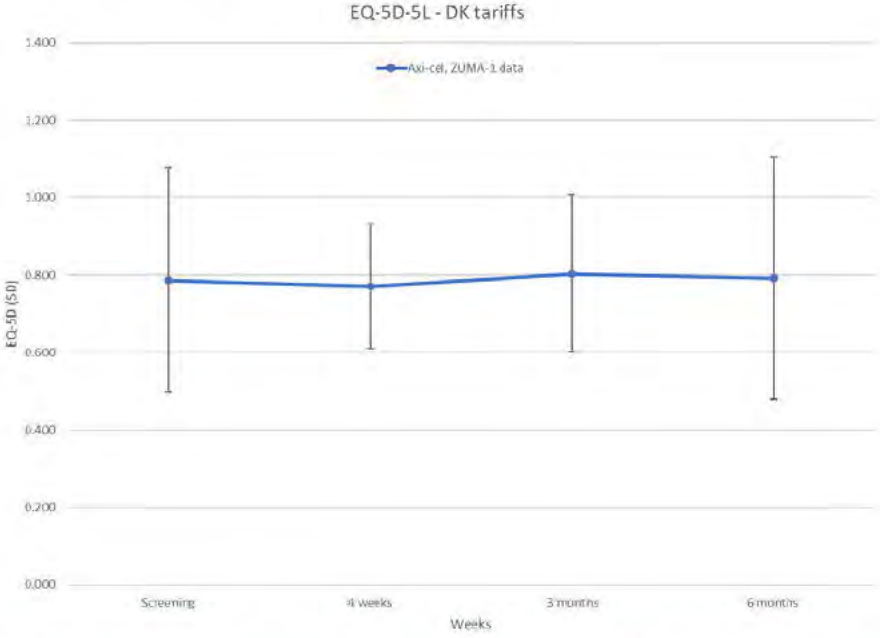


Figure 16 EQ-5D-5L (DK weighted) mean change from baseline for axi-cel, ZUMA-1

Abbreviations: EQ-5D-5L= EuroQol-5 Dimension 5-levels, axi-cel = Axicabtagene ciloleucel.

[redacted]

	Axi-cel		BSC		Axi-cel vs BSC
	N	Mean (SD)*	N	Mean (SE)	Difference (95% CI) p-value

	Axi-cel		BSC		Axi-cel vs BSC
Baseline/at screening	33	[redacted]	N/A	N/A	N/A
Week 4	27		N/A	N/A	N/A
Month 3	20		N/A	N/A	N/A
Month 6	7		N/A	N/A	N/A

Abbreviations: HRQoL = Health related quality of life; BSC = best supportive care; Axi-cel = Axicabtagene ciloleucel; EQ-5D-5L= EuroQol-5 Dimension 5-levels, N/A= not available.
Note: SE could not be reported (only by response category). SD is reported for the remaining
Source: ZUMA-1 EQ-5D-5L data (84)

The ZUMA-1 health state utilities were used in the base case analysis. With limited data available for EQ-5D in the relevant population, the ZUMA-1 estimates offer valuable insights into patient HRQoL during treatment. While acknowledging uncertainties in the PD HSUV estimate (only 5 complete observations), the UK ERG group suggested it is unlikely to be the primary driver of cost-effectiveness due to the relatively short survival time after progression for most patients (NICE TA872, committee papers, section 4.2.7.2)) (87). However, to acknowledge the limitations, scenario analyses will explore alternative scenarios and assess the robustness of our base case assumptions.

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

10.2.1 HSUV calculation

As described in section 10.1, the HSUVs for the PF and PD health state was derived from the EQ-5D-5L collected in the ZUMA-1 trial. The base case analysis of the economic model uses the HSUV using Danish tariffs, using the methodology provided by Jensen et al (85). Age and gender matched generation population utility values in the PFS state are assumed from month 24. This considers the expected long-term remission following axi-cel, for which patients are likely to have the same quality of life as the general population. This assumption has been validated by UK clinical experts (87) (NICE TA872, committee papers, section B.3.10).

For scenario analyses, tree scenarios have been explored: 1) using the EQ-5D-3L mean index scores from ZUMA-1 converted to UK value set as per Lin et al 2018 (88), 2) utilizing EQ-5D mean index scores derived from the SF-36 data from JULIET, converted to the UK value set using the mapping algorithm outlined in Rowen et al. (89), and 3) using utility values from NICE TA306/TA178 in second-line renal cell carcinoma (57, 86) (NICE TA306, ERG report, Table 27). Here, utility data was identified from published sources for similar patient populations, similar expected survival and disease progression as well as expected similar nature of the disease and QoL. Scenario analyses using NICE TA306 has been used for other scenario analyses in previous HTA assessments (56) (55).Scenario analyses using NICE TA306 has been used for other scenario analyses in previous NICEHTA assessments (55) (54).

In the base case and in all scenario analyses, HSUV are age-adjusted according to the methods described in the Appendiks: Aldersjustering for sundhedsrelateret livskvalitet of the DMC guidelines.

10.2.1.1 Mapping

For base case, the HSUVs were informed by the ZUMA-1 trial, based on EQ-5D-5L scores. HSUVs were derived using DK preference scores provided by Jensen et al. (85).

For scenario analysis using the UK EQ-5D-3L values, the EQ-5D-5L data collected in ZUMA-1 was subsequently converted to EQ-5D-3L by use of a crosswalk algorithm (Van Hout et al. 2012) (90) and the EQ-5D-3L descriptive scores were converted to the EQ-5D-3L index with UK population-based health utility values by a UK valuation algorithm (Lin et al) (88). Appendix F describes the crosswalk algorithm that was used to convert EQ-5D-5L to EQ5D-3L. Scenario analysis was also conducted using utility values (PF and PD) from the JULIET trial, based on SF-36 scores. SF-36 scores were mapped to EQ-5D scores using a mapping algorithm provided by Rowen et al. (89). Further mapping description of SF-36 to EQ-5D is described Appendix F.

10.2.2 Disutility calculation

Disutilities are included in the model as scenario analysis but as they are derived from the literature, they are presented in section 10.3.4 (refer Section 9.1 for justification). Durations were calculated as the total number of days that each patient experiences a specific AE, even if that event was experienced more than once. Source of duration of AEs are taken from the ZUMA-1 trial.

Table 43 Overview of duration of adverse events

Adverse event	Duration (days)	Source
Anaemia	14	Analysis of IPD from ZUMA-1
Cytokine release syndrome	4	Analysis of IPD from ZUMA-1
Encephalopathy	9	Analysis of IPD from ZUMA-1
Febrile neutropenia	6	Analysis of IPD from ZUMA-1
Hypophosphataemia	16	Analysis of IPD from ZUMA-1
Hypotension	5	Analysis of IPD from ZUMA-1
Leukopenia	21	Analysis of IPD from ZUMA-1
Lymphocyte count decreased	64	Analysis of IPD from ZUMA-1
Neutropenia	47	Analysis of IPD from ZUMA-1
Neutrophil count decreased	17	Analysis of IPD from ZUMA-1
Platelet count decreased	50	Analysis of IPD from ZUMA-1
Pyrexia	2	Analysis of IPD from ZUMA-1
Thrombocytopenia	63	Analysis of IPD from ZUMA-1
White blood cell count decreased	40	Analysis of IPD from ZUMA-1
Hyponatraemia	N/A	N/A
Hypoxia	N/A	N/A

Abbreviations: IPD = individual patient level data; N/A = not applicable.
Note: information on duration (days) for hypoatraemia and hypoxia was not available.

10.2.3 HSUV results

Table 44 presents an overview of HSUVs used in the model in the base case. Additionally, three scenario analyses were conducted, which are presented below in Table 44.

[redacted]

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs for progression-free (PF)				

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
PF HSUV – DK weighted (base case)	[redacted]		DK	Included values for patients who were in complete remission, partial remission, and stable disease. From ZUMA-1 trial (84). DK weighted using Danish value set provided by Jensen et al. (85)
HSUVs for progressed (PD)				
PD HSUV – DK weighted (base case)	[redacted]	EQ-5D-5L	DK	Included patients with progressive or relapsed disease. From ZUMA-1 trial (84). DK weighted using Danish value set provided by Jensen et al. (85)

Abbreviations: HSUV = health state utility value, PF = progression-free; PD = progressed disease; DK = Denmark; EQ-5D-5L= EuroQol-5 Dimension 5-levels.

Table 45 Overview of health state utility values applied as scenario in the model

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs for progression-free (PF)				
PF HSUV – UK weighted (scenario)	0.72 (0.66, 0.78)	EQ-5D-5L	UK	From ZUMA-1 trial. UK weighted. Scenario analysis applied. (91)
PF HSUV – JULIET trial (scenario)	0.83 (0.44, 0.98)	SF-36	UK	Mapped from SF-36 to UK EQ-5D tariff (55) (54). Utility weights from the JULIET trial have been accepted in other assessments (55, 56, 83).
PF HSUV – NICE TA306 (scenario)	0.76 (0.70, 0.82)	N/A	N/A	Utilities based on previous studies for similar patient populations (57, 86). Scenario analysis using NICE TA306/TA178 has been used for other scenario analyses in previous NICE assessments (TA306, ERG report, Table 27) (57, 86).
HSUVs for progressed (PD)				
PD HSUV – UK weighted (scenario)	0.65 (0.53, 0.77)	EQ-5D-5L	UK	From ZUMA-1 trial. UK weighted. Scenario analysis applied.
PD HSUV – JULIET trial (scenario)	0.71 (0.44, 0.91)	SF-36	UK	Mapped from SF-36 to UK EQ-5D tariff. Utility weights from the JULIET trial have been accepted in other assessments.
PD HSUV – NICE TA306 (scenario)	0.68 (0.60, 0.76)	N/A	UK	Utilities based on previous studies for similar patient populations. Scenario analysis using NICE TA306 has been used for other scenario analyses in previous NICE assessments (TA306, ERG report, Table 27) (57, 86)

Abbreviations: HSUV = health state utility value, PF = progression-free; PD = progressed disease; DK = Denmark; EQ-5D-5L= EuroQol-5 Dimension 5-levels, SF-36 = Short Form Survey-36, N/A= not available.

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

10.3.1 Study design

HSUVs derived from the JULIET study - scenario: JULIET is a global, single, open-label, phase 2 study of tisagenlecleucel (Kymriah®) in adult patients with r/r DLBCL. In summary, eligible participants were aged 18 or older and had undergone at least two prior lines of therapy, including rituximab and anthracycline. These individuals had experienced relapse after or were deemed ineligible for autologous stem cell transplantation. The study also encompassed patients with DLBCL transformed from follicular lymphoma and those with high-grade B-cell lymphoma featuring MYC rearrangements, along with rearrangements of BCL2, BCL6, or a combination of these genes (double- or triple-hit lymphoma). Exclusion criteria comprised a history of prior CD19-directed therapy, primary mediastinal DLBCL, prior allogenic stem cell transplantation, or active central nervous system involvement resulting from DLBCL (54, 55, 92).

As part of the secondary objectives in the JULIET study, patient-reported outcomes (PROs) were captured in Short-Form 36 (SF-36). The SF-36 questionnaire, a standard tool across diverse populations, generated a profile of HRQoL through 8 subscales. These covered physical functioning, role limitations due to emotional and physical health problems, physical pain, general health perception, vitality, social functioning, and mental health. Each subscale received an individual score, and two overall summary scores for the physical and mental components were derived (score range, 0-100) (92).

HSUVs derived from NICE TA306 (TA306, ERG report, Table 27) – scenario: For scenario analysis using utility values (PF and PD) from NICE TA306/TA178 (57, 86) (NICE TA306, ERG report). In this scenario analysis, HSUVs for PF and PD is based on second-line treatment in patients with renal cell carcinoma using utility values derived from a previous NICE assessment, TA178. Utility values were informed by the Pfizer original submission for TA178. No further details on the study design are available.

10.3.2 Data collection

HSUVs derived from the JULIET study – scenario: In the JULIET study, data were collected before clinical assessments and before the patients received any study medications or therapies. SF-36-data were collected at: Screening, Month 3, Month 6, Month 12, and Month 18 for 105, 65, 36, 24, and 9 patients, respectively (DCO 08-Dec-2017) (NoMA Kymriah®, page 64/142) (55). No further information on data collection or missing data handling is available.

HSUVs derived from NICE TA306 (TA306, ERG report, Table 27) – scenario: For scenario analysis using utility values (PF and PD) from NICE TA306/TA178, limited information on data collection is available. From TA178, The HSUVs used in the Assessment Group model were derived from trial data in the manufacturer original submissions and UK EQ–5D tariffs. Participants were assumed to be similar at baseline in terms of health-state value. Therefore, treatment specific health-state values were not applied. No further information on data collection or missing data handling is available (57, 86) (NICE TA306, ERG report).

10.3.3 HRQoL results

HSUVs derived from the JULIET study – scenario: Utility values were derived by mapping SF-36 data to utility values using the UK EQ-5D tariff. A mapping algorithm that was developed by Rowen et al. was used to map the SF-36 data to EQ-5D (89). See Table 46.

HSUVs derived from NICE TA306 (TA306, ERG report, Table 27) – scenario: Patients who were receiving second-line treatments were assumed to have a utility of 0.76 when in the PFS state and 0.68 when in the PD state; these assumptions came from the Pfizer submission (57, 86) (NICE TA306, ERG report). See Table 47.

10.3.4 HSUV and disutility results

HSUVs

HSUVs for the scenario analyses from the JULIET study and from NICE TA306 (TA306, ERG report, Table 27*)* are presented in Table 46 and Table 47.

AE disutilities

AE disutilities are not applied in the base case, as utilities captured within the trial are expected to already have captured the detrimental effect of AEs within the QoL value observed. However, the model allows the user to account for AE disutility that can arise with treatment (disutilities are included in the model as scenario analysis). AE utility decrements are informed by published literature (refer to Table 46).Table 46.

Modelled AEs for axi-cel include those defined in Section 9.2; it is conservatively assumed that no AE disutilities are applied in the BSC arm of the model. As most known AEs associated with axi-cel are expected to occur in the short-term, all AE disutilities are applied in the first model cycle. This is included in a scenario analysis. Total adverse event durations were calculated using patient-level data from ZUMA-1. Durations were calculated as the total number of days that each patient experiences a specific AE, even if that event was experienced more than once.

Table 46 Overview of health state utility values from other clinical trials

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Progression-free (PF) HSUV – JULIET trial (scenario)	0.83 (0.44, 0.98)	SF-36	UK	Mapped from SF-36 to UK EQ-5D tariff (55)(NoMA Kymriah®, page 64/142).
Progressed (PD) HSUV – JULIET trial (scenario)	0.71 (0.44, 0.91)	SF-36	UK	Mapped from SF-36 to UK EQ-5D tariff (55)(NoMA Kymriah®, page 64/142).Mapped from SF-36 to UK EQ-5D tariff (55).

Abbreviations: SF-36 = Short Form Survey 36;PF = progression-free; PD = progressed disease; EQ-5D-5L= EuroQol-5 Dimension 5-levels.

Table 47 Overview of literature-based health state utility values and disutilities

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
HSUVs				
Progression-free (PF) HSUV – NICE TA360 (scenario)	0.76 (0.70, 0.82)	N/A	N/A	Utilities based on previous studies for similar patient populations (57, 86) (NICE TA306, ERG report, Table 27).

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Progressed (PD) HSUV – NICE TA306 (scenario)	0.68 (0.60, 0.76)	N/A	UK	Utilities based on previous studies for similar patient populations (57, 86) (NICE TA306, ERG report, Table 27).
Disutilities				NICE TA306, ERG report, Table 29
Anaemia	0.12	TTO	UK	NICE pixantrone submission (Swinburn et al) (93)
Cytokine release syndrome	0.79	N/A	N/A	As in the NICE regenerative medicines report, it is conservatively assumed that those experiencing cytokine release syndrome have a quality of life of zero (i.e. the utility decrement is set to be the negative of the utility value in the progression-free health state)(94)
Encephalopathy	0.15	N/A	N/A	Equal to the maximum of the identified non-CRS adverse event disutilities was assumed (due to absence of data)
Febrile neutropenia	0.15	SG	UK	NICE pixantrone submission (Lloyd et al)(95)
Hypophosphataemia	0.15	N/A	N/A	Equal to the maximum of the identified non-CRS adverse event disutilities was assumed (due to absence of data). The approach was also taken in the NICE pixantrone submission (TA306, ERG report, Table 29) (57).
Hypotension	0.15	N/A	N/A	Refer to "hypophosphatamemia" disutility comment
Leukopenia	0.15	N/A	N/A	Refer to "hypophosphatamemia" disutility comment
Lymphocyte count decreased	0.15	N/A	N/A	Refer to "hypophosphatamemia" disutility comment
Neutropenia	0.09	SG	UK	NICE pixantrone submission (Nafees et al)(96)
Neutrophil count decreased	0.15	N/A	N/A	Refer to "hypophosphatamemia" disutility comment
Platelet count decreased	0.11	TTO/VAS	UK	NICE pixantrone submission (Tolley et al)(97)
Pyrexia	0.11	SG	UK	NICE pixantrone submission (Beusterien et al)(97)
Thrombocytopenia	0.11	TTO/VAS	UK	NICE pixantrone submission (Tolley et al)(97)
White blood cell count decreased	0.15	N/A	N/A	Refer to "hypophosphatamemia" disutility comment

Abbreviations: N/A= not available, TTO= time-trade-off, VAS= visual analogue scale, SG= standard gamble; CRS = cytokine release syndrome.

11. Resource use and associated costs

Costs and resource use vary dependent on the administered treatment and health states. The model includes direct medical costs, as well as transport costs and time spent on treatment by patients, consistent with the restricted societal perspective as described in the DMC guidelines (47). All costs are valued in 2024 Danish Krone (DKK) (except costs sourced from the DMC unit cost catalogue, 2023).

The following section regarding cost and resource use is presented per health state, containing information regarding drug acquisition costs (including leukapheresis and conditioning chemotherapy costs), disease management costs, SCT costs, AE costs, and patient time/transportation costs. Refer to Figure 47 in Appendix K for a more graphical presentation of cost components for axi-cel and comparator.

Drug costs are sourced from Medicinpriser.dk (36) and applied as pharmacy purchasing prices (AIP). Disease management and AE costs are based on Danish diagnosis related groups (DRG) tariffs from 2024 (98) and DMC catalogue for unit costs (2023) (99). Patient and transportation costs are based on the DMC catalogue for unit costs and are presented in a separate section covering all patient- and transportation costs for all health states.

11.1 Pharmaceutical costs (intervention and comparator)

Axi-cel

Costs associated with axi-cel include acquisition of axi-cel, leukapheresis, conditioning chemotherapy, infusion, and monitoring. The drug cost of axi-cel is assumed to be a one-off cost of 2,440,000 DKK, informed by medicinpriser.dk (Table 51) (36). The ITT population is used in the base case analysis, hence the axi-cel cost is adjusted by the proportion receiving axi-cel (subjects receiving axi-cel: 101, total subjects: 111). Therefore, 91% of the ITT population incurs the axi-cel acquisition/administration costs. Vial sharing was not considered when estimating the drug costs in the base case. Treatment costs for axi-cel consisted of drug/procedure acquisition costs and administration costs, which is described in the section below. For simplicity, all costs associated with axi-cel are assumed to be incurred in the first model cycle.

Retreatment

Refer to Section 8.3 for detailed description. Nine of 101 infused subjects (8.9%) were retreated with axi-cel in ZUMA-1 (9). [redacted]

Salvage therapy

As mentioned in Section 3.3, the use of DHAP/ICE/GDP/GemOx/Gem -mono/Bendamustine (in combination with rituximab) as a salvage therapy and followed by SCT for eligible patients is justified by its substantial representation (DHAP/ICE/GDP: 13%, GemOX/Gem: 4.2% and Bendamustine: 3.2%) in recent Danish clinical practice, particularly in the context of relapsed or refractory cases (3L). This ensures some coherence with both the CORAL EXT 1 & 2 MAIC data and the real-world study (8) (35).

The split of comparator is therefore comprised of 57% DHAP, 24% ICE, and 14% GDP, 2% GemOX, 2% Gem mono, and 2% Bendamustine, based on original inputs reported in the 2019 Yescarta® assessment submitted to the DMC (Yescarta assessment, section 1.3.1) and the Danish RW study (14) (35), followed by SCT in eligible patients (assumption is 7.4% of patients in 3L, see Section 3.3). Table 48 provides the cycle costs for drugs included in the comparator arm. Information regarding dose and dose per cycle was sourced from ZUMA-1 and previous HTA assessment or other literature, please refer to Table 48 and Table 50.

Table 48: Cycle costs related to the drugs included in comparator arm

Regimen	Pharmaceutical	Dose	Dose per cycle	Source
R-GDP	Gemcitabine	1000 mg/m2/day	2	DMC Yescarta® 2019 (Amgros assessment Table 5) (14)
	Dexamethasone	40 mg/day	4	
	Cisplatin	100 mg/m2/day	1	
R-DHAP	Dexamethasone	40 mg/day	4	NoMA Yescarta® 2017 (Table 19), DMC Yescarta® 2019 (Amgros assessment Table 5) (14)
	Cisplatin	100 mg/m2/day	1	
	Cytarabine	2000 mg/m2/day	2	
R-ICE	Ifosfamid	5000 mg/m2/day	1	NoMA Yescarta® 2017 (Table 19), DMC Yescarta® 2019 (Amgros assessment Table 5) (14, 83)
	Carboplatin	450 mg/day	1	
	Etopside	100 mg/m2/day	3	
R-GemOx	Gemcitabine	1000 mg/m2/day	1	NHS South East London Cancer Network (67), Kunskapsbanken(64), and DMC Minjuvi® 2022 **(section 5.2.3, Table 5)** (66).
	Oxaliplatin	100 mg/m2/day	1	
R-Gem-mono	Gemcitabine	1000 mg/m2/day	3	Assumption. Supported by Herlev Hospital (62)and Ruth Pettengell et al (65) (2019) (mentioned in the DMCG guidelines) (29)
R-Bendamustine	Bendamustine	90 mg/m2/day	2	DMC Polivy submission **2021 (section 3.2. Polatuzumab vedotin)** (25) and Hong JY et al 2018 (100)
Rituximab	Rituximab	375 mg/m2/day	1 cycle in all regimens	DMC Yescarta® 2023, 2L DLBCL (page 80/175, Table 47) (4) NoMA Yescarta® 2017 (Table 19), DMC Yescarta® 2019 (Amgros assessment Table 5) (14, 83)

Abbreviations: DMC= Danish Medicines Council, NoMA= Norwegian Medicines Agency.
Note: An average weight has been assumed to be 82.70 kg (ZUMA-1) for calculating the required mg for comparators without any specific BSA-dependent dosing data.

Cost-effective vial size combinations for BSA-dependent chemotherapy in ZUMA-1 is shown in Table 49. Proportions within each BSA range were determined using ZUMA-1 patient-level data (only BSA-dependent chemotherapy for gemcitabine, cisplatin, rituximab was informed by ZUMA-1). It was assumed that unused chemotherapy remaining in vials is wasted.

Table 49: Vial combinations by BSA from IPD data (ZUMA-1)

Pharmaceutical	BSA (m^2)	% of patients	Optimal combination of doses	Source
Gemcitabine	≤ 2.0	52%	2 x 1,000 mg	ZUMA-1

Pharmaceutical	BSA (m^2)	% of patients	Optimal combination of doses	Source
	2.0-2.2	29%	2 x 1,000 mg, 1 x 200 mg	ZUMA-1
	2.2-2.4	14%	2 x 1,000 mg, 2 x 200 mg	ZUMA-1
	> 2.4	5%	3 x 1,000 mg	ZUMA-1
Cisplatin	≤ 1.5	5%	1 x 100 mg, 1 x 50 mg	ZUMA-1
	1.5-2.0	48%	2 x 100 mg	ZUMA-1
	2.0-2.1	13%	2 x 100 mg, 1 x 10 mg	ZUMA-1
	2.1-2.2	16%	2 x 100 mg, 2 x 10 mg	ZUMA-1
	2.2-2.3	10%	2 x 100 mg, 3 x 10 mg	ZUMA-1
	2.3-2.5	7%	2 x 100 mg, 1 x 50 mg	ZUMA-1
	> 2.5	2%	3 x 100 mg	ZUMA-1
Rituximab	≤ 1.6	10%	6 x 100 mg	ZUMA-1
	1.6-1.866	21%	1 x 500 mg, 2 x 100 mg	ZUMA-1
	1.866-2.133	42%	8 x 100 mg	ZUMA-1
	2.133-2.4	23%	1 x 500 mg, 4 x 100 mg	ZUMA-1
	2.4-2.666	4%	2 x 500 mg	ZUMA-1
	> 2.666	1%	1 x 500 mg, 6 x 100 mg	ZUMA-1

Abbreviations: BSA = body surface area; DMC= Danish Medicines Council, NoMA= Norwegian Medicines Agency.

Table 50 provides the overview of the treatment cycles modelled for the comparator arm. The model applied costs (AIP) for each regimen, multiplied by their distribution of use in Denmark. An average of 4 treatment cycles was assumed.

Table 50: Treatment cycles - comparators

Chemotherapy regiment	Cycles per course	Source
R-DHAP	4	NoMA Yescarta® 2017 (Table 19), DMC Yescarta® 2019 (Amgros assessment Table 5) (14, 83), AUH (60, 61), DMCG (29)
R-GDP	4	
R-ICE	4	
R-GemOx	3	DMC Minjuvi® 2022 (section 5.2.3, Table 5) (66), Herlev Hospital (63), DMCG (29).
R-Gem mono	4	Herlev Hospital (62)
R-Bendamustine	6	DMC Polivy® 2021 (section 3.2. Polatuzumab vedotin) (25)

Abbreviations: DHAP = cisplatin, cytarabine, and dexamethasone; GDP = gemcitabine, dexamethasone, and cisplatin; ICE = ifosfamide, carboplatin, and etoposide.

Table 51 provides an overview of the pharmaceutical costs.

Table 51: Pharmaceutical costs

Pharmaceutical		Strength	Package size	Pharmacy purchase price [DKK](36)
Axicabtagene ciloleucel	Axicabtagene ciloleucel	N/A	1 infusion bag	2,440,000 (5)
DHAP	Dexamethasone	2 mg/ml	100 ml	90.00
	Cisplatin	1 mg 1mg	50 ml 100 ml	100.00 200.00
	Cytarabine	100 mg/ml	20 ml	150.00
GDP	Gemcitabine	38 mg/ml 10 mg/ml	26.3 ml 120 ml	283.00 310.00
	Dexamethasone	See previously	See previously	See previously
	Cisplatin	See previously	See previously	See previously
ICE	Ifosfamide	1000 mg	1 x IV	380.00
	Carboplatin	10mg/ml	45 ml	226.00
	Etoposide	20 mg/ml	5 ml	71.37
GemOx	Gemcitabine	See previously	See previously	See previously
	Oxaliplatin	5 mg/ml	40 mg	127.82
Gem mono	Gemcitabine	See previously	See previously	See previously
Bendamustin	Bendamustin	2.5 mg/ml	5 x 25 mg powder for IV	367.00
Rituximab	Rituximab	100 mg 500 mg	2 pcs 1 pcs	2675.806687.00

Abbreviations: DHAP = cisplatin, cytarabine, and dexamethasone; GDP = gemcitabine, dexamethasone, and cisplatin; ICE = ifosfamide, carboplatin, and etoposide, N/A= not applicable.

11.2 Pharmaceutical costs – co-administration

Pharmaceutical costs of co-administrations considered in the economic evaluation associated with axi-cel consisted of leukapheresis, conditioning chemotherapy, infusion, and monitoring. No pharmaceutical co-administration costs were assumed for the comparator.

Axi-cel: Leukapheresis

Phase 2 of ZUMA-1 enrolled 111 patients (ITT), all patients who underwent leukapheresis. The cost of leukapheresis was obtained from DRG tariffs 2024 (98) and is presented in Table 52. The cost of leukapheresis was calculated to be 12,059 DKK. It was assumed that leukapheresis is performed at an outpatient visit.

Table 52: Cost of leukapheresis used in the model

Pharmaceutical	Frequency	Unit cost [DKK]	DRG code	Reference
Leukapheresis	N/A, refer to description	12,059	16PR03	DRG 2024 (98)

Abbreviations: N/A = not available; DRG = diagnosis related group.

Axi-cel: Conditioning Chemotherapy

Phase 2 of ZUMA-1 enrolled 111 patients (ITT), all patients who underwent leukapheresis; 103 patients received conditioning therapy; and 101 were treated with axi-cel (mITT population). A multiplier of 0.93 (103/111) is applied to the conditioning chemotherapy costs. Conditioning chemotherapy includes intravenous (IV) infusions of cyclophosphamide 500 mg/m2 and fludarabine 30 mg/m2 on the 5th, 4th, and 3rd day prior to infusion of axi-cel (3 days in total. Unit costs for cyclophosphamide and fludarabine were taken from Medicinpriser.dk (36) and are presented in Table 53. It was assumed that unused chemotherapy remaining in vials is wasted.

Table 53: Cost of conditioning chemotherapy used in the model

Pharmaceutical	Frequency	Strength	Package size	Pharmacy purchase price [DKK] (36)
Cyclophosphamide	5th, 4th, and 3rd day prior to axi-cel administration	1,000 mg	1 infusion bag	330.00
		500 mg	1 infusion bag	180.00
Fludarabine	5th, 4th, and 3rd day prior to axi-cel administration	250 mg	5 x 2 ml infusion bag	6,550.50

Abbreviations: axi-cel = axicabtagene ciloleucel.

Optimal vial size combinations, minimizing costs, were chosen for ZUMA-1 patients based on body surface area ranges (see Table 54). Proportions within each range were determined using patient-level trial data.

Table 54: Vial combinations by BSA

	Fludarabine		Cyclophosphamide	
BSA (m2)	≤ 1.6	> 1.6	≤ 2.0	> 2.0
% of patients	12%	88%	48%	52%
Optimal dose combination	1 x 50 mg	2 x 50 mg	1 x 1000 mg	1 x 1000 mg, 1 x 500 mg

Abbreviations: BSA = body surface area.
Note: Fludarabin 50 mg is not available in Denmark (per 10.07.2023)

Conditioning chemotherapy is assumed to require a non-elective long-stay hospitalisation, in line with assumptions taken in the NICE regenerative medicines report (section 8.3.1.2. Administration and monitoring costs) (94). According to Rigshospitalet, patients should be hospitalised around one week prior to axi-cel infusion (101). Using the DRG 2024 tariff 27MP24, the hospitalisation cost of conditioning chemotherapy administration is 52,811 DKK (98).

Table 55: Cost of hospitalisation for conditioning chemotherapy

Item	Cost (DKK)	DRG tariff	Source
IV administration	52,811	27MP24	DRG 2024 (98)

Abbreviations: IV = intravenous, DRG = diagnosis related group.

11.3 Administration costs

Axi-cel

As previously mentioned, the axi-cel cost is adjusted by the ITT proportion receiving axi-cel (subjects receiving axi-cel: 101, total subjects: 111). Therefore, 91% of the ITT population incurs the axi-cel acquisition/administration costs. The infusion of axi-cel and subsequent monitoring is assumed to incur the cost of an elective hospitalisation in line with

the assumption taken in the NICE regenerative medicines report (section 8.3.1.2. Administration and monitoring costs) (94). The infusion assumed to incur the cost of hospitalisation for 10 days (patients are assumed to be monitored for 10 days after infusion), and the cost of cell infusion. The calculated cost is 55,063 DKK. Unit costs are summarised in Table 58.

Table 56: Administration costs used in the model – Axi-cel

Item	Cost (DKK)	DRG tariff	Source
Administration – cell infusion	6,723	16PR01	DRG 2024 (98)
Hospitalisation days	48,340	17MA01	DRG 2024 (98)

Abbreviations: DRG = diagnosis related group.
Note: For simplicity, all costs associated with axi-cel are assumed to be incurred in the first model cycle.

Salvage therapy

Some of the treatment regimens were assumed to entail 1-2 inpatient days (GDP, ICE, Bendamustine – while DHAP, GemOx and Gem mono are assumed to be carried out in outpatient clinic without any hospitalization). A weighted average monthly administration cost of 22,394 DKK was added. This was based on the DRG 2024 tariff 27MP24 "chemotherapy, basis" and 17MA98 "1-dagsgruppe, pat. Mindst 7 år" (98), refer to Table 57.

Table 57 Administration costs used in the model - comparator

Administration type	Frequency	Unit cost [DKK]	DRG code	Reference
IV administration (inpatient)	Once every month	52,811	27MP24	DRG 2024 (98)
IV administration (outpatient)	Once every month*	1,989	17MA98	DRG 2024 (98)

Abbreviations: IV = intravenous, DRG = diagnosis related group.
Note: * GemOX frequency = 2 (twice every month)

11.4 Disease management costs

The average resource utilisation for the PF state and PD state is largely based on an estimate for similar patients in 2016, based on TLV's Pixuvri® (pixantrone) assessment (58). Based on the Swedish Pixuvri® assessment, the resource utilization in the model is derived from a prior application of Pixuvri® to NICE (TA306, ERG report, section 5.2.9) (57) and has been validated through an expert opinion from a clinical expert in Sweden. These estimations have subsequently been validated by a clinical expert in Denmark (reported in the Yescarta® assessment from 2019, section: Questions for Key Opinion Leaders in Denmark regarding the treatment of B-cell lymphoma with CAR-T therapy Axicabtagene ciloleucel (Axi-cel)) (14). Danish costs were then applied to the healthcare resources that a patient may require in each PF and PD state. Costs are based on both DRG 2024 tariffs (98) , Rigshospitalets Labportal (101), and costs identified in the DMC unit cost catalogue (99). Table 58 shows the disease management costs used in the model.

As patients who are progression-free in the long-term may no longer incur the costs of medical resource use, functionality is included in the model such that no costs are incurred in the progression-free state beyond a certain time point. In the base case, this time point is assumed to be at 24 months.

Table 58 Disease management costs used in the model

Activity	Frequency	Unit cost [DKK]	DRG code	Reference
Outpatient care				
Physician visit – Oncologist or haematologist	PF: 0.22 visit per month PD: 3 visits per month	1,066.00	NA	DMC's unit cost catalogue (99)
Nurse	PF: no visit PD: 3 visits per month	453.00	NA	DMC's unit cost catalogue (99)
Inpatient care				
Inpatient days	PF: no visit PD: 7 days per month	1,989.00	17MA98	DRG2024 (98)
Tests				
Full blood counts	PF: 0.22 test per month PD: 6 tests per month	22.00	NA	Takstkort 29a (102)
LDH	PF: 0.22 test per month PD: 6 tests per month	16.00	NA	Labportal.rh (101)
Immunoglobulin	PF: 0.22 test per month PD: 0.33 test per month	928.00	NA	Labportal.rh (101)
Renal function	PF: 0.22 test per month PD: 6 tests per month	48.00	NA	Labportal.rh (101)
Liver function	PF: 0.22 test per month PD: 6 tests per month	60.00	NA	Labportal.rh (101)
Calcium phosphate	PF: 0.5 test per month PD: 1 test per month	95.00	NA	Labportal.rh (101)

Abbreviations: NA = not available; PF = progression-free; PD = progressive disease; DRG = diagnosis related group.

11.5 Costs associated with management of adverse events

Modelled AEs for axi-cel are defined in Section 9.2. It is conservatively assumed that no AE costs are incurred in the BSC arm of the model. For simplicity, all adverse event costs are assumed to be incurred in the first model cycle; this approach is in line with that taken in the NICE regenerative medicines report (94). The NICE regenerative medicines report (section 8.3.1.3 Adverse events) notes that the individual costing of AEs could result in double counting, given that the costs of cell infusion and monitoring will include the cost of resolving inpatient AEs (94). The NICE report therefore assumes that all grade 3 or 4 AEs other than cytokine release syndrome (CRS) and B-cell aplasia incur the cost of one excess bed day (section 8.3.1.3 Adverse events). Given the length of stay for axi-cel, it is assumed that the costs of all AEs other than CRS have already been accounted for.

Cytokine release syndrome

CRS is an AE that is specific to treatment with axi-cel and could be associated with additional HCRU. Costs associated with CRS are assumed to include an intensive care unit (ICU) hospitalization. According to the CSR the median time to resolving of CRS was 8 days (according to the CSR DCO 2017; CSR DCO 2018 reports 7 days) (9, 82). The proportion of patients with grade 3+ CRS was 13% in the ZUMA-1 (CSR DCO 2017; CSR DCO 2018 reports 11%, refer to Section 9.2) with the assumption that these patients would incur ICU costs (DRG 2024 17MA01), and the assumed duration is 8 days. The DRG 2024 tariff 17MA01 covers the length of stay: 8 days (diagnosis: DC833 in combination with procedure: BOHJ18B2).

Furthermore, 17% patients are assumed to be treated with tocilizumab (ZUMA-1 DCO Jan 2017; CSR DCO Aug 2018 reports 19% which is included for a scenario analysis) and assumed to incur both drug and administration costs related to tocilizumab. Treatment with

tocilizumab consists of IV tocilizumab 8 mg/kg, informed by Region Nordjylland (pri.rn.dk) (103). In the base case 2 doses of tocilizumab are assumed. This is in line with the committee papers for Yescarta® from NICE (TA872, committee papers (TA559 from 2018)). The cost was calculated by adding the costs of ICU and drug costs for treating CRS, sourced from DRG 2024 and medicinpriser.dk, refer to Table 59.

Table 59 CRS management costs

Item		Unit cost [DKK]	DRG code	Reference
Tocilizumab drug costs	8 mg/kg	81.51	NA	Medicinpriser.dk (36)
	1 dose (82.70 kg)	6,741.00	NA	Medicinpriser.dk (36), ZUMA-1
Tocilizumab administration costs		1,989.00	17MA98	DRG 2024 (98)
Inpatient days	8 days	48,340.00	17MA01	DRG 2024 (98)

Abbreviations: NA = not available, CRS = cytokine release syndrome; DRG = diagnosis related group.

B-cell aplasia (IVIG treatment) - hypogammaglobulinemia

Despite hypogammaglobulinemia did not present as a grade 3 or 4 AE in any of the patients in ZUMA-1, hypogammaglobulinemia secondary to B-cell aplasia was seen in 11% (CSR DCO Jan 2017 (82); CSR DCO Aug 2018 reports 16% (9)) (all grades; grade ≥3: none). Data on the duration of intravenous immunoglobulin (IVIG) treatment patients in ZUMA-1 received is missing. However, based on the DMC Yescarta® 2019 assessment (14), DMC pointed out that according to ZUMA-1, 25% of patients will still receive treatment after 24 months. Therefore, the proportion of patients with hypogammaglobulinemia in the base case is set to 25%, and the average duration of treatment in the base case is set to 24 months.

From the ZUMA-1 trial, 31% (CSR DCO 2017 (104); CSR DCO Aug 2018 reports 30% (9)) subjects received IV immunoglobulin therapyhypogammaglobulinemia in ZUMA-1 (CSR DCO Jan 2017). Clinical experts expect that patients will switch treatment from IV immunoglobulin to subcutaneous treatment (these treatments do not require administration costs). In the model base case, the proportion of patients treated with IV immunoglobin or SC immunoglobulin is set to 55%. However, for simplicity a unit price and IV administration costs of Privigen® has been used for the entire period of immunoglobulin treatment in the base case (36). The recommended dose for Privigen® is 400 mg/kg per kg every 3-4 weeks. An average weight has been assumed to be 82.70 kg. This corresponds to a monthly drug cost of 27,509.20 DKK. Cost for administration is sourced from DRG 2024 (16MA98) (98). This corresponds to a weighted total cost of 4,072.78 DKK per month.

Scenario analyses will explore the impact of changing the duration of treatment as well as changing the proportion treated with IVIG/SCIG, refer to Section 12.2.

Table 60 Hypogammaglobulinemia management costs

	Unit cost [DKK]	DRG code	Reference
400 mg/kg Privigen® every 4 weeks	27,509.20	NA	Medicinpriser.dk (36)
IV administration	2,111.00	16MA98	DRG 2024 (98)

Abbreviations: NA = not available, IV = intravenous, DRG = diagnosis related group.

11.6 Subsequent treatment costs

Subsequent stem cell transplant (SCT)

Two subjects of 101 (2%) underwent allogeneic SCT while in response after axi-cel retreatment in Phase 2 of ZUMA-1 (9); no subjects underwent autologous SCT after responding to axi-cel treatment. Refer to Section 8.3. The cost of allogeneic SCT is applied to 2% of patients in the axi-cel arm of the model (note: only transplants received while in remission after axi-cel are included. Therefore: mITT population). For the salvage therapy arm, the weighted cost of allogeneic SCT or autologous SCT is applied to 8% of patients in the comparator arm (4% allo-SCT/4% auto-SCT) for the base case, informed by Al-Mashhadi et al. (35). Additionally, two scenarios explore the impact of two extremes with 29% (ASCT 21.2%, allogeneic SCT 7.5%) observed from the comparative data (CORAL EXT 1 & 2), and with 0% (6). Table 61 shows the cost of subsequent SCT.

Table 61 Costs of subsequent SCT

	Unit cost [DKK]	DRG code	Reference
Allogeneic SCT	904,674.00	26MP22	DRG 2024 (98)
Autologous SCT	100,181.00	26MP24	DRG 2024 (98)

Abbreviations: SCT= stem cell transplant, DRG = diagnosis related group.

11.7 Patient costs

Patient costs for transportation and time have been included based on the requirements from the DMC. A conservative approach has been undertaken and the estimation of patient time and transportation related costs are based on the frequency of healthcare resources described in Section 11.4. Based on DMC's unit cost catalogue (2023), a unit cost of 140 DKK was applied to all visits and healthcare activities in the model to account for travel expenses, and a unit cost of 203 DDK was used for all patient hours spent on treatment-related activities (99).

The model includes patient hours spent on treatment-related activities regarding:

- Axi-cel treatment (including leukapheresis, lymphodepleting (conditioning) chemotherapy, axi-cel infusion)
- Administration of salvage therapy regimens
- Post SCT
- Disease management, monitoring, and follow-up (including doctor visits and monitoring tests). It was assumed that hours spent on disease management, monitoring, and follow-up between axi-cel and salvage therapy were the same.
- Management of AEs (only patient time/transportation time for managing CRS and hypogammaglobulinemia in axi-cel arm is included)

Table 62 below shows the activity used for patient time and transportation costs calculations. It has been assumed that one inpatient day equals 16 patient hours (base case), which has been explored in a scenario analysis of 24 hours instead of 16 hours.

Table 62 Patient time estimates used in the model

Activity	Time spent, [hours]	Comments
Drug administration time, axi-cel		
Conditioning chemotherapy	48 hours	3 days of inpatient days (SmPC) (1)
Leukapheresis	3 hours	Based on the SmPC (1).
Axi-cel administration	0.5 hours	Based on the SmPC (1).
Monitoring time, post axi-cel	160 hours	Post axi-cel monitoring time is 10 days according to the SmPC (1).

Activity	Time spent, [hours]	Comments
AE management time, axi-cel		
CRS treatment time	128 hours	8 median days in ZUMA-1 (DCO 2017)(82).
Hypogammaglobulinemia treatment time	3 hours	Privigen® Region Midtjylland (69)
Drug administration time, salvage therapy DHAP/ICE/GDP, GemOx/Gem mono, Bendamustine administration – average	35 hours	DHAP: AUH reports 2 infusion days (61). ICE: AUH reports 3 infusion days(60). GDP: Rigshospitalet reports 10 hours per infusion (105). GemOx/Gem mono: Rigshospitalet reports 2 hours per infusion(62, 63) . Bendamustin: Herlev Hospital reports 2 infusion days(106) .
SCT	768 hours	DRG tariff 26MP22 (allo-SCT) covers 69 days. DRG tariff 26MP22 (auto-SCT) covers 36 days. An estimate of 50 days has been assumed.

Abbreviations: axi-cel = axicabtagene ciloleucel, AE = adverse event; SCT = stem cell transplant; CRS = cytokine release syndrome; DHAP = cisplatin, cytarabine, and dexamethasone; GDP = gemcitabine, dexamethasone, and cisplatin; ICE = ifosfamide, carboplatin, and etoposide.

Table 63 below shows the estimated patient costs used in the model, per cycle or as one-off costs. Patient hours spent for each activity has been adjusted or weighted (e.g., proportion of patients receiving SCT in axi-cel arm is 2%).

Table 63 Patient costs used in the model

Applied in the model		Time spent [hours]	Cost [DKK]
Axi-cel			
Per cycle	PF	0.21	181.95
	PD	6.44	1,448.17
	IVIG, up to cycle 24 (base case) (14% of patients*)	2.48	642.43
One-off cost	Axi-cel monitoring (1st cycle)	160.00	32,620.00
	Drug administration (including leukapheresis and CC) (1st cycle)	115.50	39,161,50
	SCT (1st cycle) – 2%	768.00 *Weighted 15.36	*Weighted 65.16
	CRS treatment (13% of patients)	15.36	65.16
Salvage therapy			
Per cycle	PF	11.54	2,482.31
	PD	11.54	2,482.31
One-off cost	SCT (1st cycle) – 8%	61.44**	1,008.99**

Abbreviations: Axi-cel = Axicabtagene ciloleucel; PF = progression-free; PD = progressive disease; IVIG = intravenous immunoglobulin; SCT = stem cell transplant; CRS = cytokine release syndrome.
Note: * patient time and transportation costs related to IVIG treatment is weighted: 14% of patients. Refer to section 11.5 (proportion of patients with hypogammaglobulinemia: 25% (based on DMC feedback – despite that the CSR reports 16%), and the proportion of patients treated with IVIG or subcutaneous immunoglobulin (SCIG): 55%), ** weighted estimate.

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

The model allows calculation of training costs and storage costs of axi-cel. However, these cost estimations are not included in the base case. The necessary information is lacking or uncertain, hence it is excluded in the base case.

12. Results

12.1 Base case overview

The key aspects of the base case cost-effectiveness model are presented in Table 64.

Table 64 Base case overview

Feature	Description
Comparator	Salvage therapy followed by SCT for eligible patients
Type of model	Partitioned survival model
Time horizon	44 years (lifetime)
Treatment line	3rd line. Subsequent allogeneic SCT is modelled.
Measurement and valuation of health effects	Health-related quality of life measured with EQ-5D-5L in study ZUMA-1. Danish population weights were used to estimate health-state utility values.
Costs included	Pharmaceutical costs (and co-administration), administration costs, disease management costs, costs of adverse events, subsequent SCT costs, patient costs
Dosage of pharmaceutical	Target dose is 2 × 10^6 anti-CD19 CAR-positive viable T cells per kg of body weight
Average time on treatment	[redacted]
Parametric function for PFS	Axi-cel: MCM Loglogistic Salvage therapy: PFS/OS ratio from axi-cel
Parametric function for OS	Axi-cel: MCM with the Loglogistic distribution Salvage therapy: MCM with the Loglogistic distribution
Inclusion of waste	No
Average time in model health state (years)	
PF	[redacted]
PD	[redacted]

Abbreviations: Axi-cel = Axicabtagene ciloleucel, BSC = best supportive care; EQ-5D = European Quality of Life Five Dimension Five Level Scale; STM = stem cell transplant; SPM = standard parametric model; MCM = mixture cure model; PF = progression-free, PD = progressive disease; PFS = progression-free survival; OS = overall survival.

12.1.1 Base case results

In the model base case where axi-cel is compared against salvage therapy, discounted results are presented in Table 65. Using a lifetime horizon, the incremental expected total life-year gain amounts to [redacted] (discounted). The discounted incremental costs of [redacted] and incremental [redacted] resulted in an incremental cost-effectiveness ratio (ICER) of [redacted] versus salvage therapy.

Table 65 Base case results, discounted estimates

	Axi-cel	Salvage therapy	Difference
Pharmaceutical costs*	[redacted]	[redacted]	[redacted]
Pharmaceutical costs – co-administration*	[redacted]	[redacted]	[redacted]
Administration*	[redacted]	[redacted]	[redacted]
Disease management costs	[redacted]	[redacted]	[redacted]
Costs associated with management of adverse events	[redacted]	[redacted]	[redacted]
Subsequent treatment costs	[redacted]	[redacted]	[redacted]
Patient costs	[redacted]	[redacted]	[redacted]
Palliative care costs	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]
Life years gained, PF	[redacted]	[redacted]	[redacted]
Life years gained, PD	[redacted]	[redacted]	[redacted]
Total life years	[redacted]	[redacted]	[redacted]
QALYs, PF	[redacted]	[redacted]	[redacted]

	Axi-cel	Salvage therapy	Difference
QALYs, PF	[redacted]	[redacted]	[redacted]
QALYs (adverse reactions)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
Incremental costs per life year gained			[redacted]
Incremental cost per QALY gained (ICER)			[redacted]

Abbreviations: Axi-cel = Axicabtagene ciloleucel, NA = not available, QALY = quality-adjusted life-year; PF = progresssion-free; PD = progressive disease.
*Note: Pharmaceutical costs covers drug acquisition costs, co-administration costs and administration costs.

12.2 Sensitivity analyses

Parameter uncertainty was investigated both deterministically and probabilistically. Full details of parameter specifications, including details of how they varied in the model can be found in Appendix G.

12.2.1 Deterministic sensitivity analyses

Univariate parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range determined by ±15% or by a specific standard errors or predefined upper and lower limits (hence lower value and upper value are provided in the table below). The 10 most influential model parameters with regards to impact on range of impact on the base case ICER are presented in Table 66 and as a tornado diagram in Figure 17.

[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]	NA	[redacted]	[redacted]	[redacted]
Mean age (years) – lower value	[redacted]	Range of impact on the base case ICER	[redacted]	[redacted]	[redacted]
Mean age (years) – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Utility value, progressed disease (DK weighted ZUMA-1 safety population) – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Utility value, progressed disease (DK weighted ZUMA-1 safety population) – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Medical resource use (AC) - progressed disease – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Medical resource use (AC) - progressed disease – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Medical resource use (BSC) - progressed disease – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Medical resource use (BSC) - progressed disease – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Utility value, progression-free disease (DK weighted ZUMA-1 safety population) – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Utility value, progression-free disease (DK weighted ZUMA-1 safety population) – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
DHAP, proportion – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
DHAP, proportion – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

	Change (%)	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Multiplier for conditioning chemotherapy/acquisition costs – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Multiplier for conditioning chemotherapy/acquisition costs – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
% female – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
% female – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Hospitalisation cost for administration of AC– lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Hospitalisation cost for administration of AC– upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Proportion treated with IVIG – lower value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]
Proportion treated with IVIG – upper value	[redacted]	Same as above	[redacted]	[redacted]	[redacted]

Abbreviations: AC = Axicabtagene ciloleucel; BSC = best supportive care; QALY = quality-adjusted life- year.

[redacted]

Abbreviations: BSC = best supportive care, SCT = stem cell transplant, AC = axicabtagene ciloleucel, QALY = quality-adjusted life-year.
Note: BSC in the model refers to salvage therapy

A number of scenarios were considered in the deterministic sensitivity analyses exploring variations from the base model settings (Table 67). Important factors for estimating the ICER of treatment with axi-cel include choice of time horizon, BSC progression assumption and axi-cel PFS distribution. It may be expected that reduced time horizons would be associated with significantly increased ICERS. It is also expected that the BSC progression assumption may have high impact on the ICER, however, in the absence of PFS data to inform the BSC arm, two extreme scenarios were explored. No modelled scenarios were associated with an ICER impact above 30%.

Table 67 Scenario analyses results

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Base case	[redacted]	N/A	[redacted]	[redacted]	[redacted]
Time horizon = 20 years	[redacted]	Alternative time horizon was considered.	[redacted]	[redacted]	[redacted]
Modelling approach, SPM (AC + BSC), Loglogistic	[redacted]	Alternative modelling approach.	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Axi-cel PFS – SPM (gompertz)	[redacted]	Alternative modelling approach.	[redacted]	[redacted]	[redacted]
100% progression-free in BSC arm	[redacted]	Due to absence of PFS data from the CORAL EXT 1 & 2 MAIC.	[redacted]	[redacted]	[redacted]
100% progressed in BSC arm	[redacted]	Due to absence of PFS data from the CORAL EXT 1 & 2 MAIC.	[redacted]	[redacted]	[redacted]
Utility from UK weights	[redacted]	Alternative utility values.	[redacted]	[redacted]	[redacted]
Utility from JULIET trial	[redacted]	Alternative utility values.	[redacted]	[redacted]	[redacted]
Utility from NICE TA306/178	[redacted]	Alternative utility values.	[redacted]	[redacted]	[redacted]
AC OS distribution (MCM): exponential	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
AC OS distribution (MCM): Weibull	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
AC OS distribution (MCM): Lognormal	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
AC OS distribution (MCM): Gompertz	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
BSC OS distribution (MCM): exponential	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
BSC OS distribution (MCM): Weibull	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
BSC OS distribution (MCM): Lognormal	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
BSC OS distribution (MCM): Gompertz	[redacted]	Alternative OS distribution	[redacted]	[redacted]	[redacted]
Duration of IVIG therapy: 6.5 months (NICE submission)	[redacted]	Based on the SACT data submitted to NICE.	[redacted]	[redacted]	[redacted]
Duration of IVIG therapy: 12 months (original DMC submission 2019)	[redacted]	Original submitted duration of IVIG treatment	[redacted]	[redacted]	[redacted]
Duration of IVIG therapy: 4 years	[redacted]	Alternative IVIG treatment duration	[redacted]	[redacted]	[redacted]
Duration of IVIG therapy: lifetime	[redacted]	Alternative IVIG treatment duration	[redacted]	[redacted]	[redacted]
CRS + HGG (AE) rate from DCO 2018, 11% and 16%	[redacted]	Alignment with clinical efficacy data reported, refer to Section 9.2)	[redacted]	[redacted]	[redacted]
Axi-cel: proportion of retreated patients	[redacted]	Extreme compared to base case of 9% (which is considered implausibly high)	[redacted]	[redacted]	[redacted]
Multiplier for DLBCL/PMBCL/TFL patients in long-term remission (general population utility values)	[redacted]	No data is currently available to inform this parameter, and so the effects of alternative assumptions are tested	[redacted]	[redacted]	[redacted]
Apply AE decrements/disutility	[redacted]	HRQoL is captured in trial and assumed to capture any utility decrements from AEs.	[redacted]	[redacted]	[redacted]

	Change	Reason / Rational / Source	Incremental cost (DKK)	Incremental benefit (QALYs)	ICER (DKK/QALY)
Proportion of patients in BSC receiving SCT, CORAL EXT 1 & 2 MAIC	[redacted]	Alignment with estimates from CORAL EXT 1 & 2 MAIC data.	[redacted]		
Proportion of patients in BSC receiving SCT, 0%	[redacted]	Conservative estimate.			
IVIG proportion treated with IVIG SCIG (ZUMA-1 proportion)	[redacted]	30% observed in the ZUMA-1 trial (base case i set to 55%)			
SMR 1.0		Sets the SMR equal to 1, indicating that observed mortality is in line with e pected mortality.			
IVIG – proportion aligned with SACT data (UK)		SACT data submitted to NICE reported 16%			
Population: mITT		Alternative patient popu-lation.			
Duration of 1 inpatient day		Alternative estimate of 1 inpatient day			
Medical resource use costs halved		Extreme scenario			
Medical resource use costs doubled	[redacted]	Extreme scenario			

Abbreviations: AC = Axicabtagene ciloleucel; AE = Adverse event; BSC = Best supportive care; CRS = Cytokine release syndrome; DCO = Data cut; DKK = Danish Kroner; DLBCL = Diffuse large B-cell lymphoma; DMC = Danish Medicines Council; HHG = Hypogammaglobulinemia; HRQoL = Health-related quality of life; IVIG = Intravenous immunoglobulin; MAIC = Matching-adjusted indirect comparisons; MCM = Mixture cure models; NICE = The National Institute for Health and Care Excellence's; OS = Overall survival; PFS = Progression free survival; PMBCL = Primary mediastinal large B-cell lymphoma; SACT = systemic anti-cancer treatment; SCIG = Subcutaneous immunoglobulin; SCT = Stem cell transplantation; SMR = Standard mortality ratio; SPM = Standard parametric model; TFL = Transformed follicular lymphoma; UK = United Kingdom, N/A= not applicable.

12.2.2 Probabilistic sensitivity analyses

A scatter plot of 1,000 simulations, including a 95% confidence cloud, is presented in [redacted] with a cost-effectiveness acceptability curve presented in [redacted] The full set of parameters included in the model (including details of distributional forms) and the PSA analysis are presented in Appendix G.

[redacted]

13. Budget impact analysis

The budget impact model is developed to estimate the expected budget impact of recommending axi-cel for treatment of DLBCL 3L in Denmark. The budget impact analysis has been embedded within the cost-effectiveness model and therefore any changes in the settings of the cost per patient model would affect the results of the budget impact model. The budget impact result is representative of the populations in the cost per patient model. The costs included in the budget impact model are undiscounted, and patient cost and transportation cost have not been included as per the guidelines by the DMC. The analysis is developed by comparing the costs for the Danish regions per year over five years in the scenario where axi-cel is recommended and the scenario where axi-cel is not recommended. The total budget impact per year is the difference between the two scenarios.

13.1 Number of patients (including assumptions of market share)

According to the clinical expert, it was estimated that approximately 14 patients would be candidates for axi-cel in 3L, given that axi-cel is recommended for r/r DLBCL patients in 2L. The expert estimated that of the 14 candidates, only half (n=7) would finally be eligible and receive axi-cel due to, among others, complications, progression of disease and CNS involvement. The proportion of patients receiving axi-cel in 3L is not expected to grow over time given that patients are treated in earlier lines. For the purpose of estimating the budget impact of the introduction of axi-cel (3L), a starting prevalence population of 7 eligible patients every year starting from Year 1 is assumed (discussed in Section 3.2), this estimate remains constant for each subsequent year. Table 68 presents the numbers of new patients expected to be treated over the next 5 years if axi-cel is introduced for 3L treatment.

Table 68 Number of new patients expected to be treated over the next five-year period if axi-cel is introduced (adjusted for market share)

	Year 1	Year 2	Year 3	Year 4	Year 5
			Recommendation		
Axi-cel	7	7	7	7	7
Salvage therapy	0	0	0	0	0
			Non-recommendation		
Axi-cel	0	0	0	0	0
Salvage therapy	7	7	7	7	7

13.2 Budget impact

The budget impact is informed by comparing the costs for the Danish healthcare system per year over five years in the scenario where axi-cel is recommended as standard treatment (3L) and the scenario where axi-cel is not recommended as standard treatment (3L). The total budget impact per year is the difference between the two scenarios. The budget impact estimated in Table 69 is based on non-discounted cost outputs (2024 DKK) from the cost-effectiveness model for five years, and the assumed eligible patients described above, as well as the assumed uptake of axi-cel for the treatment of eligible Danish r/r DLBCL 3L patients.

Table 69 Expected budget impact of recommending the pharmaceutical for the indication (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Axi-cel is recommended	[redacted]				
Axi-cel is NOT recommended					
Budget impact of the recommendation					

14. List of experts

Judith Jørgensen, Haematologist at Aarhus University Hospital was consulted for this submission dossier as a Danish clinical expert.

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Appendix A. Main characteristics of studies included

Table 70 Main characteristic of ZUMA-1

Trial name: ZUMA-1	NCT number: NCT02348216
Objective	The primary objectives of this study are: • Phase 1 Study: Evaluate the safety of axi-cel regimens • Phase 2 Pivotal Study: Evaluate the efficacy of axi-cel
Publications – title, author, journal, year	Five-year follow-up of ZUMA-1 supports the curative potential of axicabtagene ciloleucel in refractory large B-cell lymphoma. Neelapu SS, Jacobson CA, Ghobadi A, Miklos DB, Lekakis LJ, Oluwole OO, Lin Y, Braunschweig I, Hill BT, Timmerman JM, Deol A, Reagan PM, Stiff P, Flinn IW, Farooq U, Goy AH, McSweeney PA, Munoz J, Siddiqi T, Chavez JC, Herrera AF, Bartlett NL, Bot AA, Shen RR, D0ong J, Singh K, Miao H, Kim JJ, Zheng Y, Locke FL. Blood. 2023 (7) Long-Term (≥4 Year and ≥5 Year) Overall Survival (OS) By 12- and 24-Month Event-Free Survival (EFS): An Updated Analysis of ZUMA-1, the Pivotal Study of Axicabtagene Ciloleucel (Axi-Cel) in Patients (Pts) with Refractory Large B-Cell Lymphoma (LBCL). Caron Jacobson, Frederick L. Locke, Armin Ghobadi, David B. Miklos, Lazaros J. Lekakis, Olalekan O. Oluwole, Yi Lin, Brian T. Hill, John M. Timmerman, Abhinav Deol, Patrick M. Reagan, Patrick Stiff, Ian W. Flinn, Umar Farooq, Andre H. Goy, Javier Muñoz, Tanya Siddiqi, Rhine R. Shen, Adrian Bot, Jinghui Dong, Kanwarjit Singh, Clare Spooner, Roshan Karalliyadda, Jenny J. Kim, Yan Zheng, Sattva S. Neelapu. Blood 2021 (70) Predicting Survival for Chimeric Antigen Receptor T-Cell Therapy: A Validation of Survival Models Using Follow-Up Data From ZUMA-1. Vadgama S, Mann J, Bashir Z, Spooner C, Collins GP, Bullement A. Value Health. 2022 (71) Prophylactic corticosteroid use in patients receiving axicabtagene ciloleucel for large B-cell lymphoma. Oluwole OO, Bouabdallah K, Muñoz J, De Guibert S, Vose JM, Bartlett NL, Lin Y, Deol A, McSweeney PA, Goy AH, Kersten MJ, Jacobson CA, Farooq U, Minnema MC, Thieblemont C, Timmerman JM, Stiff P, Avivi I, Tzachanis D, Kim JJ, Bashir Z, McLeroy J, Zheng Y, Rossi JM, Johnson L, Goyal L, van Meerten T. Br J Haematol. 2021 (72) Long-term safety and activity of axicabtagene ciloleucel in refractory large B-cell lymphoma (ZUMA-1): a single-arm, multicentre, phase 1-2 trial. Locke FL, Ghobadi A, Jacobson CA, Miklos DB, Lekakis LJ, Oluwole OO, Lin Y, Braunschweig I, Hill BT, Timmerman JM, Deol A, Reagan PM, Stiff P, Flinn IW, Farooq U, Goy A, McSweeney PA, Munoz J, Siddiqi T, Chavez JC, Herrera AF, Bartlett NL, Wiezorek JS, Navale L, Xue A, Jiang Y, Bot A, Rossi JM, Kim JJ, Go WY, Neelapu SS. Lancet Oncol. 2019 (73) Axicabtagene Ciloleucel CAR T-Cell Therapy in Refractory Large B-Cell Lymphoma. Neelapu SS, Locke FL, Bartlett NL, Lekakis LJ, Miklos DB, Jacobson CA, Braunschweig I, Oluwole OO, Siddiqi T, Lin Y, Timmerman JM, Stiff PJ, Friedberg JW, Flinn IW, Goy A, Hill BT, Smith MR, Deol A, Farooq U, McSweeney P, Munoz J, Avivi I, Castro JE, Westin JR, Chavez JC, Ghobadi A, Komanduri KV, Levy R, Jacobsen ED, Witzig TE, Reagan P, Bot A, Rossi J, Navale L, Jiang Y, Aycock J, Elias M, Chang D, Wiezorek J, Go WY. N Engl J Med. 2017 (74)

Trial name: ZUMA-1	NCT number: NCT02348216
Study type and design	Phase 1/2 study. No randomisation or blinding due to open label single group assignment. The trial was completed the 10th of September 2020.
Sample size (n)	111 patients (cohort 1 and cohort 2)
Main inclusion criteria	1. Histologically confirmed: o DLBCL o PMBCL o TFL o HGBCL 2. Chemotherapy-refractory disease, defined as one of more of the following: o No response to last line of therapy i. PD as best response to most recent therapy regimen ii. Stable disease as best response to most recent therapy with duration no longer than 6 month from last dose of therapy OR o Refractory post-ASCT i. Disease progression or relapsed less than or equal to 12 months of ASCT (must have biopsy proven recurrence in relapsed individuals) ii. If salvage therapy is given post-ASCT, the individual must have had no response to or relapsed after the last line of therapy 3. Individuals must have received adequate prior therapy including at a minimum: o anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20-negative and o an anthracycline containing chemotherapy regimen o for individual with transformed FL must have chemorefractory disease after transformation to DLBCL. 4. At least one measurable lesion per revised IWG Response Criteria 5. ECOG performance status of 0 or 1 6. Absolute neutrophil count (ANC) ≥ 1000/uL 7. Absolute lymphocyte count ≥ 100/uL 8. Platelet count ≥ 75,000/uL 9. Adequate renal, hepatic, pulmonary and cardiac function defined as: o Creatinine clearance (as estimated by Cockcroft Gault) > 60 mL/min o Serum alanine aminotransferase (ALT)/aspartate aminotransferase (AST) < 2.5 upper limit of normal (ULN) o Total bilirubin < 1.5 mg/dL, except in individuals with Gilbert's syndrome o Cardiac ejection fraction >50%, no evidence of pericardial effusion as determined by an echocardiogram, and no clinically significant pleural effusion o Baseline oxygen saturation >92% on room air 10. All individuals or legally appointed representatives/caregivers, must personally sign and date the Institutional Review Board

Trial name: ZUMA-1	NCT number: NCT02348216
	(IRB)/Independent Ethics Committee (IEC) approved consent form before initiating any study specific procedures or activities. 11. Relapsed or refractory large B-cell lymphoma including DLBCL, PMBCL, TFL, and HGBCL after two systemic lines of therapy
Main exclusion criteria	1. History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) or follicular lymphoma unless disease free for at least 3 years 2. History of allo-SCT 3. Prior CAR therapy or other genetically modified T cell therapy 4. Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring IV antimicrobials for management. Simple urinary tract infection and uncomplicated bacterial pharyngitis are permitted if responding to active treatment 5. History of human immunodeficiency virus infection or acute or chronic active hepatitis B or C infection. Individuals with history of hepatitis infection must have cleared their infection as determined by standard serological and genetic testing per current Infectious Diseases Society of America guidelines 6. Individuals with detectable cerebrospinal fluid malignant cells, or brain metastases, or with a history of CNS lymphoma or primary CNS lymphoma, cerebrospinal fluid malignant cells or brain metastases 7. History or presence of CNS disorder such as seizure disorder, cerebrovascular ischemia/hemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
Intervention	A single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T cells/kg (n=101). Patients underwent leukapheresis followed by lymphodepleting chemotherapy (fludarabine 30 mg/m2 per day and cyclophosphamide 500 mg/m2 per day) on days –5 through –3.
Comparator(s)	N/A
Follow-up time	Median follow-up of 63.1 months from infusion (range 58.9-68.4) (date of data cutoff: 11 August 2021)
Is the study used in the health economic model?	Yes.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** *Primary outcome measures* • Phase 2 Pivotal Study (Cohorts 1 and 2): ORR as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma *Secondary outcome measures* • Phase 2: DOR as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma • Phase 2: PFS as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma • Phase 2: OS

Aadditional efficacy end points included in the 5-year follow study (7)

- DSS
- TTP
- Time to next therapy
- EFS

Endpoints not included in this application:

Primary outcome measures

- Phase 1 Study: Number of Participants Experiencing AEs Defined as Dose Limiting Toxicities
- Phase 2 Safety Management Study (Cohort 3): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades
- Phase 2 Safety Management Study (Cohort 4): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades
- Phase 2 Safety Management Study (Cohort 5): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades
- Phase 2 Safety Management Study (Cohort 6): Percentage of Participants With Treatment-Emergent CRS and Neurologic Toxicities by Severity Grades

Secondary outcome measures

- Phase 1 Study: ORR as Assessed by Investigator Per Revised IWG Response Criteria for Malignant Lymphoma
- Phase 2 Pivotal Study (Cohorts 1 and 2): ORR Per Independent Radiological Review Committee (IRRC)
- Phase 2 Safety Management Study (Cohorts 3, 4, 5, and 6): ORR as Assessed by Investigator Per the Revised IWG Response Criteria for Malignant Lymphoma
- Phase 2 Pivotal Study (Cohorts 1 and 2): DOR Using IRRC Per Cheson et al. 2007 (48)
- Phase 2 Pivotal Study (Cohorts 1 and 2): Best Overall Response Using IRRC Per Cheson 2007 (48)
- Phase 2 Pivotal Study (Cohorts 1 and 2): PFS Using IRRC Per Cheson 2007 (48)
- Percentage of Participants Experiencing TEAEs
- Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 4 and Grade 3 or Higher Resulting From Increased Parameter Value
- Percentage of Participants Experiencing Laboratory Toxicity Grade Shifts to Grade 4 and Grade 3 or Higher Resulting From Decreased Parameter Value
- Percentage of Participants With Anti-Axicabtagene Ciloleucel Antibodies
- Pharmacokinetics: Peak Level of Anti-CD19 CAR T Cells in Blood
- Pharmacodynamics: Peak Level of Cytokines in Serum (Phase 1 and Phase 2 Cohorts 1, 2, and 3)

Trial name: ZUMA-1	NCT number: NCT02348216
	• Pharmacodynamics: Peak Level of Cytokines (IP-10, Granzyme B, IFN-gamma, IL-1 RA, IL-10, IL-15, IL-2, IL-6, IL-7, IL-8, TNF Alpha, and GM-CSF) in Serum • Pharmacodynamics: Peak Level of Cytokines (Ferritin, ICAM-1, IL-2 R, Perforin, and VCAM-1) in Serum (Phase 2 Cohorts 4, 5, and 6) • Pharmacodynamics: Peak Level of Cytokine (CRP) in Serum • Pharmacodynamics: Peak Level of Cytokine (Ferritin) in Serum (Phase 1 and Phase 2 Cohorts 1 and 2) • Pharmacodynamics: Peak Level of Cytokine (Ferritin) in Serum (Phase 2 Cohort 3) • Percentage of Participants With Positive Replication Competent Retrovirus • Phase 2 Safety Management Study: Number of Participants With the EQ-5D Score • Phase 2 Safety Management Study: EQ-5D Visual Analogue Scale (VAS) Score
Method of analysis	Two-sided 95% confidence intervals (CIs) for response rates were assessed using the Clopper-Pearson method. Time-to-event outcomes were assessed using Kaplan-Meier methodology.
Subgroup analyses	The following subgroup analyses were conducted for ORR, CR, ongoing response, and OS: • ECOG performance status (0, 1) • Age (< 65 years, ≥ 65 years) • Disease type (DLBCL, PMBCL, or TFL) • Refractory subgroup (primary refractory, refratory to ≥ 2L therapy, relapsed to ≥ 2L therapy, relapse post ASCT) • Refractory to first line therapy (yes, no) • Refractory to ≥ 2 consecutive lines of therapy (yes, no) • Disease stage (I-II, III-IV) • Number of prior chemotherapies (1, 2-3, ≥4) • History of bone marrow involvement (yes, no) • Tumour burden (≤ median, > median) • Sex (male, female) • Race (white, asian, other) • CD19 at baseline (positive, negative) Corresponding forest plots were provided based rates for each subgroup. The following subgroup analyses were conducted for AEs: • Age (< 65 years, ≥ 65 years) • Sex (male, female) The subgroup analyses conducted for AEs were presented in the clinical study report in tabular form and based on percentages. All subgroup analyses were pre-specified.
Other relevant information	In addition to cohort 1 and 2 (both included in the phase 2 pivotal study) included in this application, the ZUMA-1 trial also includes cohort 3-6 for the phase 2 safety management study.

Abbreviations: 2L = second line; AE = adverse event; ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ASCT = autologous stem cell transplant; CAR = chimeric antigen receptor; CI = confidence interval; CNS = central nervous system; CR = complete response; CRS = cytokine release syndrome; DLBCL = diffuse large B cell lymphoma; DOR = duration of response; DSS = disease-specific survival; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; EQ-5D = European Quality of Life Five Dimension Five Level Scale; HGBCL = high grade B-cell lymphoma; IEC = Independent Ethics Committee; IRB = Institutional Review Board; IRRC = Independent Radiological Review Committee; IL = interleukin; IV = intraveneous; IWG = International Working Group; N/A = not applicable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PMBCL = primary mediastinal large B Cell lymphoma; TEAE = Treatment-Emergent Adverse Events; TFL = transformation follicular lymphoma; TTP = time to progression; ULN = upper limit normal; VAS = Visual Analogue Scale
Sources: Clinicaltrials.gov, 2022 (49), Kite Pharma Inc., 2018 (9), Neelapu et al., 2023 (7)

Table 71 Main characteristic of CORAL EXT 1 & 2

Trial name: CORAL EXT 1 & 2	NCT number: NCT00137995
Objective	CORAL EXT 1 & 2 are continuation studies of the CORAL study described Gisselbrecht et al. 2010 (10) and Gisselbrecht et al. 2012 (11). CORAL EXT 1: The objective was to define the efficacy of the 3L regimen and prognostic factors for a better outcome in patients who had an initial response to first salvage treatment but relapsed after carmustine, etoposide, cytarabine and melphalan (BEAM)/ASCT. CORAL EXT 2: To investigate the characteristics and survival of patients included in the CORAL study, who did not proceed to *per-protocol* ASCT and who were candidates for a 3L regimen.
Publications – title, author, journal, year	Outcomes of diffuse large B-cell lymphoma patients relapsing after autologous stem cell transplantation: an analysis of patients included in the CORAL study. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, Bouadballah R, Radford J, Bargetzi M, Ribrag V, Dührsen U, Ma D, Briere J, Thieblemont C, Bachy E, Moskowitz CH, Glass B, Gisselbrecht C. Bone Marrow Transplant. 2017 Feb;52(2):216-221. doi: 10.1038/bmt.2016.213. Epub 2016 Sep 19. PMID: 27643872. (52) Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, Milpied N, Radford J, Ketterer N, Shpilberg O, Dührsen U, Ma D, Brière J, Thieblemont C, Salles G, Moskowitz CH, Glass B, Gisselbrecht C. Bone Marrow Transplant. 2016 Jan;51(1):51-7. doi: 10.1038/bmt.2015.213. Epub 2015 Sep 14. PMID: 26367239. (6)
Study type and design	Observational follow-up studies of an unblinded, randomised phase III study comparing the two chemotherapy regimens. Patients enrolled in the original CORAL study were parallel assigned.
Sample size (n)	CORAL EXT 1: 75 patients CORAL EXT 2: 222 patients
Main inclusion criteria	General inclusion criteria in the CORAL study: • Patients with CD20-positive DLBCL. Disease must be histologically proven in case of relapse or partial response. • Aged 18 to 65 years. • First relapse after CR, less than partial remission or PR to first line treatment not achieving documented or confirmed CR. • Eligible for transplant • Previously treated with chemotherapy regimen containing anthracyclines with or without rituximab. • ECOG performance status 0 to 2.

Trial name: CORAL EXT 1 & 2	NCT number: NCT00137995
	• Minimum life expectancy of 3 months. • Signed written informed consent prior to randomisation. Additional inclusion criteria in the CORAL EXT 1 study: • Patients included in the CORAL study who relapsed after ASCT either before or after randomisation between rituximab and observation. Additional inclusion criteria in the CORAL EXT 2 study: • Patients who did not proceed to planned transplantation according to the protocol because of an event leading to withdrawal between cycle 1 and scheduled ASCT.
Main exclusion criteria	General exclusion criteria in the CORAL study: • Burkitt, mantle-cell and T-cell lymphoma. • CD20-negative diffuse large cell lymphoma. • Documented infection with human immunodeficiency virus and hepatitis B virus (in the absence of vaccination). • CNS or meningeal involvement by lymphoma. • Not previously treated with anthracycline-containing regimens. • Prior transplantation. • Contra-indication to any drug contained in the chemotherapy regimens. • Any serious active disease or co-morbid condition (according to the investigator's decision and information provided in the Investigational Drug Brochure). • Poor renal function (creatinine level > 150µmol/l or 1.5-2.0 x ULN); poor hepatic function (total bilirubin level > 30mmol/l [> 1.5 x ULN], transaminases > 2.5 maximum normal level) unless these abnormalities are related to the lymphoma; poor bone marrow reserve as defined by neutrophils < 1.5G/l or platelets < 100G/l, unless related to bone marrow infiltration. • Any history of cancer during the last 5 years with the exception of non-melanoma skin tumours or stage 0 (in situ) cervical carcinoma. • Treatment with any investigational drug within 30 days before planned first cycle of chemotherapy and during the study. • Pregnant women. • Adult patients unable to provide informed consent because of intellectual impairment. Additional exclusion criteria in the CORAL EXT 1 study: • Patients included in the CORAL study who did not relapse after ASCT. Additional exclusion criteria in the CORAL EXT 2 study: • Patients who proceeded to planned transplantation according to the protocol.
Intervention	R-ICE

Trial name: CORAL EXT 1 & 2	NCT number: NCT00137995
	• R-ICE + R-BEAM /ASCT Rituximab, Etoposide, Carboplatine, Ifosfamide + Mesna BCNU, Etoposide, Cytarabine, Melphalan Autologous Stem Cell Transplantation • Interventions: o Drug: Rituximab (375 mg/m² D-2/D1) o Drug: Etoposide (100 mg/m² D1-D2-D3) o Drug: Carboplatine (max 800mg D2) o Drug: Ifosfamide + Mesna (5 g/m² from D2 to D13) o Procedure: ASCT o Drug: BCNU (300mg/m² on D-6) o Drug: Etoposide (200 mg/m² D-6 to D-3) o Drug: Cytarabine (100 mg/m² from D-6 to D-3) o Drug: Melphalan (140 mg/m² on D-2) The intention-to-treat population was 202, and 197 received the induction treatment with R-ICE.
Comparator(s)	R-DHAP • R-DHAP + R-BEAM /ASCT Rituximab, Cisplatine, Cytosine Arabinoside, Dexamethasone BCNU, Etoposide, Cytarabine, Melphalan Autologous Stem Cell Transplantation • Interventions: o Drug: Rituximab (375 mg/m² D-2/D1) o Drug: Cisplatine (100 mg/m² from D1 to D13) o Drug: Cytosine Arabinoside (2000 mg/m²/12 h D2 D3) o Drug: Dexamethasone (40 mg From D1 to D4) o Procedure: ASCT o Drug: BCNU (300mg/m² on D-6) o Drug: Etoposide (200 mg/m² from D-6 to D-3) o Drug: Cytarabine (100 mg/m² from D-6 to D-3) o Drug: Melphalan (140 mg/m² on D-2) The intention-to-treat population was 194, and 191 received the induction treatment with R-DHAP.
Follow-up time	CORAL EXT 1: Median follow-up of 32.8 months (range 24.3–45.8 months). CORAL EXT 2: Median follow-up of 30.1 months.
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** • Overall response rate as assessed by the investigators using conventional methods that included computed tomography (CT) scans according to the IWG criteria (76) • CR/CRu as assessed by the investigators using conventional methods that included CT scans according to the IWG criteria (76) • PR as assessed by the investigators using conventional methods that included CT scans according to the IWG criteria (76) • OS **Endpoints not included in this application:**

Trial name: CORAL EXT 1 & 2	NCT number: NCT00137995
	• Tumour biology reviewed centrally
Method of analysis	The Kaplan–Meier method was used to estimate the OS. The Wilcoxon's signed-rank test or $\chi 2$ -test was used to compare the patient characteristics. Cox regression analysis was used to calculate the hazard ratio between different patient categories. All reported P-values are two-sided, and P-values < 0.05 were considered significant. In the CORAL EXT 2, the overall response rate (including the CR/CRu and PR) was analysed as an intention-to-treat analyses.
Subgroup analyses	The following subgroup analyses were conducted for OS in CORAL EXT 1: • Tertiary International Prognosis Index (IPI) at second relapse (0-2, >2) • Disease-free interval after ASCT[a] (<6 months, ≥6 months to <12 months, ≥12 months) • Response to third-line therapy (CR/CRu, PR, SD/PD) • Transplantation (yes, no) The following subgroup analyses were conducted for response to 3L regimen in CORAL EXT 2: • Response to 2L regimen (CR/CRu, PR, SD/PD, unknown) • Type of third-line regimen (ICE-type, DHAP-type, gemcitabine-containing, dexa-BEAM, CHOP-like regimens) The following subgroup analyses were conducted for OS in CORAL EXT2: • Tertiary IPI (0-2, >2) • 3L immunotherapy (yes, no) • Response to 3L regimen (CR/CRu, PR, SD/PD) • Transplantation (yes, no) • Transplantation (type, ASCT) • Allo-SCT o *BCL2/18q21* rearrangement[b] (yes, no) o *C-MYC/8q24* rearrangement[b] (yes, no) o Cell of origin[c] (germinal center, non-germinal center)
Other relevant information	N/A

Abbreviations: 2L = second line; 3L = third line; allo-SCT = allogeneic stem cell transplantation; ASCT = autologous stem cell transplantation; BEAM = carmustine, etoposide, cytarabine and melphalan; CI = confidence interval; CHOP = cyclophosphamide, vincristine, doxorubicin, and prednisone; CNS = central nervous system; CR = complete response; CRu= complete response unconfirmed; CT = computed tomography; D = day; DHAP = cisplatin, cytarabine, and dexamethasone; DLB = diffuse large B cell lymphma; DOR = duration of response; ECOG = Eastern Cooperative Oncology Group; EFS = event-free survival; ICE = ifosfamide, carboplatin, and etoposide; IPI = International Prognosis Index; IWG = International Working Group; N/A = not applicable; OS = overall survival; PD = progressive disease; PFS = progression-free survial; PR = partial response; R-DHAP = rituximab, cisplatin, cytarabine, and dexamethasone; R-ICE = rituximab, ifosfamide, carboplatine, and etoposide; SD = stable disease; ULN = upper limit normal

Notes: [a], Interval between CORAL-scheduled ASCT and relapse; [b], fluorescent *in situ* hybridization; [c], immunohistochemistry

Source: Clinicaltrials.gov, 2019 (53); Van Den Neste et al., 2017, (52), Van Den Neste et al., 2016 (6)

Appendix B. Efficacy results per study

Results per study

Table 72 Results per ZUMA-1 study

Results of ZUMA-1 NCT02348216											
				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		
ORR (11 August 2021)	Axi-cel	101	83% (74–90)*	N/A	N/A	N/A	N/A	N/A	N/A	Percentage of participants achieving either a complete response or a partial response per the revised IWG Response Criteria for Malignant Lymphoma (48). 95% CI was calculated by Clopper-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
ORR (11 August 2018)	Axi-cel	111	77% (69–85)*	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48). 95% CI was calculated by Clopper-Pearson method.	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A
CR (11 August 2021)	Axi-cel	101	58% (48–68)*	N/A	N/A	N/A	N/A	N/A	N/A	95% CI was calculated by Clopper-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
CR (11 August 2018)	Axi-cel	111	55% (N/A–N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48).	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A
PR (11 August 2021)	Axi-cel	101	25% (17–34)*	N/A	N/A	N/A	N/A	N/A	N/A	95% CI was calculated by Clop-per-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
PR (11 August 2018)	Axi-cel	111	23% (N/A–N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48).	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A
SD (11 August 2021)	Axi-cel	101	10% (5–17)*	N/A	N/A	N/A	N/A	N/A	N/A	95% CI was calculated by Clop-per-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
SD (11 August 2018)	Axi-cel	111	9% (N/A–N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48).	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
PD (11 August 2021)	Axi-cel	101	5% (2–11)*	N/A	N/A	N/A	N/A	N/A	N/A	95% CI was calculated by Clop-per-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
PD (11 August 2018)	Axi-cel	111	5% (N/A–N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48).	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A
Not done (11 August 2021)	Axi-cel	101	2% (0–7)*	N/A	N/A	N/A	N/A	N/A	N/A	95% CI was calculated by Clop-per-Pearson method.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Note done (11 August 2018)	Axi-cel	111	9% (N/A–N/A)	N/A	N/A	N/A	N/A	N/A	N/A	Based on the 24-month data cut, as this estimate has not changed. Disease status used are investigator assessment of disease status per Cheson et al. 2007 (48).	Kite Pharma Inc., 2018 (9)
	N/A	N/A	N/A								N/A
Ongoing objective response	Axi-cel	101	31%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Ongoing CR (11 August 2021)	Axi-cel	101	30%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
Ongoing PR	Axi-cel	101	1%	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Neelapu et al., 2023 (7)
(11 August 2021)	N/A	N/A	N/A								N/A
Median OS (11 August 2021)	Axi-cel	101	25.8 (12.8–NE)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median OS is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median OS (11 August 2021)	Axi-cel	111	17.4 (11.6–49.5)*	N/A	N/A	N/A	N/A	N/A	N/A	The median OS is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
	N/A	N/A	N/A								N/A
5-year OS rate	Axi-cel	101	42.6% (32.8–51.9)*	N/A	N/A	N/A	N/A	N/A	N/A	The 5-year OS rate is based on the KM estimator	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median DSS (11 August 2021)	Axi-cel	101	Not reached (15.4–NE)*	N/A	N/A	N/A	N/A	N/A	N/A	The median DSS is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
5-year DSS rate	Axi-cel	101	51.0% (40.4–60.6)*	N/A	N/A	N/A	N/A	N/A	N/A	The 5-year DSSS rate is based on the KM estimator	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median PFS	Axi-cel	101	5.9 (3.3–15.0)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median PFS is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
(11 August 2021)											
Median PFS	Axi-cel	111	6.3 (4.0–12.7)*	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessment per Cheson 2007 (48). The median PFS is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
(11 August 2021)	N/A	N/A	N/A								N/A
5-year PFS rate	Axi-cel	101	31.8% (22.9–41.1)*	N/A	N/A	N/A	N/A	N/A	N/A	The 5-year PFS rate is based on the KM estimator	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median TTP	Axi-cel	101	6.1 (4.4–29.7)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median TTP is based on the KM estimator.	Neelapu et al., 2023 (7)
(11 August 2021)	N/A	N/A	N/A								N/A
Median time to next therapy	Axi-cel	101	8.7 (6.9–34.9)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median time to next therapy is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median time to next therapy	Axi-cel	111	9.0 (7.3–22.0)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median time to next therapy is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
	N/A	N/A	N/A								N/A
Median DOR	Axi-cel	101	11.1 (4.2–51.3)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median DOR is based on the KM estimator.	Neelapu et al., 2023 (7)
(11 August 2021)	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
Median DOR (11 August 2021)	Axi-cel	111	11.1 (4.2–51.3)*	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessment per Cheson 2007 (48) among subjects with objective response. The median DOR is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
	N/A	N/A	N/A								N/A
Median duration of CR (11 August 2021)	Axi-cel	101	62.2 (12.9–NE)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median CR is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median duration of CR (11 August 2021)	Axi-cel	111	62.2 (12.9–NE)* months	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessment per Cheson 2007 (48) among subjects with objective response. The median CR is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
	N/A	N/A	N/A								N/A
Median duration of PR (11 August 2021)	Axi-cel	101	1.9 (1.3-2.1)*	N/A	N/A	N/A	N/A	N/A	N/A	The median PR is based on the KM estimator.	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A
Median duration of PR (11 August 2021)	Axi-cel	111	1.9 (1.3-2.1)*	N/A	N/A	N/A	N/A	N/A	N/A	Investigator assessment per Cheson 2007 (48) among subjects with objective response. The median PR is based on the KM estimator.	Kite Pharma Inc., 2021 (77)
	N/A	N/A	N/A								N/A

Results of ZUMA-1 NCT02348216											
				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		
Median EFS	Axi-cel	101	5.7 (3.1–13.9)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median EFS is based on the KM estimator.	Neelapu et al., 2023 (7)
(11 August 2021)	N/A	N/A	N/A								N/A
5-year EFS rate	Axi-cel	101	30.3% (21.5–39.6)*	N/A	N/A	N/A	N/A	N/A	N/A	The 5-year EFS rate is based on the KM estimator	Neelapu et al., 2023 (7)
	N/A	N/A	N/A								N/A

Abbreviations: Axi-cel = axicabtagene ciloleucel; CI = confidence interval; CR = complete response; DOR = duration of response; DSS = disease-specific survival; EFS = event-free survival; IWG = International Working Group; KM = Kaplan-Meier; N/A = not applicable; NE = not estimable; ORR = objective response rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease; TTP = time to progression.
Notes: * 95% CI.
Sources: Clinicaltrials.gov, 2022 (49); **Neelapu et al., 2023 (7);** Kite Pharma Inc., 2018 (9); Kite Pharma Inc., 2021 (77).

Table 73 Results per CORAL EXT 1 & 2 study pooled

Results of CORAL EXT 1 & 2 pooled (NCT00137995)											
				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 response rate	FAS	170	31%	N/A	N/A	N/A	N/A	N/A	N/A	Response was measured by an investigator using the 1999 IWG response criteria (76), in which CRu was included under CR.	Van Den Neste et al., 2017 (52); Van Den Neste et al., 2016 (6); Maziarz et al., 2022 (8)

Results of CORAL EXT 1 & 2 pooled (NCT00137995)				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		
	N/A	N/A	N/A								N/A
Overall response rate	ITT	205	30%	N/A	N/A	N/A	N/A	N/A	N/A	Response was measured by an investigator using the 1999 IWG response criteria (76), in which CRu was included under CR.	Van Den Neste et al., 2017 (52); Van Den Neste et al., 2016 (6); Maziarz et al., 2022 (8)
	N/A	N/A	N/A								N/A
OS	FAS	170	5.36 (4.34–6.37)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median survival is based on the KM estimator.	Maziarz et al., 2022 (8)
	N/A	N/A	N/A								N/A
OS	ITT	205	5.13 (3.88–6.21)* months	N/A	N/A	N/A	N/A	N/A	N/A	The median survival is based on the KM estimator.	Maziarz et al., 2022 (8)
	N/A	N/A	N/A								N/A

Abbreviations: CI = confidence interval; CR = complete response; CRu = complete response unconfirmed; FAS = full analysis set; ITT = intention-to-treat; IWG = International Working Group; KM = Kaplan-Meier; N/A = not applicable; OS = overall survival.
Notes: *, 95% CI
Source: Maziarz et al., 2022 (8); Van Den Neste et al., 2017 (52); Van Den Neste et al., 2016 (6)

Appendix C. Comparative analysis of efficacy

C.1 Methodology

ZUMA-1 was compared to CORAL EXT 1 & 2 in an unanchored MAIC. Using the unanchored MAIC approach allows for the indirect comparison of treatments within a disconnected network (an unanchored network) where IPD are available for only a subset of the studies. Thus, a MAIC to examine the relative efficacy of axi-cel compared historical salvage therapy data from the CORAL EXT 1 & 2 studies was conducted.

C.1.1 Data sources

The MAIC approach allows for population adjustment, when IPD is only available from one trial and aggregated data from another. In this case IPD was available for ZUMA-1 (74) and aggredated data for CORAL (11, 107).

Data for ZUMA-1 was obtained from the 48-month DCO (August 11, 2020) on Cohorts 1 & 2, and these were used to define a FAS of 101 patients (all patients that were infused with axi-cel) and an ITT dataset consisting of 111 patients (all patients that were enrolled, regardless of whether they were infused). By way of background, ZUMA-1 included 6 cohorts. The primary trial used for regulatory approval consisted of Cohorts 1 & 2. Cohorts 3 and 5 considered axi-cel in combination with other treatments and therefore were not of interest to the present study. Cohorts 4 and 6 considered alternative strategies for preventing AEs (108, 109); however, they have considerably shorter follow-up. Given that the objective of the study was focused on OS and ORR (i.e., that outcomes for the MAIC did not consider safety), there was no need to include the data from Cohorts 4 and 6 (108, 109).

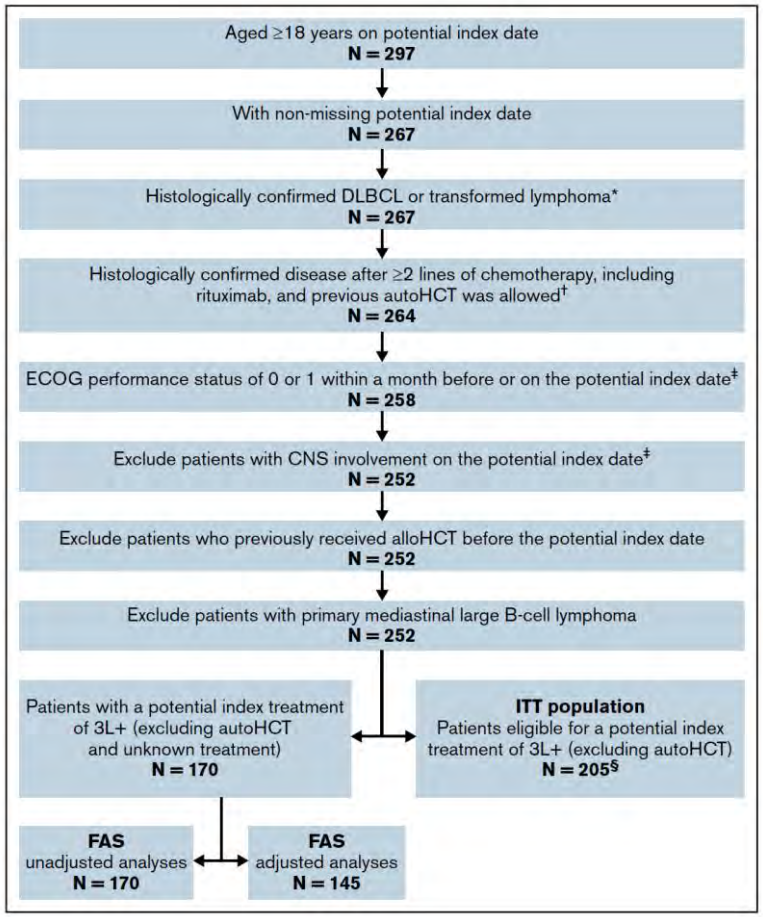
The CORAL study was a phase III RCT that compared two chemo immunotherapies – R-ICE and R-DHAP – as 2L therapy in DLBCL patients (107). Although CORAL was a 2L trial, large amounts of data from subsequent lines was collected as part of the extension studies CORAL EXT 1 & 2, which was used for these analyses. As the therapies used were beyond the R-ICE and R-DHAP 2L therapy, they were dubbed salvage therapy. Data from CORAL EXT 1 & 2 was included in a MAIC comparing tisa-cel to salvage therapy published by Maziarz and colleagues (2022) (8). Data from CORAL EXT 1 & 2 was extracted from the publication by Maziarz et al., as this publication contained more detailed information on prognostic factors and effect modifiers than the original CORAL publications.

Time-to-event outcomes were extracted from survival curves using DigitizeIt software, and the Guyot algorithm was used to construct pseudo-IPD reflective of the curves (110).

In the MAIC comparing axi-cel to salvage therapy, the CORALITT data set included all patients meeting the JULIET inclusion criteria (JULIET is a trial included in Maziarz et al. (2022), see section 6.1.2) and having non-ASCT 3L+ line of treatment (N = 205). The FAS analysis set further removed patients that had unknown 3L+ treatments and had a sample size of

145 when adjusted to match the JULIET trial. Note that these data sets were prepared by Maziarz et al. (2022) (8). Four datasets were extracted for CORAL: these are defined by the two analysis populations from CORAL, FAS (N=145) and ITT (N=205) as shown in Figure 20; and two different forms of population weighting (SMRW and fine stratification weight [FSW] approaches). As a result, patient characteristics and outcomes were extracted for each combination: FAS SMRW, ITT SMRW, FAS FSW and ITT FSW. SMRW analyses in the Maziarz et al. (2022) (8) study involved keeping the JULIET patients unweighted and re-weighting the CORAL patients to align with JULIET. As such, the SMRW analysis aligns the CORAL population to the JULIET population. Only results based on the SMRW approach are presented, as FSW is an alternative approach that can be viewed as a sensitivity analysis to the SMRW.

Figure 20 Sample selection for CORAL EXT 1 & 2 as reported by Maziarz et al. (2022)



Abbreviations: CNS = central nervous system; DLBCL = diffuse larbe B-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; FAS = full analysis set; HCT = haemotopic cell transplant; ITT = intention-to-treat.
Notes: *All patients in CORAL follow-up were assumed to have histologically confirmed DLBCL or transformed lymphoma based on the CORAL studies. †CORAL patients were randomly assigned to receive rituximab-based 2L treatment, although 3 patients did not ultimately receive rituximab in 2L and were excluded in this step. ‡A large proportion of patients in CORAL follow-up did not have an ECOG or CNS assessment; those with a missing/unknown ECOG status or CNS assessment were included in the analyses to preserve the sample size. §The ITT population had N 5 205 in both the adjusted and unadjusted analyses.
Source: Maizarz et al., 2022 (8).

C.1.2 Study endpoints

Thie MAIC was restricted to two outcomes: Overall survival and overall response rate. OS was defined as time from index date to death or censoring date for patients not experiencing a death event (death due to any reason). For CORAL EXT 1 & 2, the index date was start of therapy for the FAS population and in the ITT population, the index was defined as the date of the selected index treatment initiation, if known, or the date of relapse from last line if the initiation date of the index treatment was missing. In ZUMA-1, the index date for the FAS analysis set was the date of axi-cel infusion, while the index date for the ITT analysis set was the leukapheresis date. This emulates the methods used in Maziarz et al (8) and informs the comparative analysis for this submission. Date of censoring was the last follow-up date.

ORR was measured in both studies, but the criteria used were different. CORAL EXT 1 & 2 used the 1999 International Working Group (IWG) response criteria, while ZUMA-1 used the revised 2007 IWG criteria. This is of minimal concern given that the more important difference between the two criteria are how complete response are assessed rather than how ORR is measured. For both studies, patients with unknown response or without an index treatment were considered non-responders.

C.1.3 Statistical analyses

Statistical analyses consisted of population adjusted, unanchored indirect treatment comparisons. The individual patients from ZUMA-1 were re-weighted in terms of their alignment with the summary statistics of the CORAL EXT 1 & 2 trial. The result is an alignment of patient characteristics for the variables used to calculate the weights. Therefore, the first step of the analysis was to calculate the weights and verify how patient characteristics aligned post-weighting. The weights were calculated based on the identified prognostic factors and effect-modifiers. Once the weights were available, comparative effectiveness estimates were obtained.

C.1.3.1 Estimation of weights for ZUMA-1

Weights were derived for both the FAS and ITT populations from ZUMA-1. The propensity score was defined as the probability of treatment assignment conditional on baseline covariates. This was determined via logistic regression, based on the IPD from the index trial:

$$\text{logit}(\text{T}) = \beta_0 + \sum_{i=1}^{C} X_i \qquad (1)$$

where *T* represents the treatment group and X_i are the $i=1…C$ covariates under consideration. Importantly, in an unanchored MAIC, where there is no common comparator between trials, both prognostic factors and effect modifiers must be included in the model used to obtain the weights. When the weights have been obtained. Outcomes for the index treatment in the target population can be estimated by reweighting the observed outcomes from the index trial.

In a MAIC, the mean outcomes in the target population are estimated by taking a weighted average of the outcomes of individuals in the index trial. The weighting is defined as:

$$\widehat{Y_{(T)}} = \frac{\sum_{i=1}^{N} Y_{i(I)} w_i}{\sum_{i=1}^{N} w_i} \quad (2)$$

where $\widehat{Y_{(T)}}$ is the estimated mean outcome in the target population, $Y_{i(I)}$ is the observed outcome for individual i in the index population, w_i is the weight for individual i, and N is the number of individuals in the index trial. When the weights are estimated with a propensity score logistic regression model, these weights represent the odds of being enrolled in the target trial versus the index trial.

The validity of a MAIC model depends upon the overlap between the IPD and the aggregate population. When there is little overlap between the populations, the estimates become heavily influenced by relatively few individuals. The extent of overlap is represented with the ESS:

$$\text{ESS} = \frac{\left(\sum_{t=1}^{T} \sum_{i=1}^{N} w_{it}\right)^2}{\sum_{t=1}^{T} \sum_{i=1}^{N} w_{it}^2} \quad (3)$$

ESS is an adjustment of the sample size that accounts for the weighting of the observations, and the resulting correlations between estimated responses. As with the typical sample size, a large value is preferable to a small value, as the larger sample contains more information. The NICE Decision Support Unit technical support document 18 reports that in a sample of three studies that used an MAIC, the effective sample size was reduced by 80% of the original sample size on average (78).

As described above, the validity of the MAIC depends on how well the propensity score weights account for differences between the index trial and the target population in each comparator study

C.1.3.1.1 Variables included in weighting model

When reweighting patients as part of a MAIC, it is a requirement that there is reasonable overlap between the included trials. One way to ensure this is by making sure that the inclusion and exclusion criteria of the trials match, and potentially exclude patients from the trial with IPD, that would not be includable in the trial with only aggregated data.

Table 74 presents and compares the inclusion criteria for each study. The inclusion/exclusion criteria were very similar across the studies, and only slight differences were observed. For example, both studies included adults, however the CORAL trial had a maximum age of 65, while ZUMA-1 did not. This difference was mitigated by the fact that the lines of treatment used in the analyses were post-trial – meaning that patients were older by the time they were included in the analysis. While CORAL allowed the inclusion of ECOG

performance score of 2, these patients were excluded from the Maziarz analyses (see Figure 20). The application of the JULIET criteria to the CORAL study resulted in a population that is similar to the ZUMA-1 trial.

Table 74 Inclusion criteria across included trials

Inclusion criteria	ZUMA-1	CORAL	CORAL (Matched to JULIET)
Demographics			
Adults aged 18 or more	✓	X	X
Adults aged 18-65	X	✓	✓
Men and women eligible	✓	✓	✓
Histologically confirmed large B cell lymphoma including the following types			
Diffuse large B-cell lymphoma	✓	✓	✓
Primary mediastinal B-cell lymphoma	✓	unspecified	unspecified
Transformed follicular lymphoma	✓	unspecified	unspecified
High grade B-cell lymphoma	✓	unspecified	unspecified
Other criteria			
Relapsed or refractory disease after at least 1 line of treatment with combination chemoimmunotherapy	X	✓	X
Relapsed or refractory disease after at least 2 lines of treatment with combination chemoimmunotherapy	✓	X	✓

ECOG performance status of 0 or 1	✓	X	✓
ECOG performance status of 0 - 2	X	✓	X
No known history or suspicion of central nervous system involvement by lymphoma	✓	✓	✓
Not pregnant or breastfeeding	✓	✓	✓
Adequate organ function	✓	✓	✓
No prior CAR-T therapy	✓	✓	✓

Abbreviations: CAR = chimeric antigen receptor; ECOG = Eastern Cooperative Oncology Group.

The choice of variables on which to adjust followed those identified in the Maziarz et al study. In their study, confounders were identified through a systematic literature review, followed by ranking of their importance by clinical experts. The identified confounders were:

- Age at diagnosis
- Ann Arbor disease stage (III-IV vs I-II)
- Extranodal site involvement (0-1 vs ≥2)
- Status of disease
    - Relapsed after last line
    - Refractory to all lines
    - Refractory to last line, but not all lines
- Time to 2L start after diagnosis (<12 months, 12-24 months, >24 months)
- Prior ASCT (described as Hematopoietic cell transplant in CORAL)

- Number of relapses excluding refractory
- Serum LDH level (Normal vs. Elevated)
- ECOG (0-1 vs >2)

Variables that were identified as of less interest (dubbed other baseline variables) were:

- Baseline age
- Sex
- Ann Arbor stage at diagnosis
- International prognostic index (IPI; <2 vs ≥2)
- Number of prior lines of therapy

In the Maziarz et al analysis, Serum LDH was excluded from the model due to missing values. Similarly, ECOG was excluded from the model as everyone was 0-1 and there was no patients in the >2 category. The extranodal site involvement variable was only included in the FAS analyses and not the ITT analyses, presumably due to missing values in the ITT set.

There have been other MAICs conducted with ZUMA-1 data in the past, and these have selected slightly different variables. For starters, both IPI and number of prior lines were included. The likely reason that number of prior lines was not included in the Maziarz analysis is that all patients included in CORAL start at 3L, which may lead to computational complications relative to a sample that has more diverse line numbers in the CAR-T trials. Other variables included in the prior ZUMA-1 MAIC are cell of origin (DLBCL vs other LBCL) and double/triple hit (yes vs no). It also included relapsed vs refractory, but this is a simplified parameterization of *status of disease* used in Maziarz et al.

Neither histology nor double/triple hit were available for alignment in the analysis. Furthermore, the parameterization of number of prior lines used in the ZUMA-1 MAIC was not available for CORAL. Use of the IPI score was considered in the modeling step despite not being included in the Maziarz et al analysis.

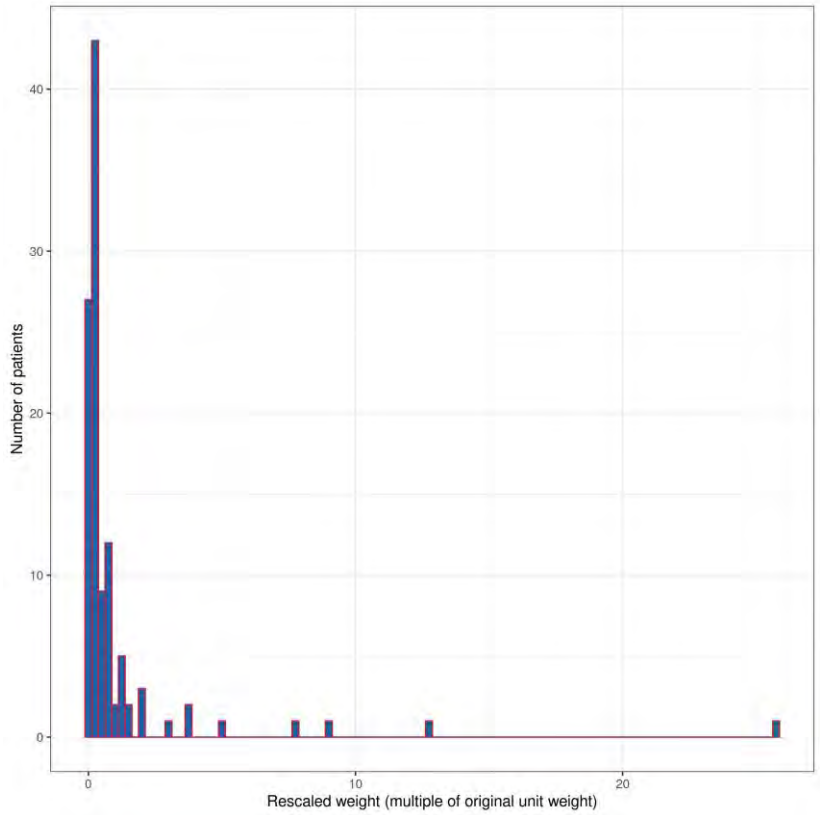
Additional data considerations for the modeling were as follows. First, date of diagnosis was not available for 8 patients in ZUMA-1. For these patients, date of start of first-line therapy was used instead. Among the remaining patients the median time from diagnosis to initiation of first-line therapy was 15 days (IQR: 6-26). An inspection of the time to 2L variable was conducted to determine if this change could influence categorization and none of the patients were near the 12- and 24-month thresholds. As such, this form of imputation is unlikely to have a material impact on the analyses.

Second, the available data for extranodal disease in ZUMA-1 was restricted to a yes/no parameterization, rather than the 0-1 vs ≥2 parameterization used by CORAL. This made it infeasible to adjust to this variable. As noted earlier, extranodal disease was not matched in all of the analyses by Maziarz et al. Third, LDH was not available for all patients, but was generally well reported. Although an explicit value of what the upper limit of normal (ULN) used by Maziarz et al was not provided, we used ≤250 and >250 units/L to categorize patients in ZUMA-1 as this appears to be the most common threshold used. Moreover, prior work with ZUMA-1 has used 500 units/L as a 2xULN threshold.

C.1.3.1.2 Results of population adjustment

The weighting procedure was conducted with three different sets of prognostic factors. The first set consisted of the set of variables targeted in the feasibility assessment; specifically: Age at diagnosis, Ann Arbor stage at baseline, number of relapses, disease status (relapsed/refractory status for lines of therapy), time to 2L from diagnosis, and Prior HCT. This weighting resulted in a poor distribution of weights and a very low ESS. This was a result of poor overlap in the relapse/refractory variable, which led to a few patients having extreme weights. This occurred for both the ITT (ESS=12.78) and FAS (ESS=10.53) populations. The reduction in ESS was 88.5% for ITT and 89.6% for the FAS. These large reductions lead to unreliable estimates of effect, as they are based on relatively few observations. The distribution of the weights is presented in Figure 21. As can be seen, one patient had a weight equivalent to over 25 patients.

Figure 21 Distribution of weights when including all variables



The second set of prognostic factors was the same as above, but with the number of relapses variable removed. This variable was removed because it was balanced across the two studies, and the concept of relapse is captured in the disease status variable. Removing it resulted in a much better distribution of weights (Figure 22), and a more reasonable ESS. The ESS for ITT population was 44.58, and for the FAS it was 41.93. The reduction from the total sample size is now less than 60%, which is in line with the values reported in the NICE DSU TSD 18. Estimates from these results were considered the primary results. While it is important to include all prognostic factors in unanchored analyses, the exclusion of

this variable was not considered problematic, as information on the number of relapses is captured in other prognostic factors such as disease status. Because the prognostic factors are correlated, excluding one should not cause a severe reduction in the amount of information available.

Figure 22 Distribution of weights after removing number of relapses

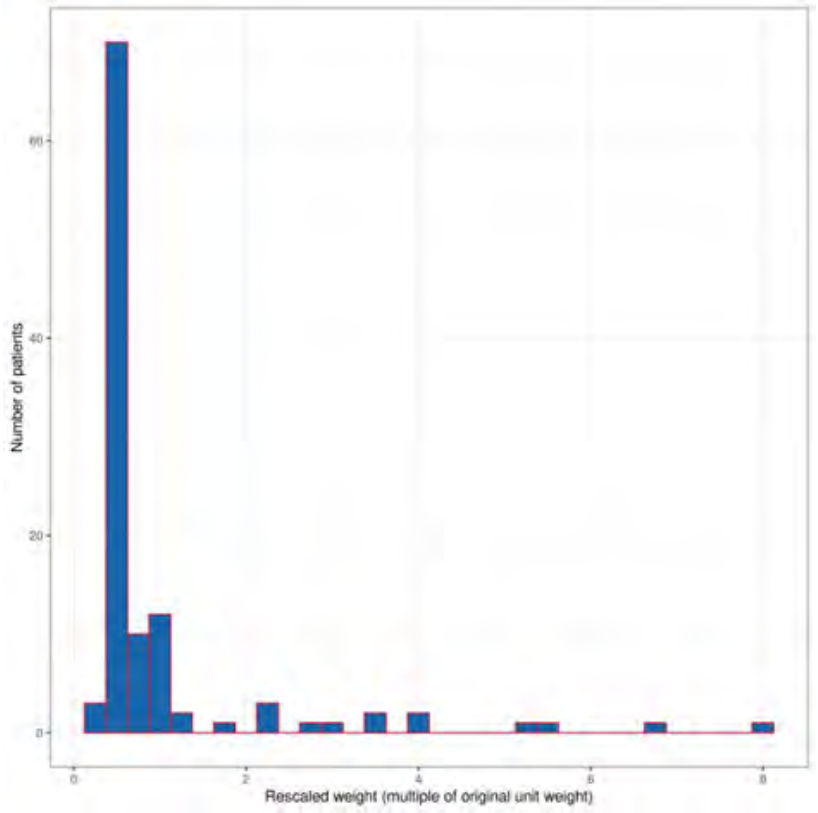


Table 75 provides a summary of variables included in each of the analyses. As mentioned above, the number of prior lines of therapy and IPI were both considered for deriving the weights, but led to low ESS and were excluded on that basis.

Table 75 Variables included in the weighting model

Baseline characteristic	Target variables	Used variables
Age at diagnosis	✓	✓
Ann Arbor disease stage	✓	✓
Extranodal involvement	x	x
Disease status	✓	✓
Time from diagnosis to 2nd line	✓	✓
Prior autologous SCT	✓	✓
Number of relapses	✓	x
IPI	✓	x
Number of prior lines	✓	x

Abbreviations: SCT: Stem cell transplant

The weighting procedure led to populations that were more similar than they were without weights. Table 76 shows the effect of the weightings. Patient characteristics are presented for the main cohorts of ZUMA-1 and CORAL, along with the ZUMA-1 patient characteristics after weighting. The weighting procedure leads to exact matches for variables included in the MAIC. For other variables, the weightings resulted in more similar, but not exact, distributions. There was a slightly larger separation of the number of relapses, which may explain why aligning on this variable led to a low ESS.

Table 76 Patient characteristics for all population, pre- and post-adjustment

	FAS					ITT				
		FSW		SMRW			FSW		SMRW	
Characteristic	ZUMA-1	CORAL	ZUMA-1 weighted	CORAL	ZUMA-1 weighted	ZUMA-1	CORAL	ZUMA-1 weighted	CORAL	ZUMA-1 weighted
Characteristics included in model										
Age > 60	33.7%	28.9%	28.9%	28.6%	28.6%	32.4%	29.6%	29.6%	36.9%	36.9%
Age at diag. (mean)	56.3	54.1	56.3	54.1	56.2	56.2	53.9	56.3	54.7	57.2
Age (sd)	12.1	11.5	11.7	11.5	11.8	11.9	11.5	12.1	11.5	12.2
Stage III-IV	85.1%	76.1%	76.1%	75.9%	75.9%	84.7%	66.0%	66.0%	63.6%	63.6%
Prior autologous SCT	24.8%	52.4%	52.4%	51.0%	51.0%	23.4%	47.4%	47.4%	43.8%	43.8%
Status of disease										
Relapsed after last	11.9%	49.4%	49.4%	47.5%	47.5%	11.7%	47.5%	47.5%	52.6%	52.6%
Refractory to all	22.8%	17.6%	17.6%	17.6%	17.6%	22.5%	15.2%	15.2%	16.1%	16.1%
Refractory to last, not all	65.3%	33.0%	33.0%	34.9%	34.9%	65.8%	37.3%	37.3%	41.3%	41.3%
Time to 2L from di-agnosis										
< 12 months	76.2%	53.3%	53.3%	54.6%	54.6%	75.7%	57.5%	57.5%	59.5%	59.5%
12 to 24 months	14.9%	24.2%	24.2%	23.2%	23.2%	13.5%	24.3%	24.3%	23.6%	23.6%
> 24 months	8.9%	22.5%	22.5%	22.2%	22.2%	10.8%	18.3%	18.2%	16.9%	16.9%
Characteristics not included in model										
Relapses; mean (sd)	1.5 (1.4)	1.5 (0.9)	2.2 (1.5)	1.5 (0.9)	2.1 (1.5)	1.5 (1.5)	1.5 (0.9)	2.2 (1.5)	1.4 (0.9)	2.1 (1.5)
Prior LoT; mean (sd)	3.3 (1.5)	2.4 (0.7)	3.4 (1.2)	2.4 (0.7)	3.4 (1.2)	3.4 (1.5)	2.4 (0.7)	3.5 (1.2)	2.4 (0.7)	3.4 (1.3)
IPI >= 2	75.2%	87.1%	77.6%	87.1%	77.4%	76.6%	88.7%	75.1%	89.7%	75.8%
ECOG 0/1	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%	100.0%
Other variables										
Male	67.3%	65.5%	63.1%	65.7%	63.5%	69.4%	53.9%	68.3%	54.7%	70.6%
LDH high	57.0%	28.3%	55.1%	27.7%	54.6%	57.0%	32.5%	55.1%	36.1%	54.6%

Overall, the MAIC weighting procedure led to better balance across the two trials, with respect to the prognostic and effect modifying factors. This weighting results in the ZUMA-1 population more closely resembling that of CORAL. The initial weighting approach was revised to exclude number of relapses as this led to very low effective sample sizes (ESS). Removing this variable resulted in a much better distribution of weights, and a more reasonable ESS: 41.93 in the FAS and 44.58 in the ITT.

This MAIC has some limitations. These primarily pertain to the unanchored design of the study. Unanchored MAICs require very strong assumptions; including that of conditional constancy of absolute effects. Specifically, the absolute treatment effects are assumed constant at any given level of the effect modifiers and prognostic variables, and all effect modifiers and prognostic variables are known. It is impossible to assess the validity of this assumption. We attempted to adjust for as many factors as is feasible. Nonetheless, there are known prognostic factors that were not included in the model. While extranodal disease was identified as a potential prognostic factor, the differences in reporting precluded its inclusion in the analyses. Despite this, it is not expected that this will invalidate the results. In fact, this variable was not included in the ITT analyses by Maziarz et al. (2022) (8), and so its exclusion here is consistent with those results. A lesser, yet noteworthy limitation, is the use of different assessment criteria for response. CORAL used the 1999 IWG response criteria (76), while ZUMA-1 used the revised 2007 IWG criteria (48). As the differences are centered around complete response rather than overall response, this should be of negligible concern.

C.1.3.2 Estimation of relative treatment effects

For the categorical outcome (ORR), meta-analysis of the proportion for the evidence base were obtained using meta-analyses for proportions using the DerSimonian-Laird method and the proportion for axi-cel was obtained using a weighted mean as described in equation (2) above (75).

For OS, the analyses were weighted Cox regressions, which modeled the IPD from ZUMA-1 simultaneously with the pseudo-IPD from CORAL. The patients from ZUMA-1 were weighted according to the propensity weights, while all patients from CORAL were given a weight of 1.

Cox regression relies on the assumption of proportional hazards, which was tested using the global test for proportionality based on Schoenfeld residuals. The p-value for the global Schoenfeld test was 0.00013 and 0.00177 for the ITT and FAS populations, respectively. This strongly indicates violation of the proportional hazards assumption; thus, the hazard ratios obtained from Cox regression may not appropriately reflect the actual hazards for each treatment arm and should be interpreted with caution(75).

As only one estimate was available for each comparison, only a fixed effect model was used (75).

As mentioned above, CORAL used the 1999 IWG response criteria (76), while ZUMA-1 used the revised 2007 IWG criteria (48). As the differences are centered around complete response rather than overall response, this should be of negligible concern.

C.2 Results

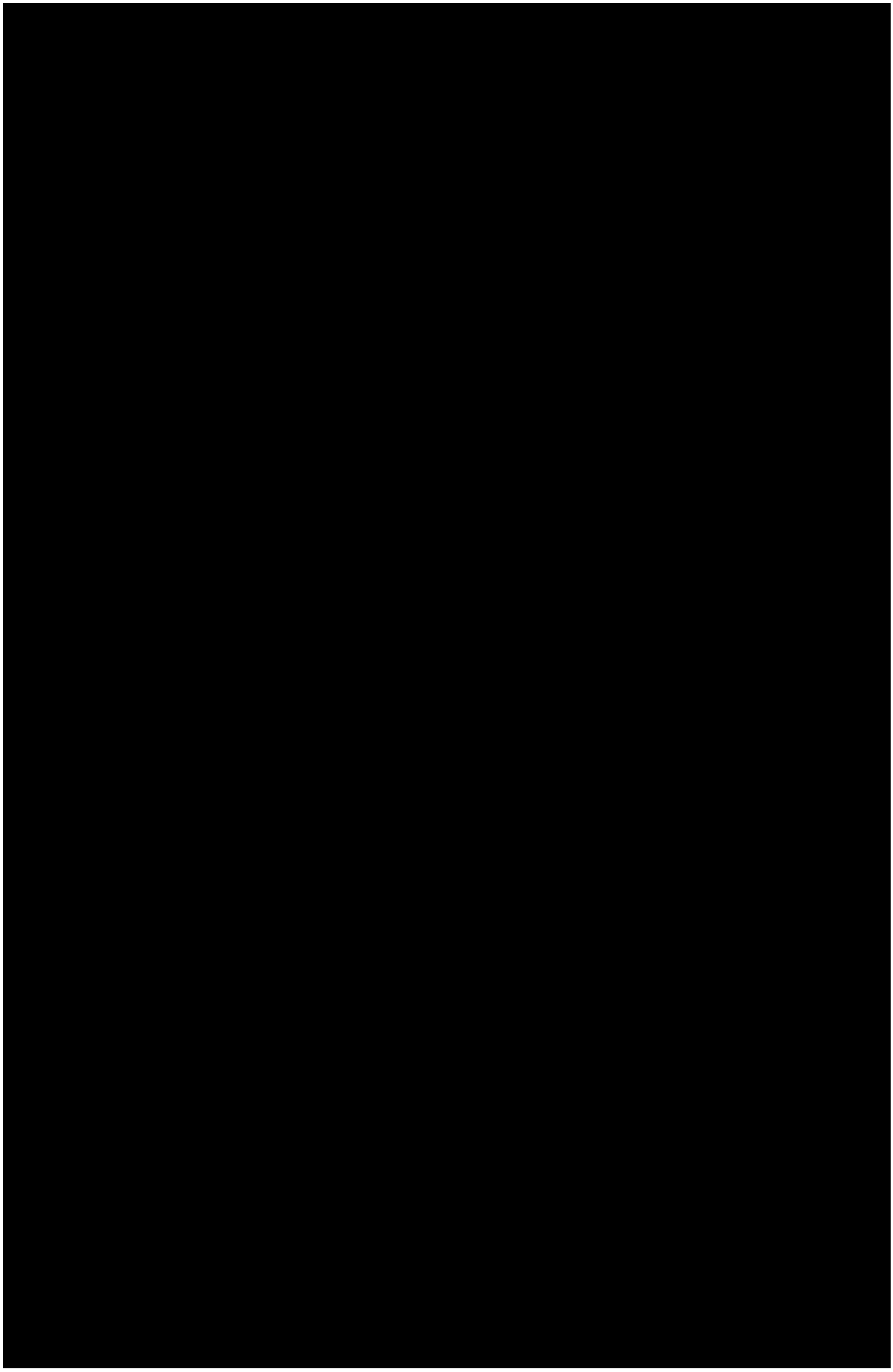
The results of the MAIC are shown in Table 77. As described above, the proportional hazards assumption was not met for any of the analysed populations. Therefore, the hazard ratios presented should be interpreted with caution. While the hazard ratios themselves may not appropriately reflect the hazards in each treatment arm, it is clear from the results that the reweighting of ZUMA-1 patient to match the characteristics of CORAL patients led to improved results for axi-cel (e.g., median OS in the ITT population increased from 17.3 to 36.1 months). Of note, the health economic model used for this submission does not rely on the OS estimates from the ZUMA-1 versus CORAL EXT 1 & 2 MAIC, rather parametric survival curves were independently fitted to the reweighted IPD from ZUMA-1 and the pseudo-IPD from CORAL EXT 1 & 2; thus, the results included in the health economic analysis are not reliant on the proportional hazards assumption

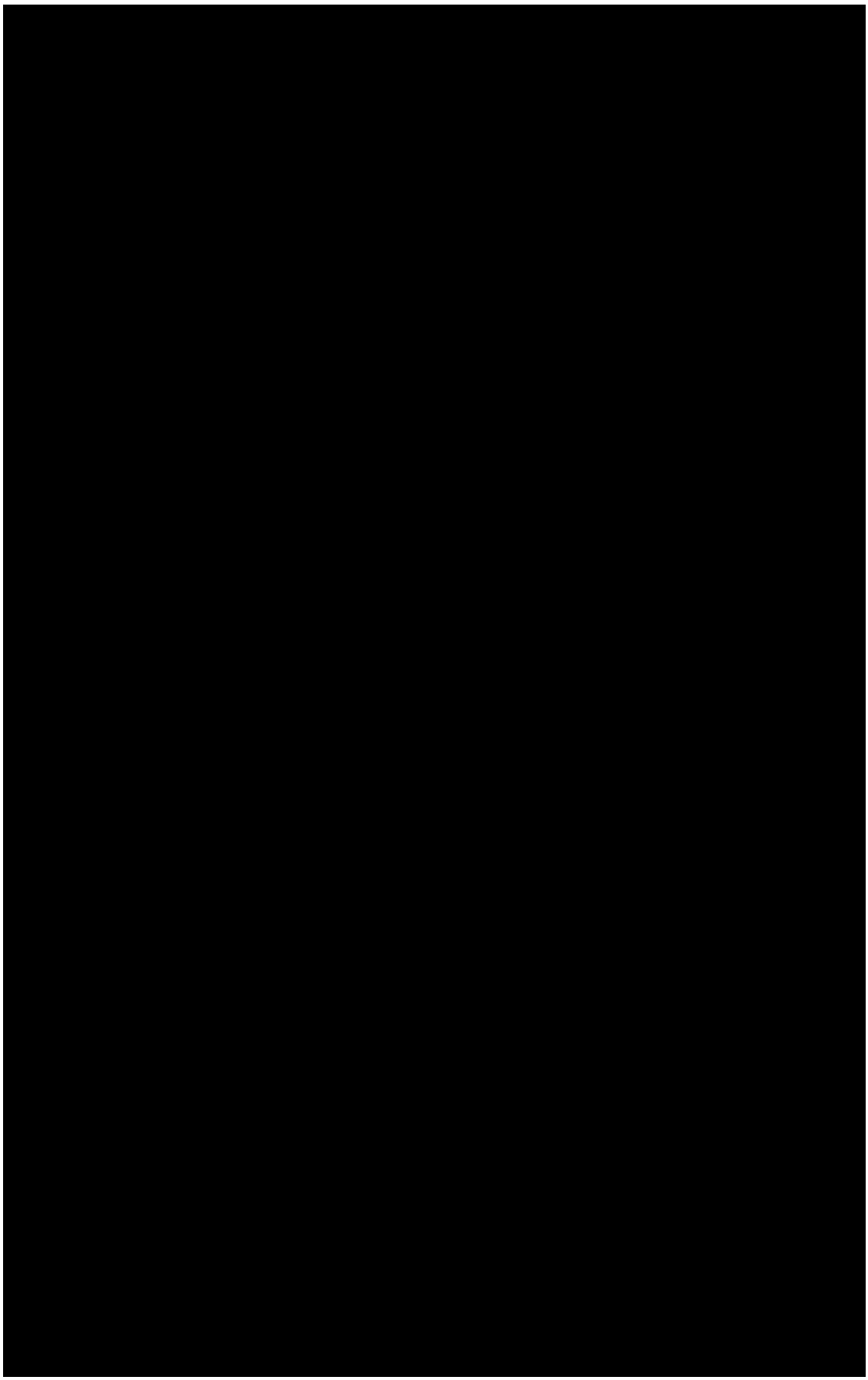
Table 77 Comparative analysis of studies comparing axi-cel to standard of care for patients with for patients with r/r DLBCL; 48-month DCO

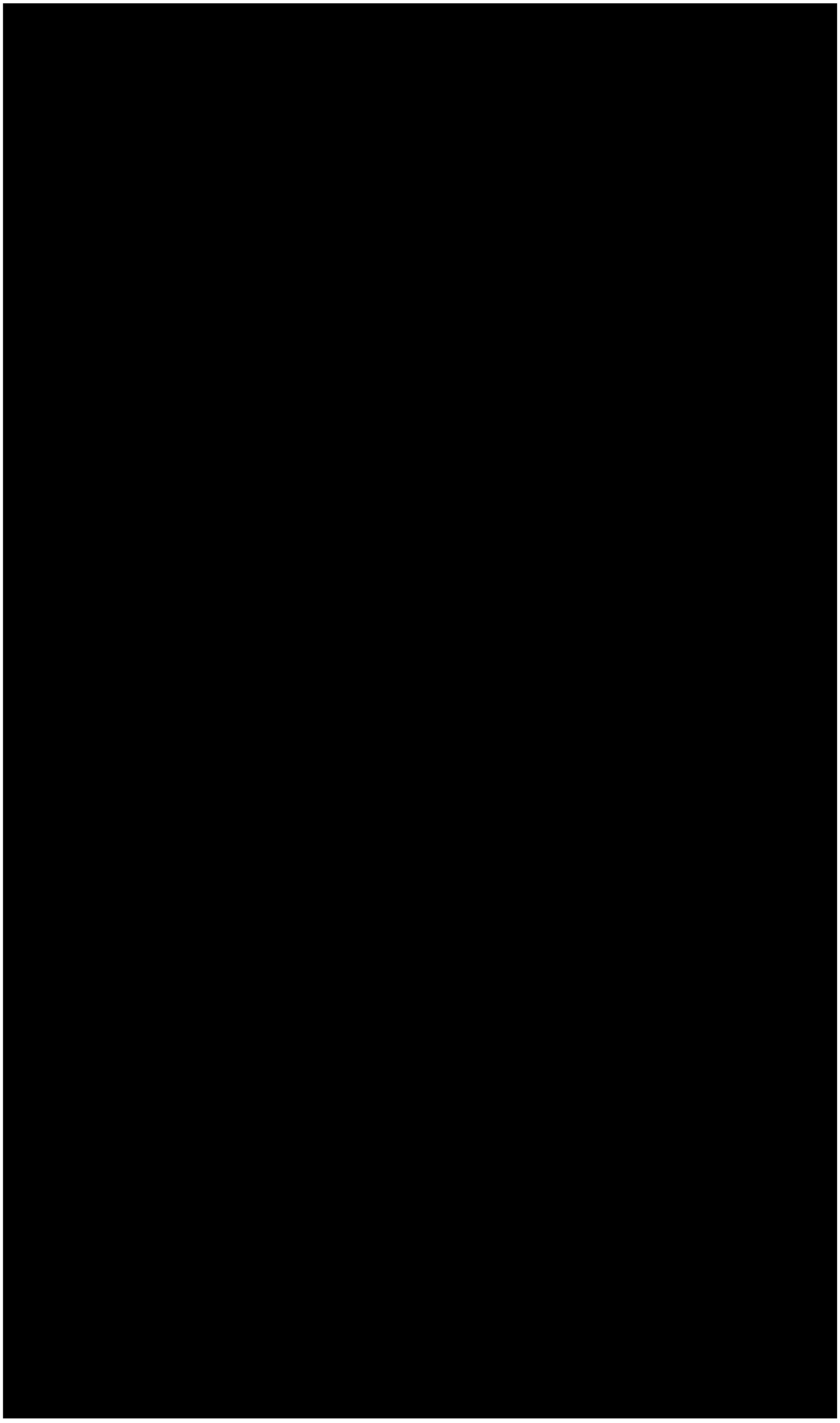
				Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**		
Median OS	Axi-cel	101	25.8 months (14.6-NR)	HR: 0.30	0.22-0.42	N/A	Unadjusted SMRW, FAS population.	No
	Salvage therapy	145	4.34 months (3.48-5.39)					
Median OS	Axi-cel	63	NR (25.8-NR)	HR: 0.24	0.16-0.36	N/A	Adjusted SMRW, FAS population.	No
	Salvage therapy	145	4.34 months (3.48-5.39)					
Median OS	Axi-cel	111	17.3 months (12.3-NR)	HR: 0.38	0.28-0.50	N/A	Unadjusted SMRW, ITT population.	No
	Salvage therapy	205	4.04 months (3.25-5.75)					
Median OS	Axi-cel	72	36.1 months (12.0-NR)	HR: 0.31	0.22-0.45	N/A	Adjusted SMRW, ITT population.	No

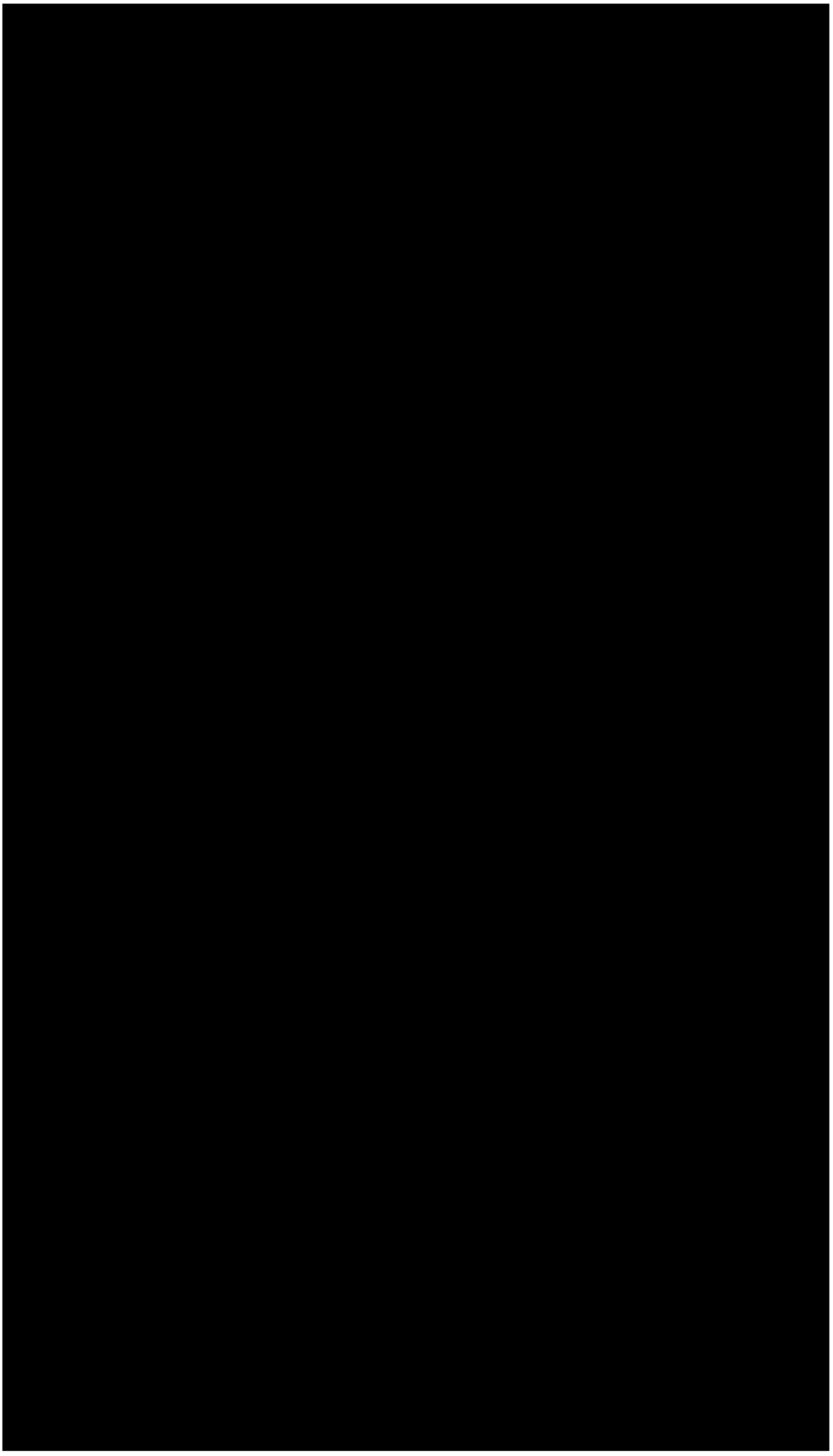
				Relative difference in effect			Method used for quantitative synthesis	Result used in the health economic analysis?
Outcome	**Study arm**	**N**	**Result (95% CI)**	**Difference**	**95% CI**	***P* value**		
	Salvage therapy	205	4.04 months (3.25-5.75)					
Overall response rate	Axi-cel	101	74.3% (64.4 – 82.2)	OR: 11.06	6.07 – 20.16	N/A	Unadjusted SMRW, FAS population.	No
	Salvage therapy	145	31.2% (24.4 – 38.8)					
Overall response rate	Axi-cel	63	80.9% (68.7 – 89.4)	OR: 15.26	7.32 – 31.80	N/A	Adjusted SMRW, FAS population.	No
	Salvage therapy	145	20.7% (14.6 – 28.4)					
Overall response rate	Axi-cel	111	67.6% (57.9 – 76.0)	OR: 5.68	3.43 – 9.40	N/A	Unadjusted SMRW, ITT population.	No
	Salvage therapy	205	30.2% (24.1 – 37.1)					
Overall response rate	Axi-cel	72	76.4% (64.7 – 85.3)	OR: 9.05	4.83 – 16.97	N/A	Adjusted SMRW, ITT population.	No
	Salvage therapy	205	26.8% (21.0 – 33.5)					

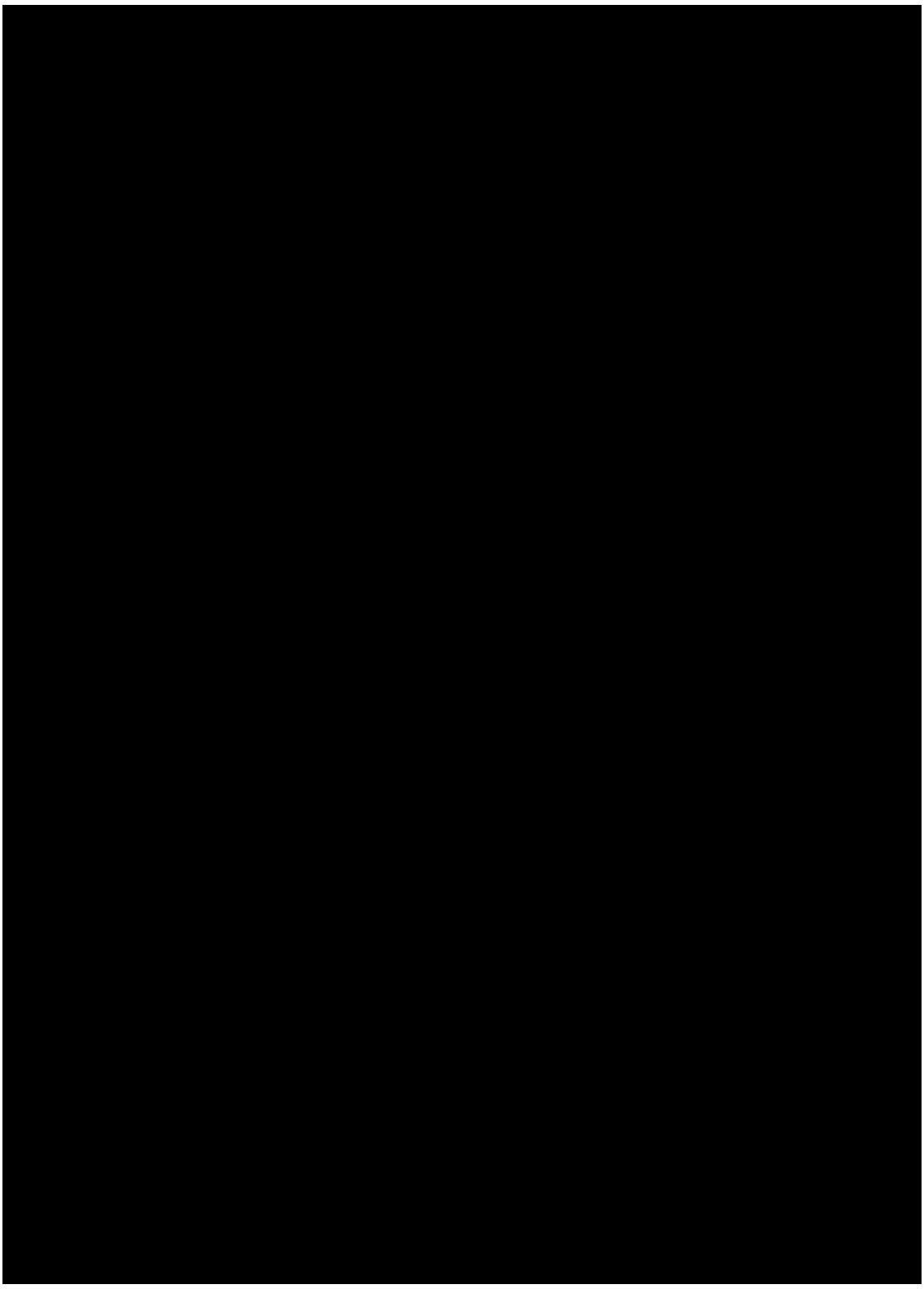
Abbreviations: Axi-cel = axicabtagene ciloleucel; CI = confidence interval; FAS = full analysis set; HR = hazard ratio; ITT = intention-to-treat; N/A = not applicable; NR = not reached; OR = odds ratio; OS = overall survival; SMRW = standardised mortality ratio weights, DCO= data cut-off.
Source: Kite Pharma Inc., 2022; table 8 and 10 (75).

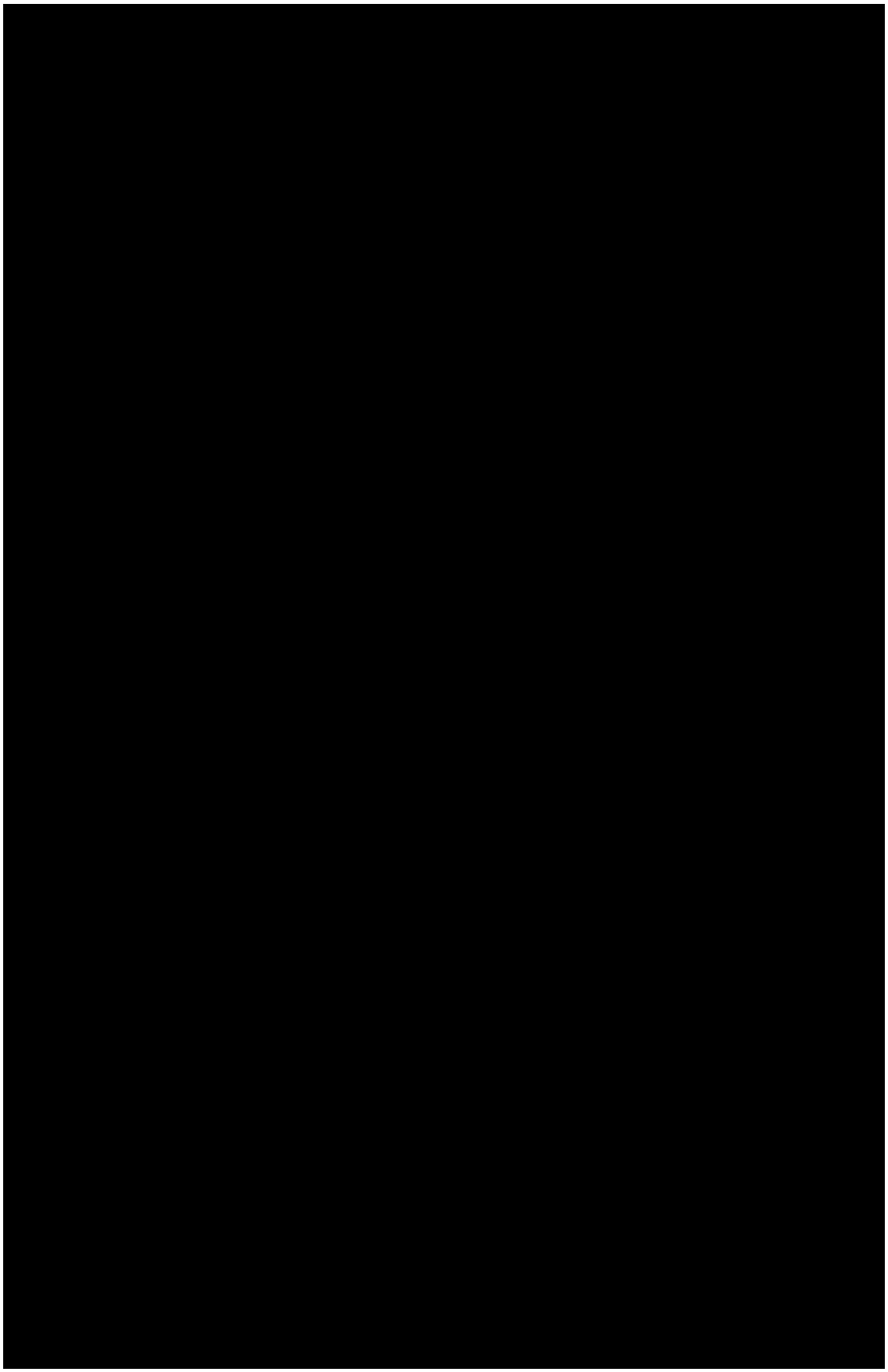


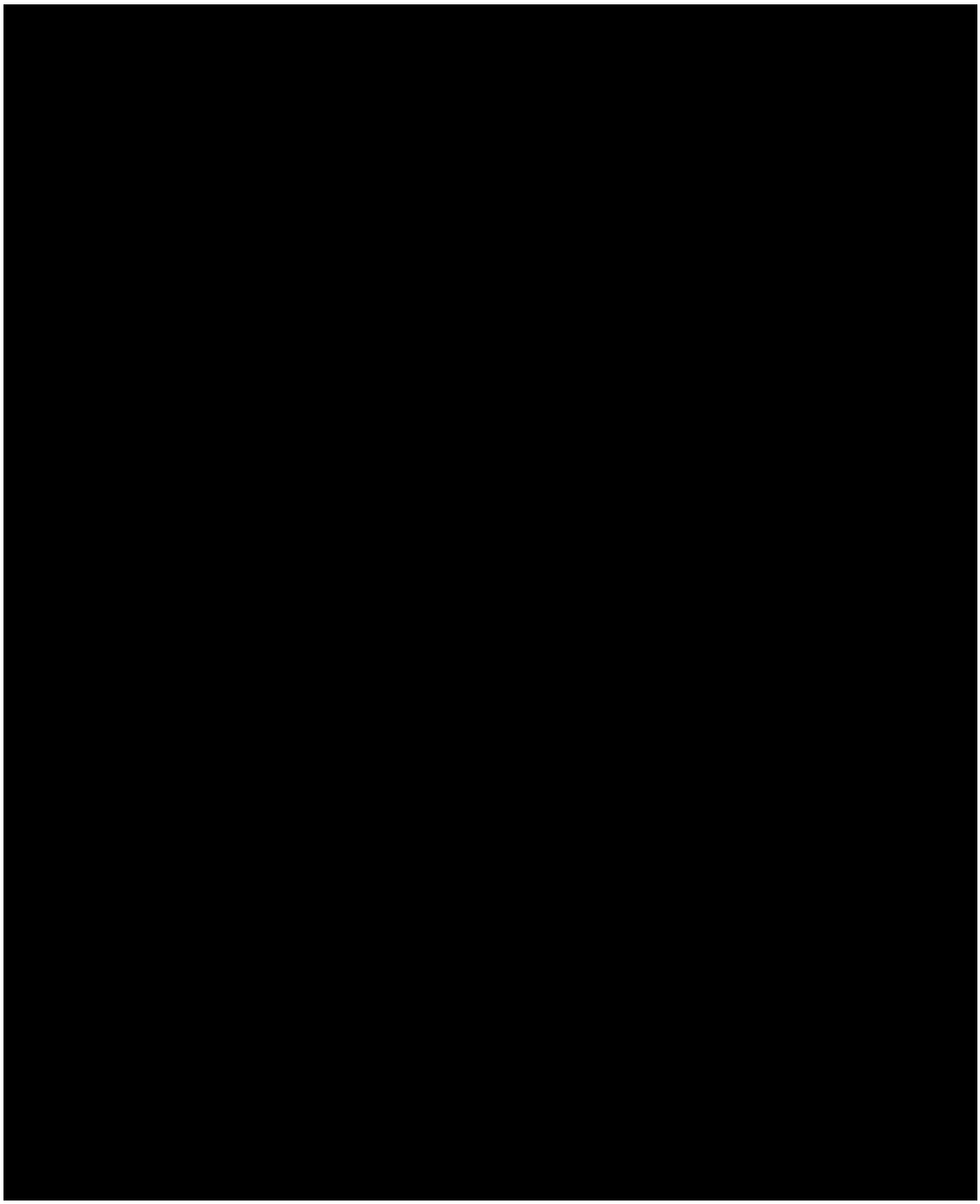


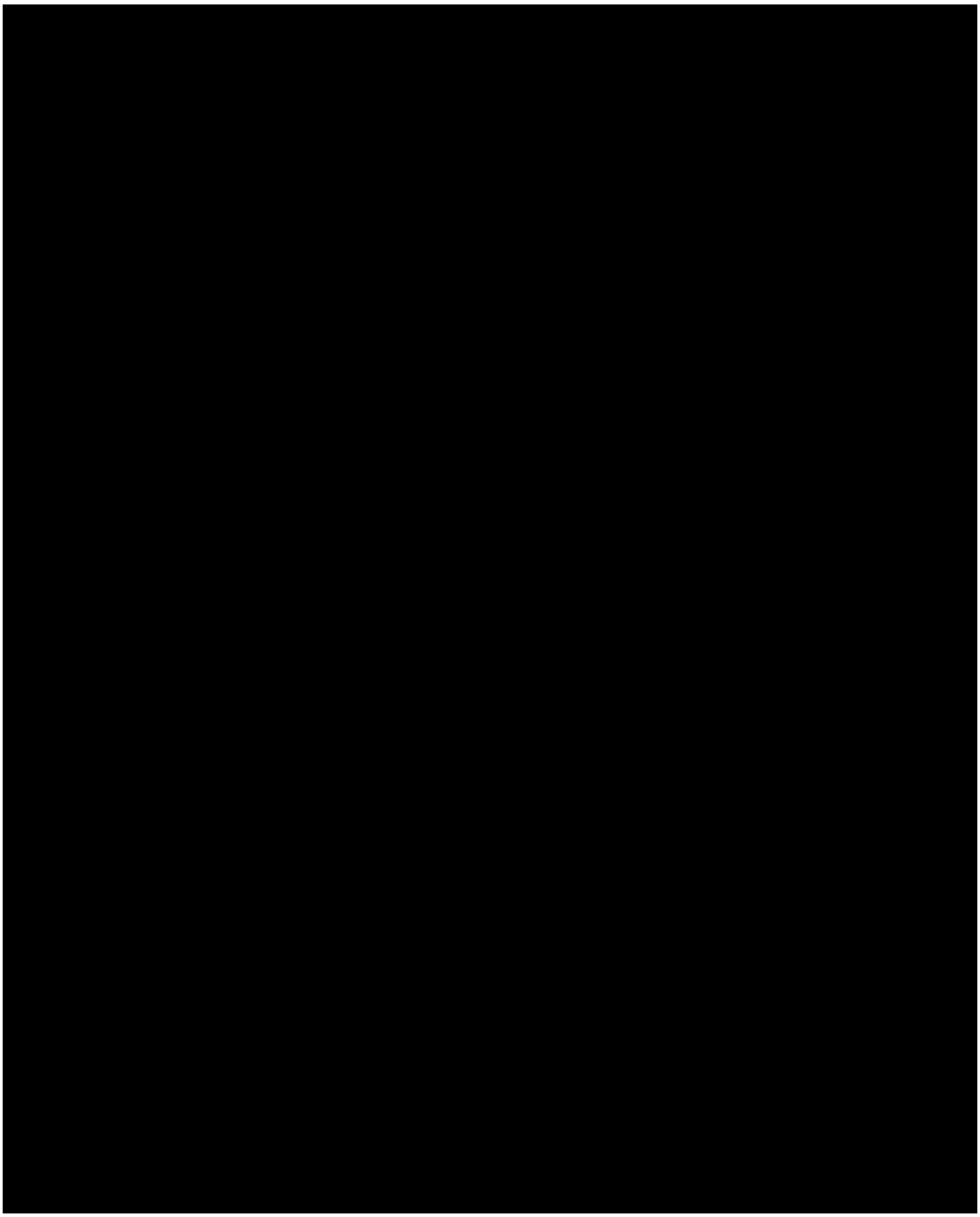


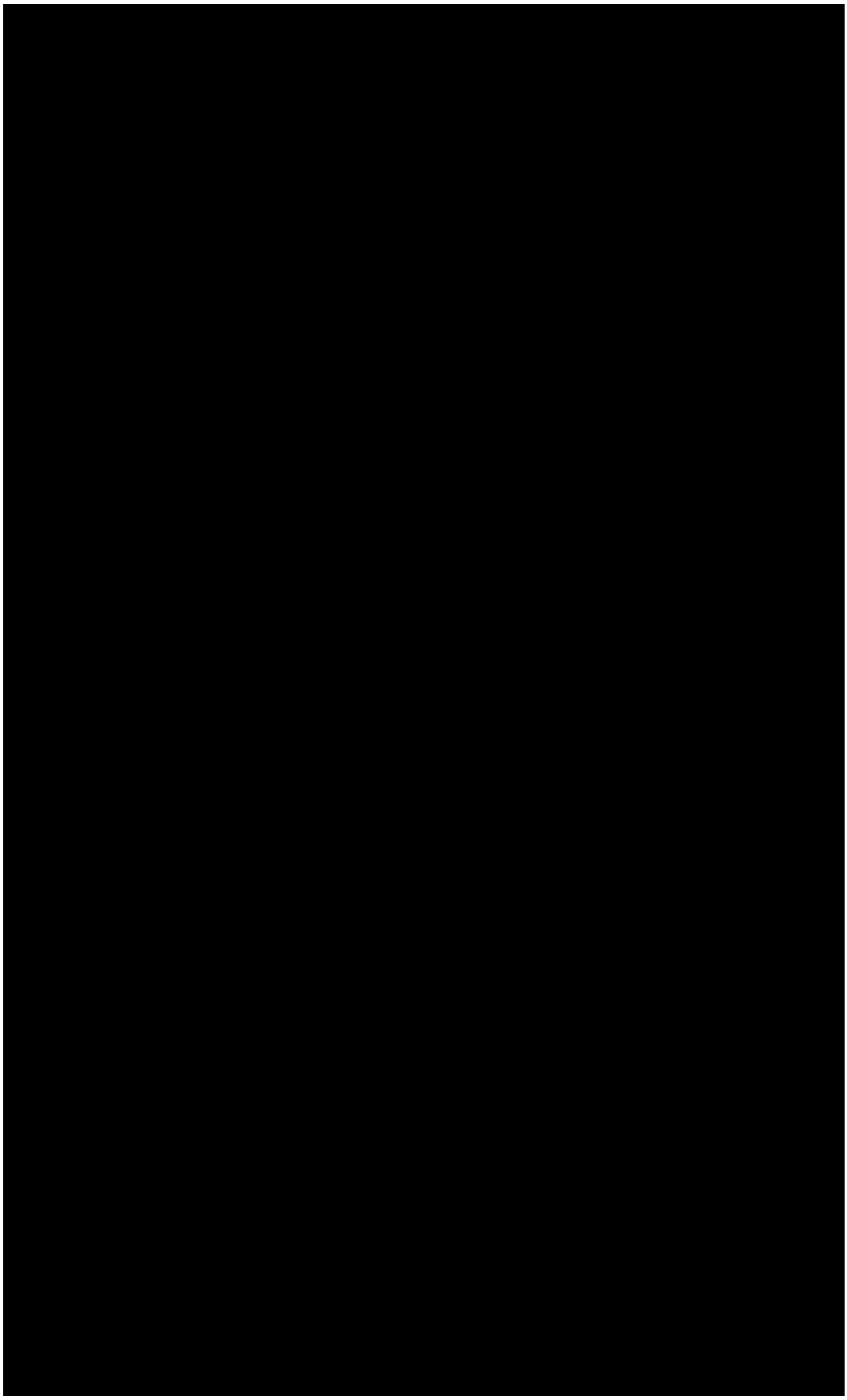


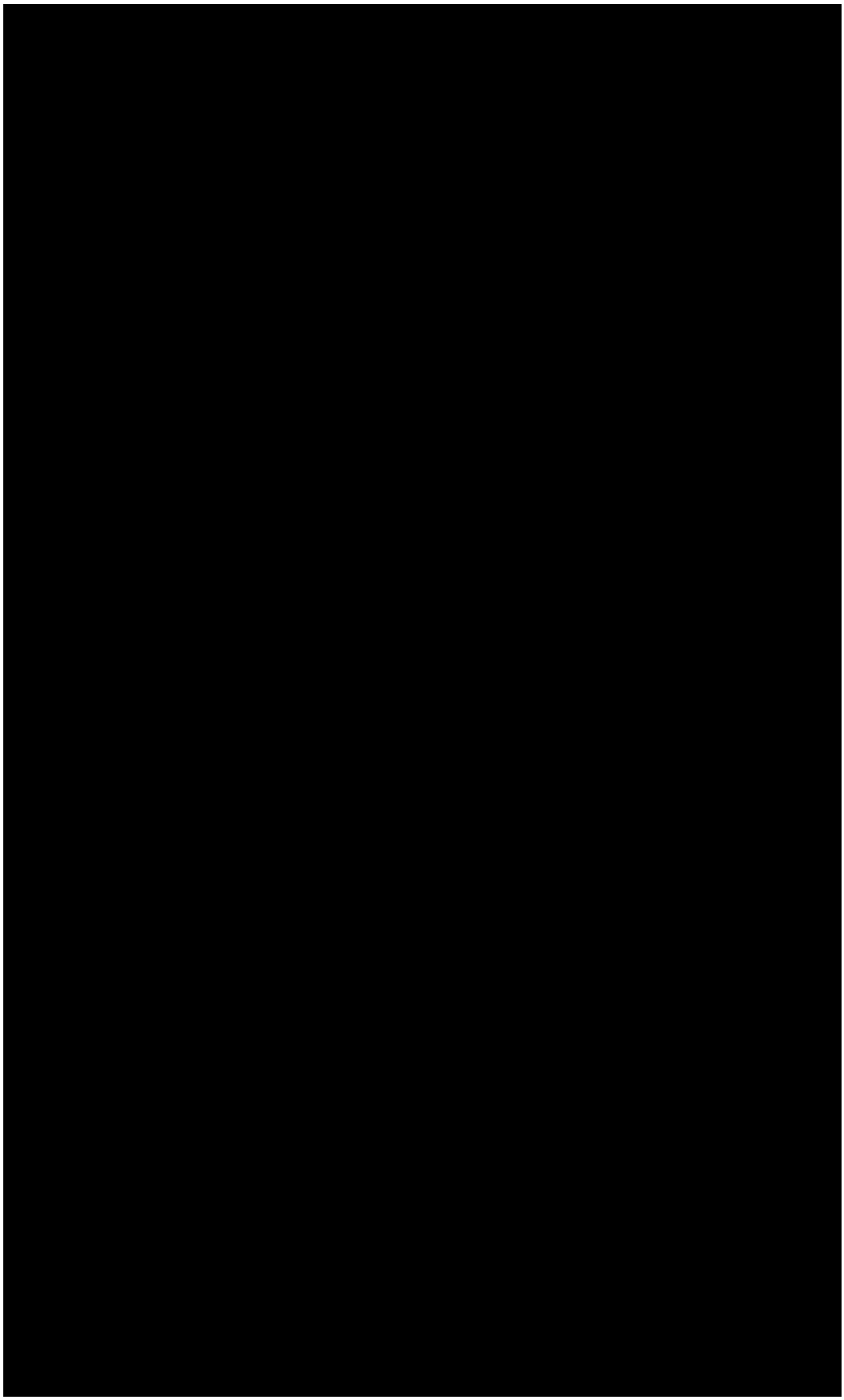


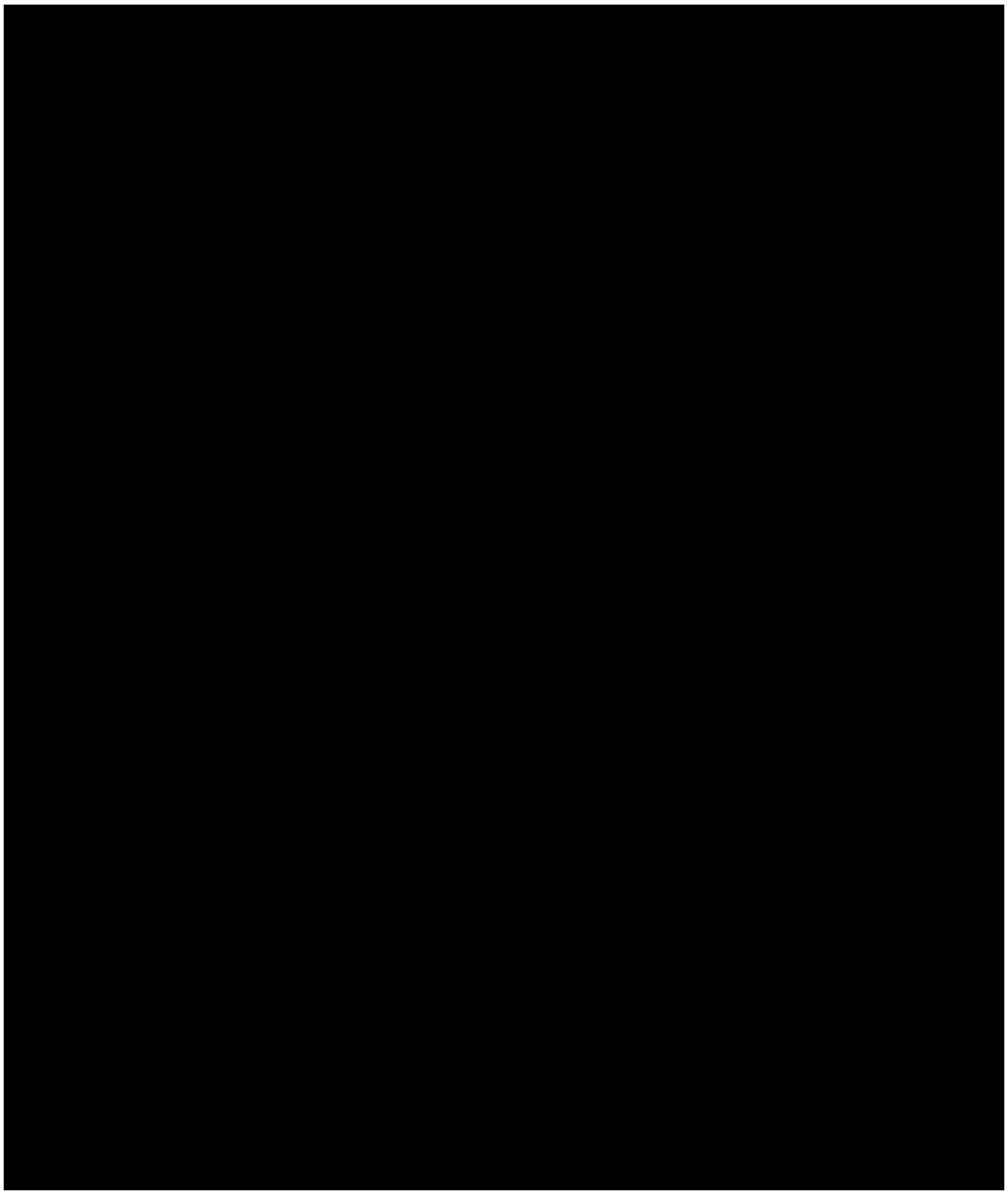


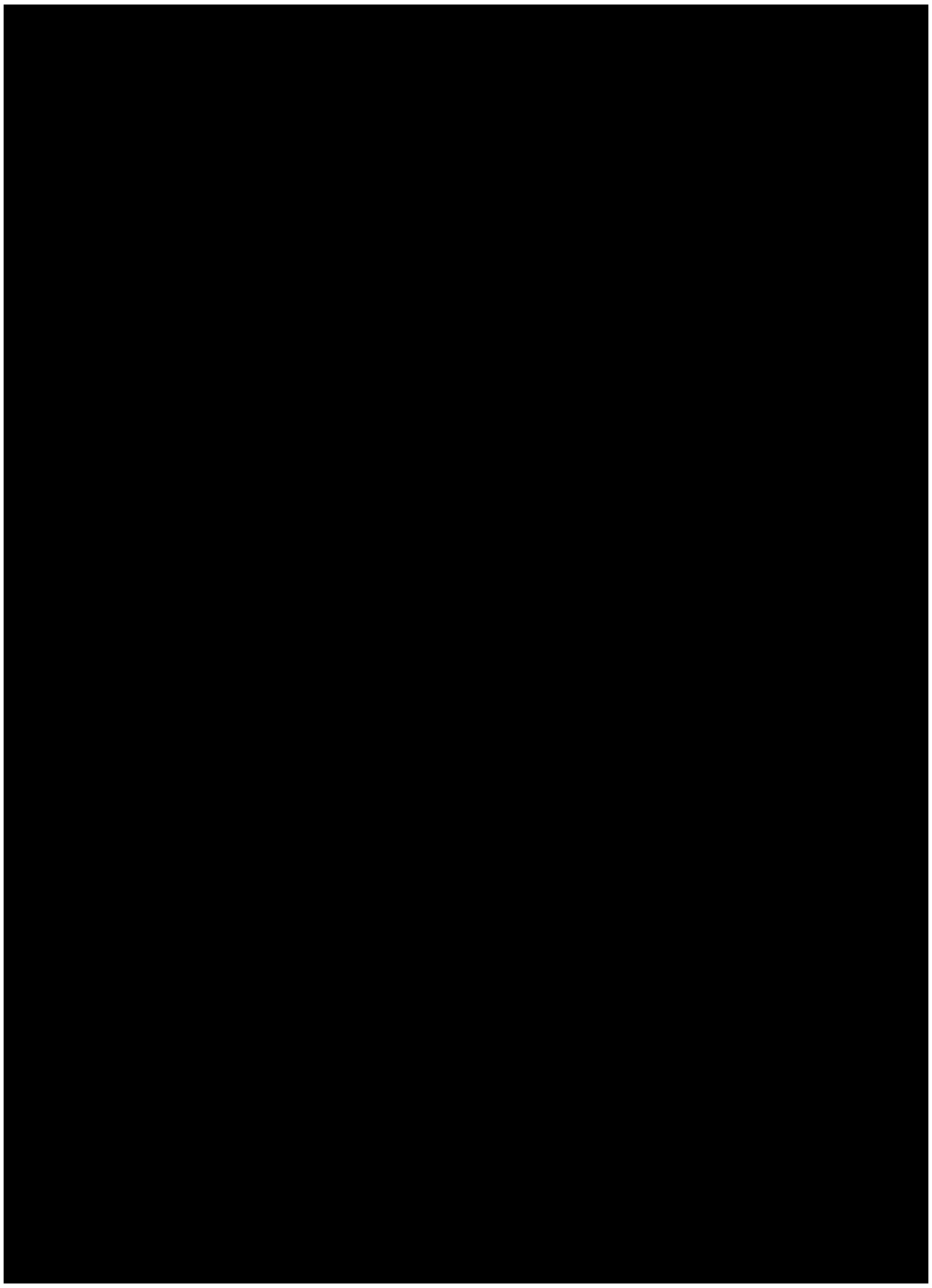


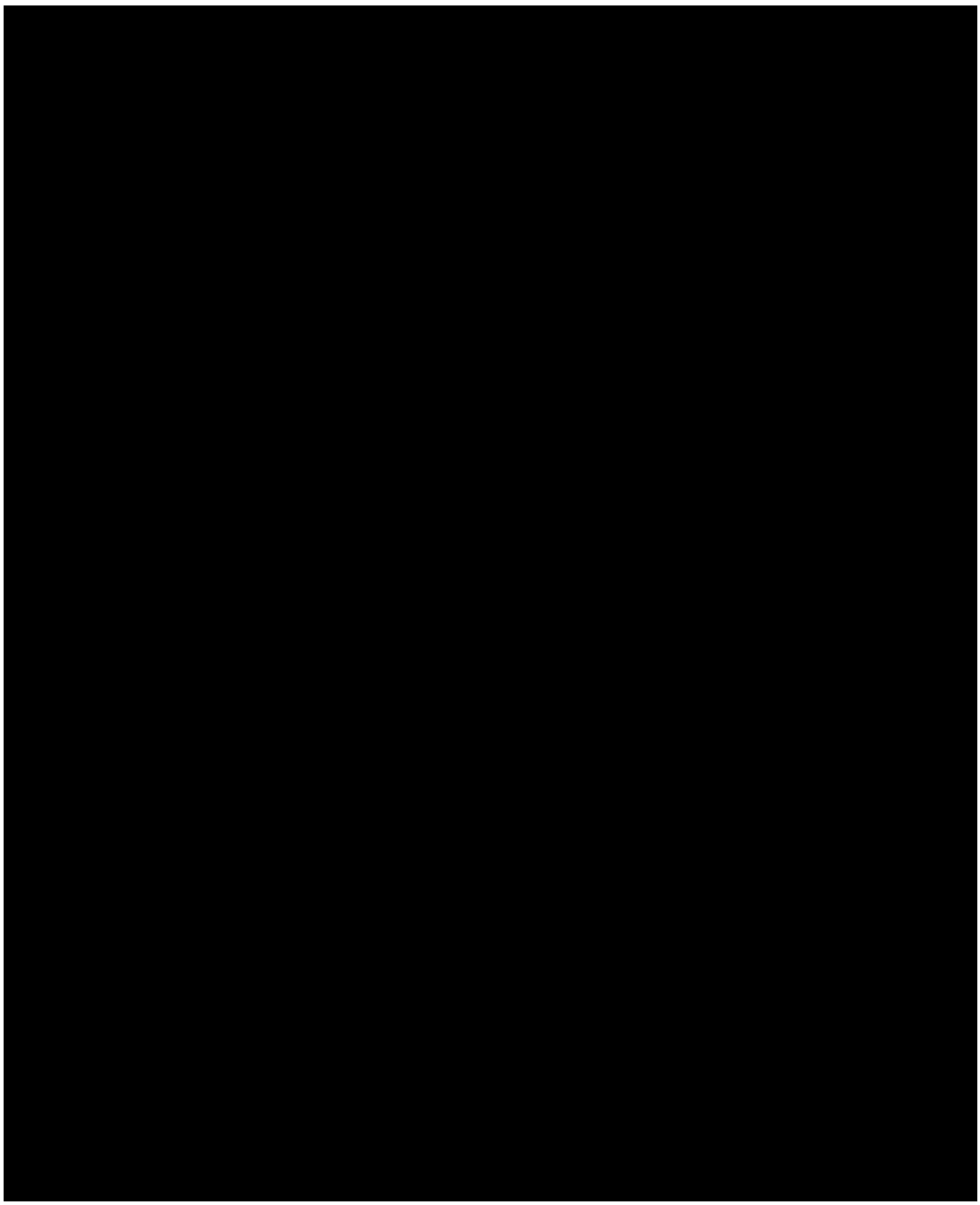


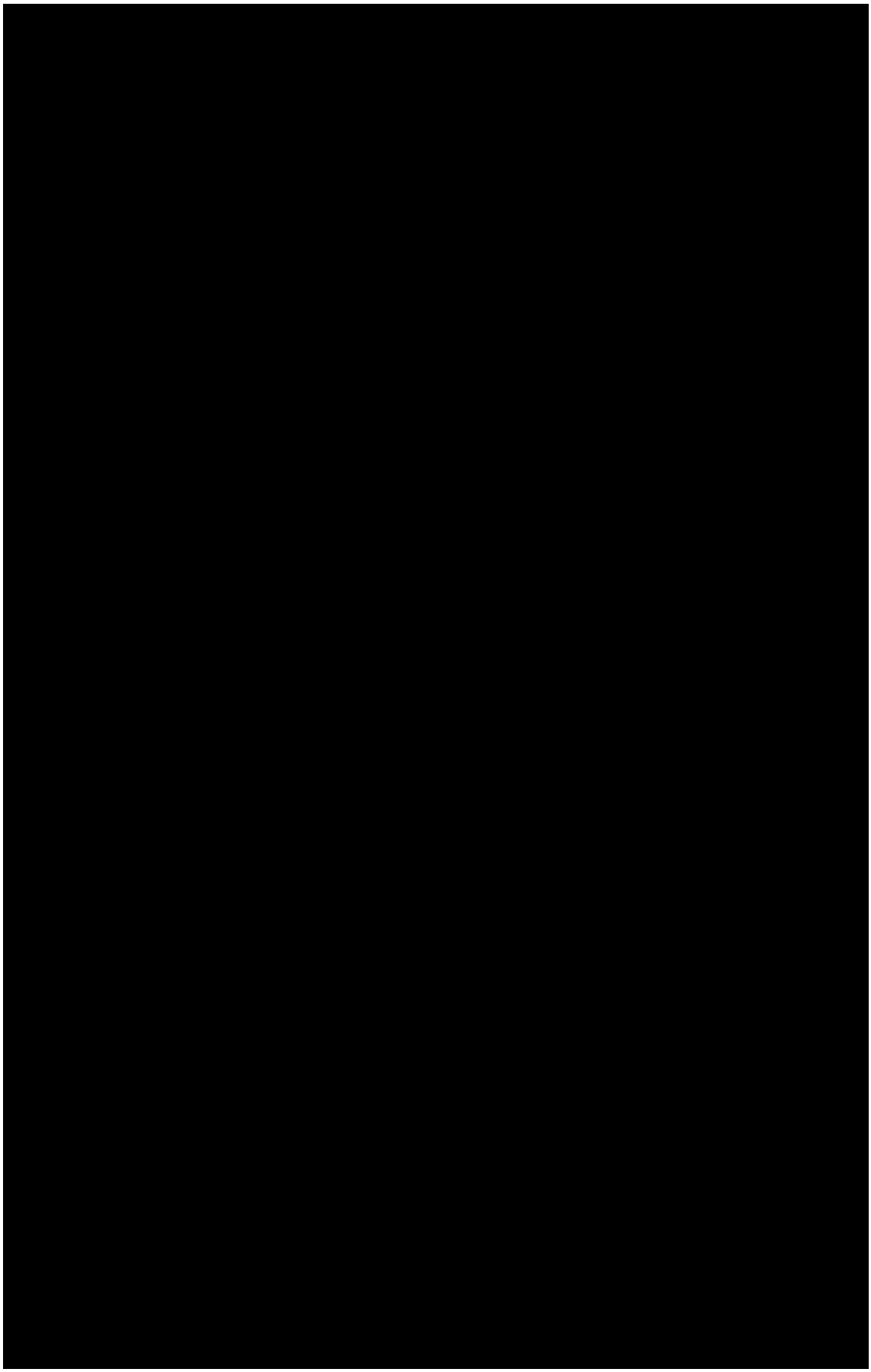


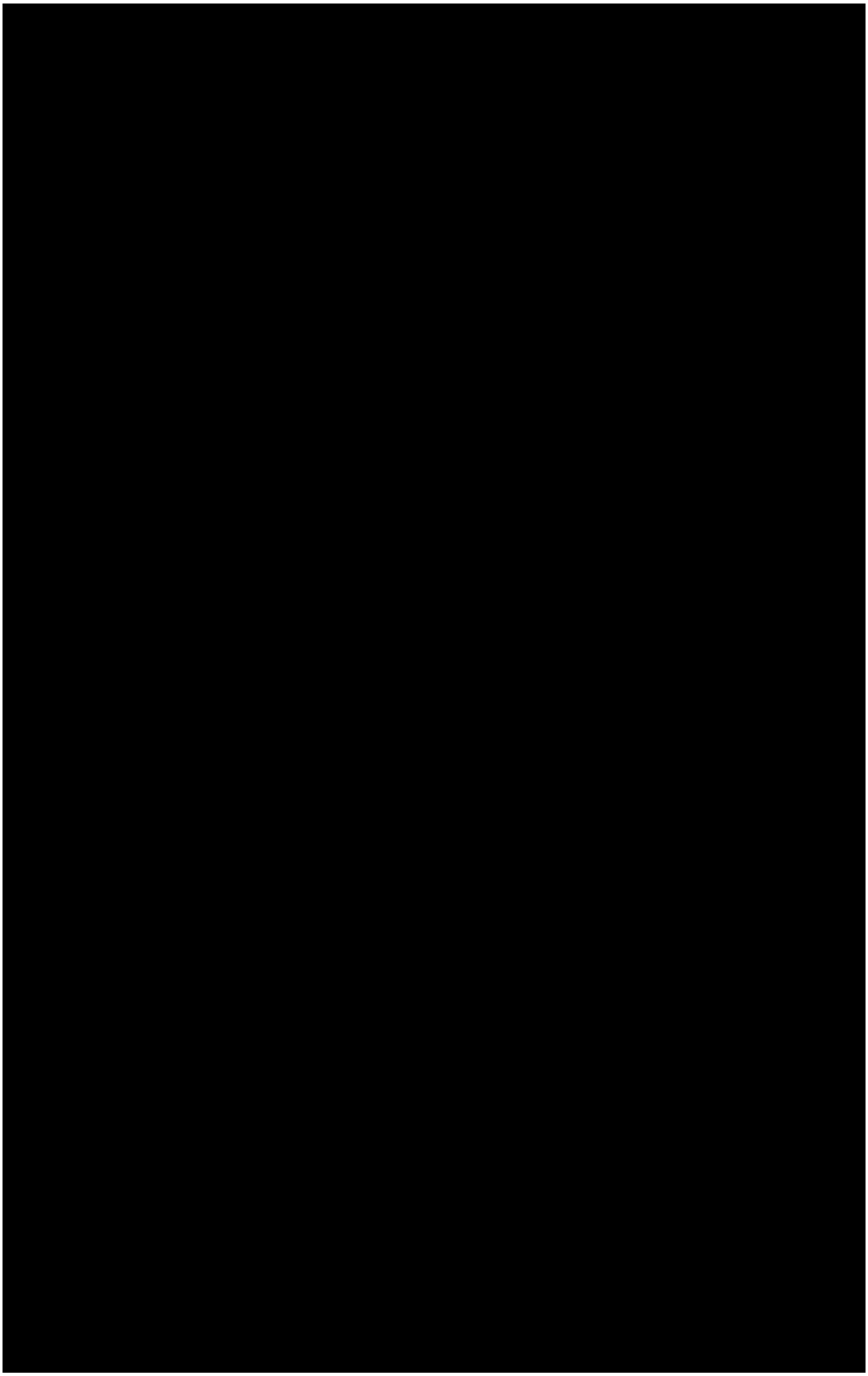


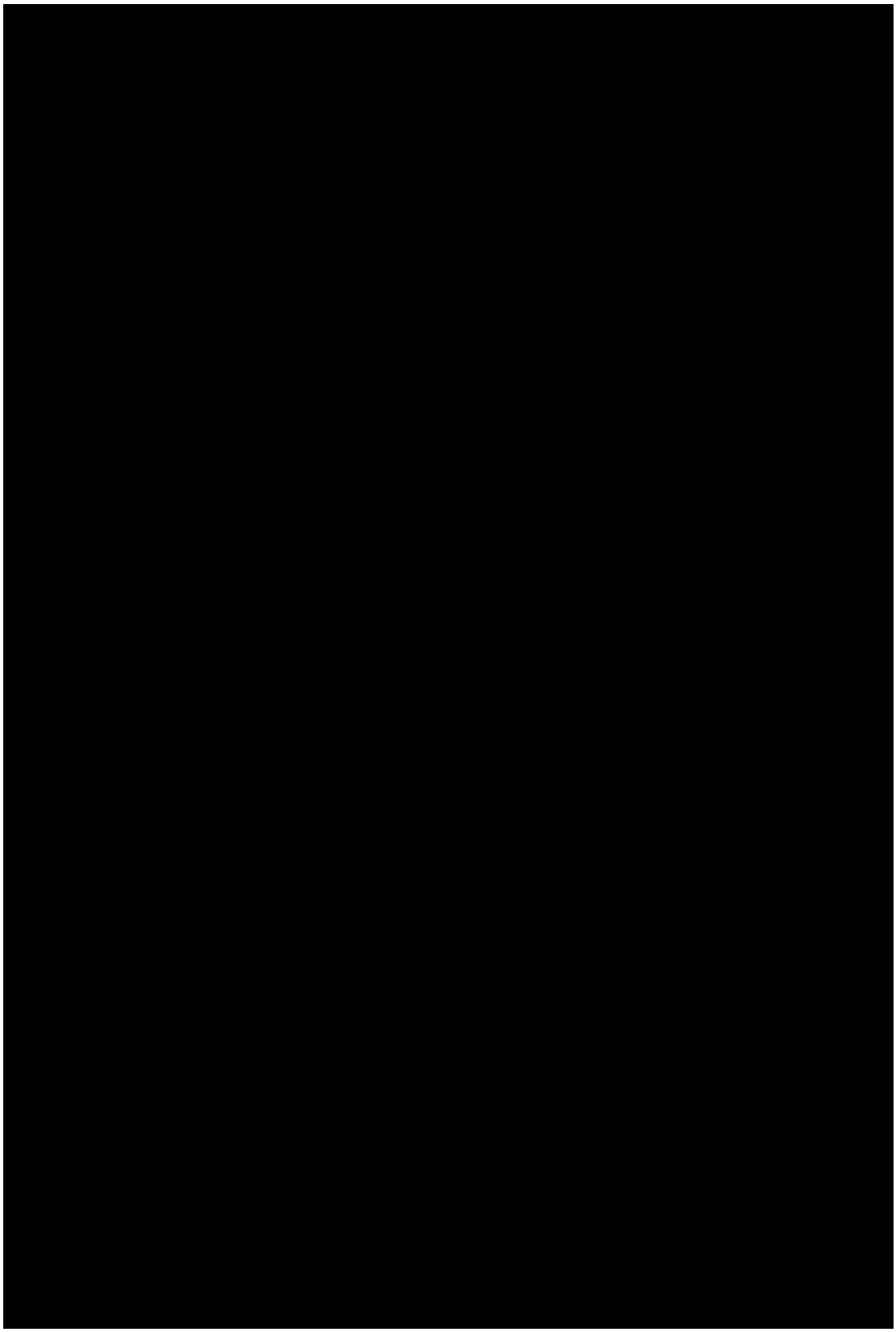


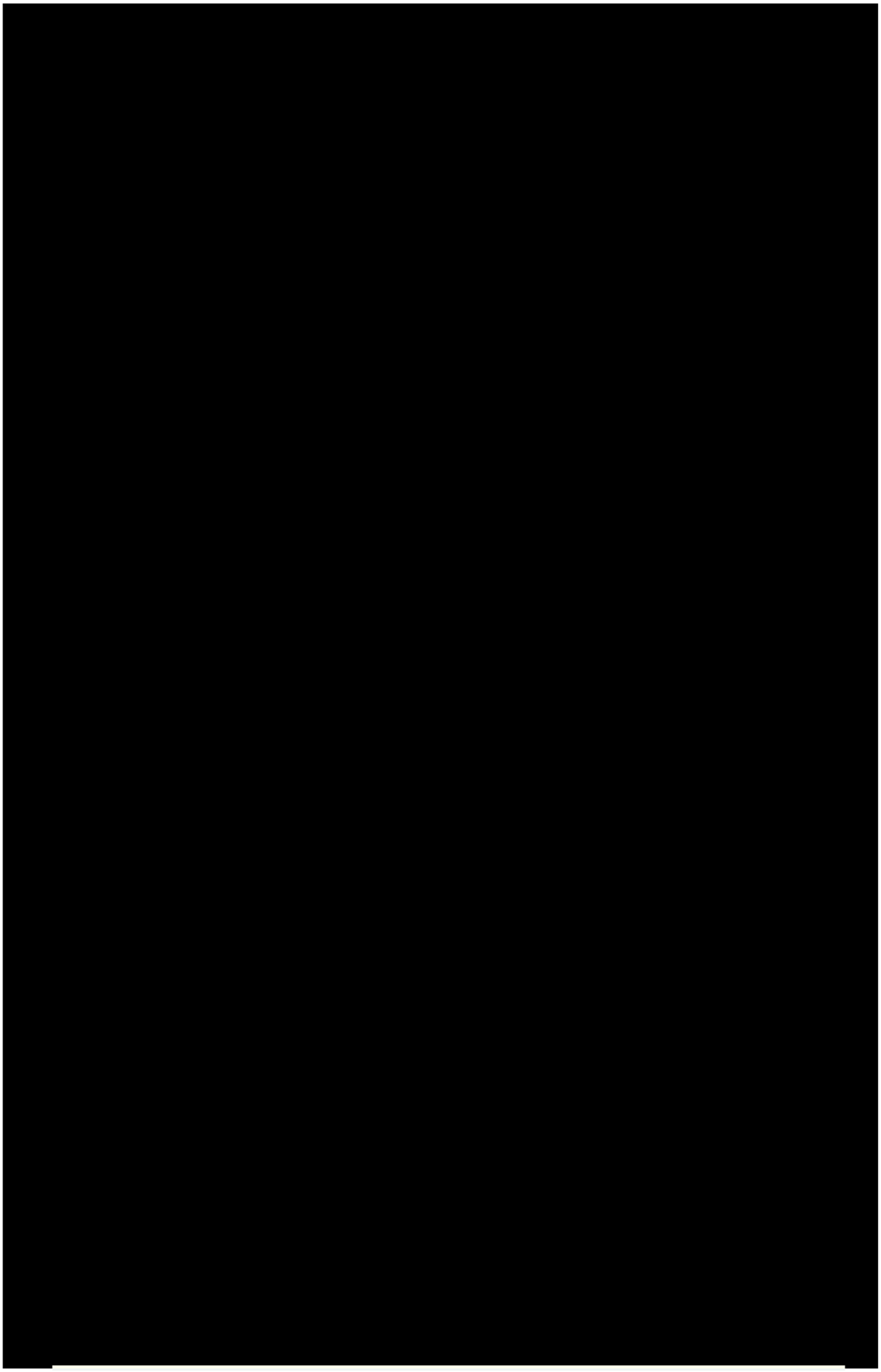


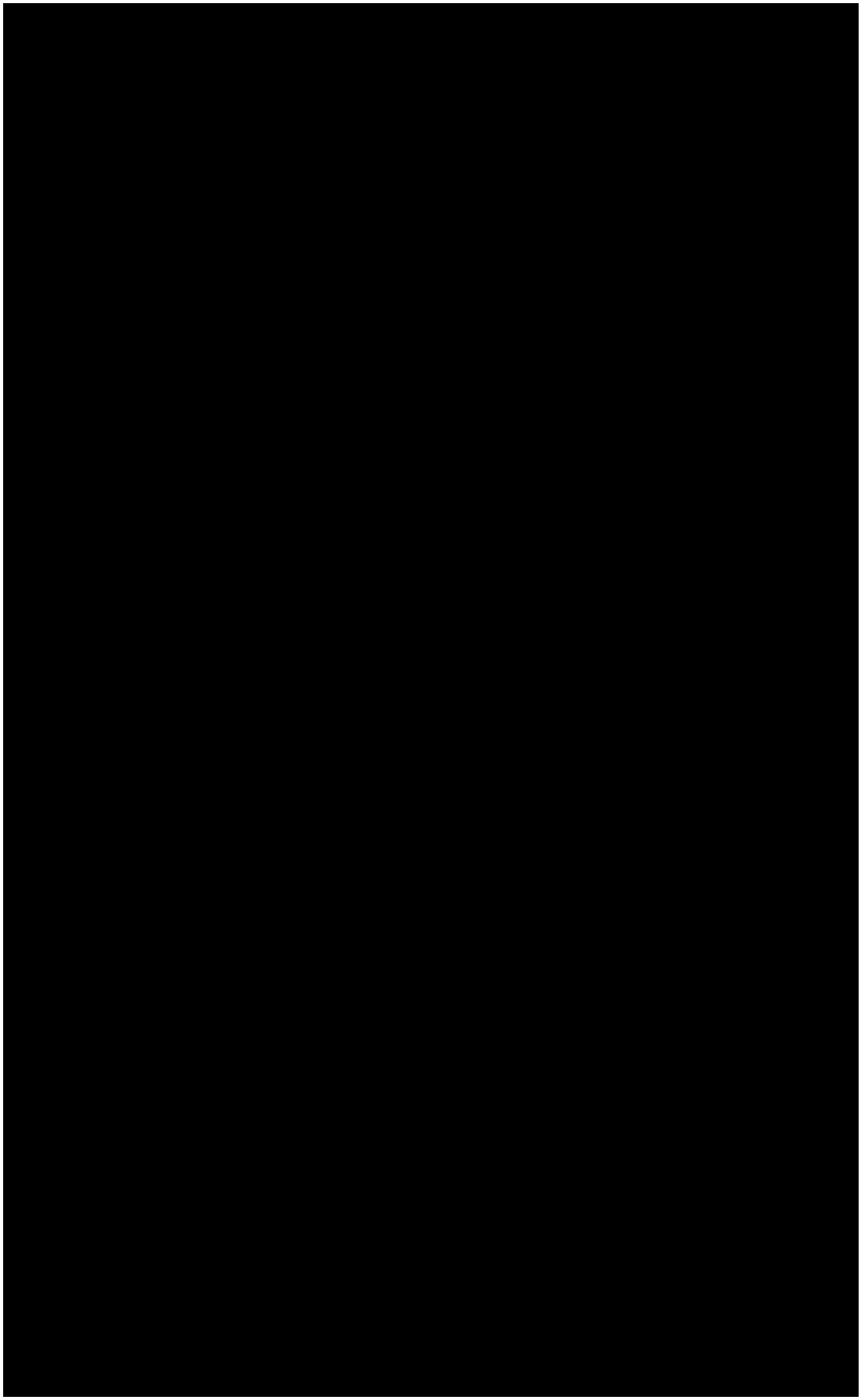


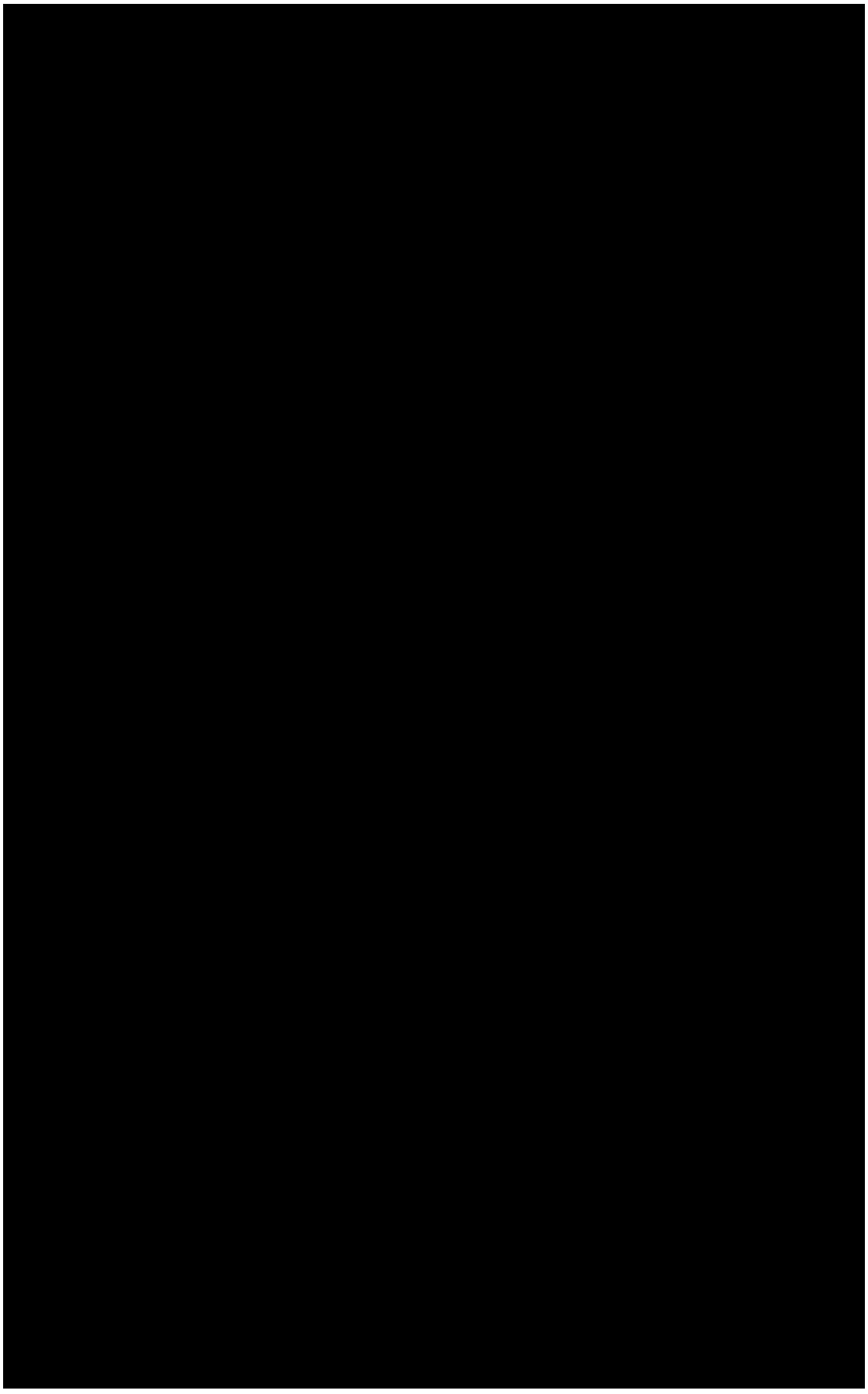


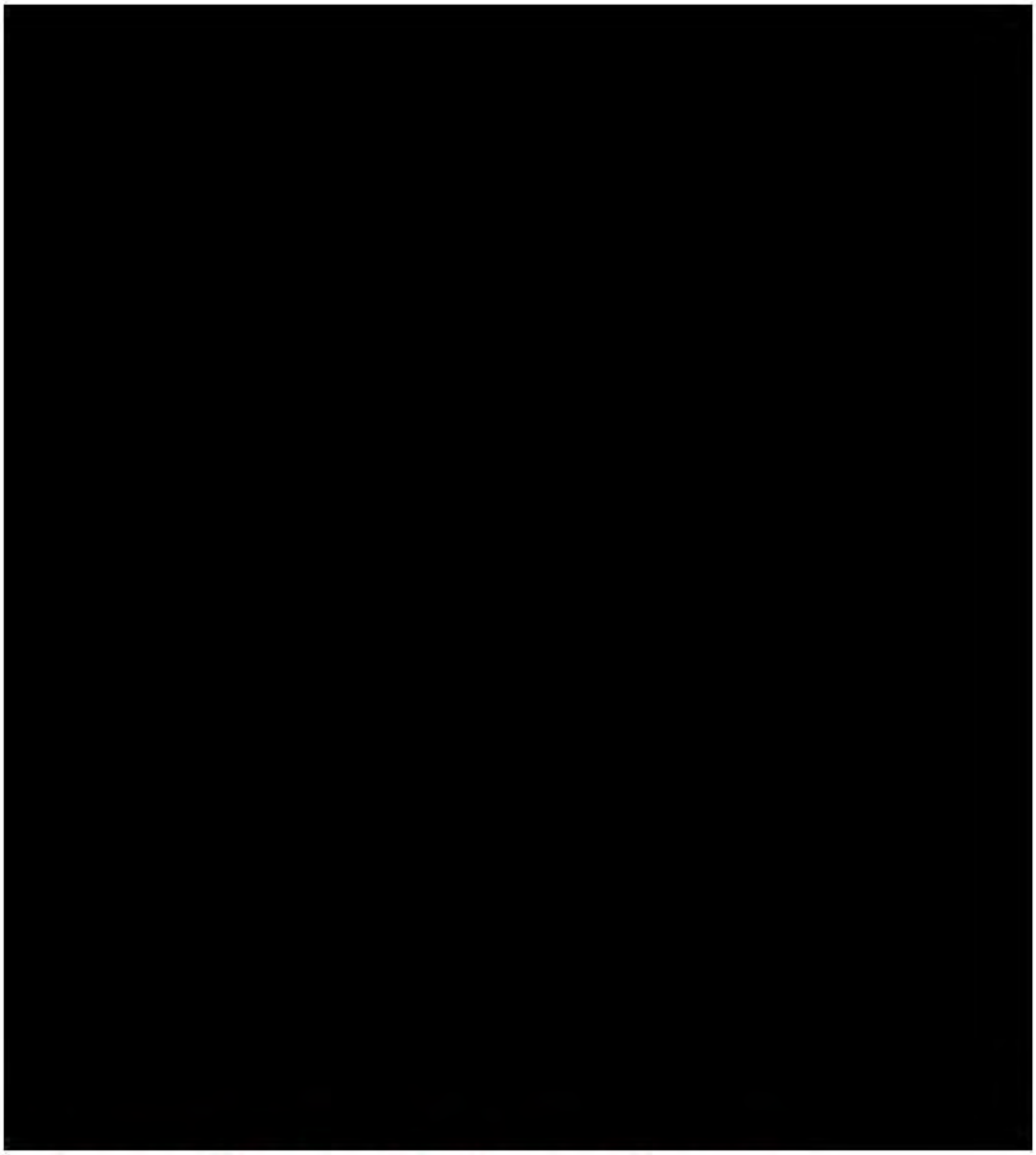












Appendix E. Serious adverse events

In Table 38, all serious adverse events in ZUMA-1 are listed. This information was not available for CORAL EXT 1, CORAL EXT 2, CORAL 1, or CORAL 2.

Table 85 Serious adverse events in ZUMA-1 (24-month data cut)

Adverse events, n (%)	Axi-cel (N=108)
	Number of patients with adverse events
Any serious adverse event	60 (56)
Encephalopathy	20 (19)
Lung infection	8 (7)

Pyrexia	8 (7)
Febrile neutropenia	6 (6)
Pneumonia	6 (6)
B-cell lymphoma	5 (5)
Confusional state	5 (5)
Aphasia	4 (4)
Atrial fibrillation	4 (4)
Cardiac arrest	4 (4)
Urinary tract infection	4 (4)
Acute kidney injury	3 (3)
Agitation	3 (3)
Ejection fraction decreased	3 (3)
Hypotension	3 (3)
Hypoxia	3 (3)
Somnolence	3 (3)
Atrial flutter	2 (2)
Bacteraemia	2 (2)
Delirium	2 (2)
Escherichia bacteraemia	2 (2)
Mental status changes	2 (2)
Myelodysplastic syndrome	2 (2)
Neutropenia	2 (2)
Acidosis	1 (1)
Acute left ventricular failure	1 (1)
Acute respiratory failure	1 (1)
Aspiration	1 (1)
Back pain	1 (1)
Bacterial sepsis	1 (1)
Bone marrow failure	1 (1)
Bone pain	1 (1)
Brain injury	1 (1)
Carcinoma in situ	1 (1)
Clostridium difficile colitis	1 (1)
Clostridium difficile infection	1 (1)
Cytomegalovirus enteritis	1 (1)

Abbreviations: Axi-cel = axicabtagene ciloleucel.
Source: ZUMA-1 CSR, 2018, table 14.3.2.4.0.1 (9).

Appendix F. Health-related quality of life

This Appendix F specify/describe details regarding the HSUV estimates used in the HRQoL scenario analyses: ZUMA-1 HSUVs (with UK weights), HSUVs from JULIET trial and HSUVs from TA306. Hence, these do not relate to the base case.

HSUVs from the ZUMA-1 trial

An analysis of the safety population (n=34) of the ZUMA-1 trial was performed using the EQ-5D-5L which was then cross walked to EQ-5D-3L UK value set using the Van Hout algorithm as preferred by NICE (90). This cohort captured HRQL data using the EQ-5D-5L at screening, Week 4, Month 3, and Month 6 post axi-cel infusion, as well as results by response category and for progression-free and progressed patients. The UK EQ-5D-3L results by time point are reported in Table 86.

ZUMA-1 data:

Complete case analysis was undertaken i.e. patients with both disease status and corresponding EQ 5D 5L data were included in the analysis, regardless of the time point and intra patient correlation. Patients without complete EQ-5D-5L or disease status were excluded from the analysis as multiple imputation was not undertaken. The 95% confidence interval around the mean utility value was estimated assuming a normal distribution. The progression free (PF) health state included patients who were in complete remission (CR), partial remission (PR) or stable disease (SD). The progressed disease (PD) health state includes patients with progressive or relapsed disease (PD). Descriptive analyses were conducted by health states most applicable for oncology economic analyses (progression free, progressed disease, and death). Complete case analysis was undertaken i.e. patients with both disease status and corresponding EQ-5D-5L data were included in the analysis, regardless of the time point and intra patient correlation. Patients without complete EQ-5D-5L or disease status were excluded from the analysis as multiple imputation was not undertaken. The 95% confidence interval around the mean utility value was estimated assuming a normal distribution.

EQ-5D-3L mapping

Van Hout et al (2012). provide an option for mapping, which we refer to henceforth as the "Crosswalk". It is the approach recommended in the NICE 2013 Methods Guide. Van Hout et al estimate 3L from 5L responses using a series of modified cross-tabulations of responses to the 3L and 5L instruments, for each dimension of health separately. The approach is based on data provided by the EuroQol Group (EQG).

Brief description of the mapping method (2012) (90):

Data*:*

Respondents in six countries (Denmark, England, Italy, the Netherlands, Poland, and Scotland) completed both EQ-5D-3L and EQ-5D-5L questionnaires.

Mapping models:

Two general approaches explored, including 1) direct and 2) indirect methods: 1) using linear regression to directly transfer 5L responses to 3L preference-based index values, and 2) prediction of 3L responses from 5L responses, and probabilities associated with 3L responses are applied to their index values to obtain 5L values.

Modelling approaches:

Four types of statistical models were considered for deriving crosswalks: 1) direct linear regression models with various specifications, 2) indirect nonparametric model using frequencies obtained from cross-tabulating 3L and 5L responses, 3) indirect logistic regression model for ordered categories, and 4) indirect model using the partial credit model, an item-response theory-based model.

Model selection:

4 criteria were used to assess model performance: theoretical background, in-sample prediction (fit), out-of-sample prediction (predictive power), and parsimony.

<u>HSUVs from the other clinical trials and literature (scenarios)</u>

JULIET trial

The utility inputs for PF and PD that were from SF-36 data collected in the JULIET trial which were then mapped to EQ-5D using Rowen et al. (89) As reported in NICE TA567 (currently not available). Health state utilities sourced from JULIET are as follows: 0.830 for progression-free disease and 0.710 for progressed disease.

Data:

The patient population was selected from the Health Outcomes Data Repository (HODaR), a dataset from a prospective survey at Cardiff and Vale NHS Hospitals Trust (both inpatient and outpatient samples). The inpatient sample has 31,236 eligible observations across 27,620 individuals from August 2002 to November 2004, and of these there are 25,783 complete responses across 23,179 individuals for SF-36 and EQ-5D questions and hence this is the sample used here. The outpatient sample has 9,081 eligible observations across 8,610 individuals collected from June 2002 to November 2004, and of these there are 7,465 complete responses across 7,122 individuals. The dataset covers a wider range of

conditions and severity than the general population datasets used in existing mapping approaches, and hence may be more similar to datasets used in economic evaluation.

Statistical methods:

Regression analysis was employed to establish the relationship between SF-36 and EQ-5D using eight-dimension scores. Different model specifications were tested (three models are employed: (1) all dimensions, (2) all dimensions and squared terms, and (3) all dimensions, squared terms, and interactions). The mapping relationship is examined across different medical conditions and settings) Statistical measures such as within, between, and overall R-squared, root mean squared error (RMSE), mean square error (MSE), and Wald chi-squared were utilized to evaluate model performance.

Model section:

Among the models tested, the one including SF-36 dimensions, squared and interaction terms estimated using random effects GLS demonstrated the most accurate predictions, indicated by lower MAE. Model selection was based on diagnostic measures, predictive ability, and overall model fit.

Validation:

A validation process was not explicitly mentioned. However, Rowen et al. emphasizes the reliability and accuracy of the mapping relationship across diverse patient datasets, encompassing different settings and medical conditions.

Appendix G. Probabilistic sensitivity analyses

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. Given that the utility values for progression-free and progressed disease are ordered (i.e. utility value for progression-free disease > utility value for progressed disease), the method described by Ren et al (114) has been used to ensure that this order is maintained for all simulations. 1,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distribution. Results were plotted on the cost-effectiveness plane (CEP) and a cost-effectiveness acceptability curve (CEAC) was generated. The confidence interval around the expected ICER was estimated using Fieller's theorem. Functionality is included in the model such that either costs and QALYs are presented, or costs and LYs.

Table 87 shows the distributional assumptions of model parameters (point estimate, and lower and upper bound).

Table 87. Overview of parameters in the PSA

Input parameter	Point estimate	Lower bound	Upper bound	Probability distribution
Population characteristics				
Mean age	56	53.66	58.34	Not varied
% female	0.33	0.28	0.38	Not varied
Clinical				
Progression-free survival				
PFS (axicabtagene ciloleucel, PSM, ITT) - exponential, constant - 24M	-2.98	-3.01	-2.95	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, constant - 24M	1.17	0.54	1.80	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, ln(sigma) - 24M	0.58	0.31	0.84	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, kappa - 24M	-1.56	-2.48	-0.63	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - gompertz, constant - 24M	-0.18	-0.24	-0.12	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - gompertz, gamma - 24M	-1.79	-1.81	-1.78	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - log-logistic, constant - 24M	-0.16	-0.37	0.04	Multivariate normal

PFS (axicabtagene ciloleucel, PSM, ITT) - log-logistic, ln(gamma) - 24M	2.28	1.98	2.58	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - lognormal, constant - 24M	2.38	1.97	2.78	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - lognormal, ln(sigma) - 24M	0.65	0.41	0.90	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - weibull, constant - 24M	-0.48	-0.69	-0.27	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, ITT) - weibull, ln(p) - 24M	3.11	2.81	3.40	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - exponential, constant - 24M	-3.00	-3.01	-2.95	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - Gen. gamma, constant - 24M	1.17	0.54	1.80	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - Gen. gamma, ln(sigma) - 24M	0.58	0.31	0.84	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - Gen. gamma, kappa - 24M	-1.58	-2.48	-0.63	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - gompertz, constant - 24M	-0.18	-0.24	-0.12	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - gompertz, gamma - 24M	-1.79	-1.81	-1.78	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - log-logistic, constant - 24M	-0.17	-0.37	0.04	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - loglogistic, ln(gamma) - 24M	2.31	1.98	2.58	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - lognormal, constant - 24M	2.40	1.97	2.78	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - lognormal, ln(sigma) - 24M	0.66	0.41	0.90	Multivariate normal

PFS (axicabtagene ciloleucel, PSM, mITT) - weibull, constant - 24M	-0.48	-0.69	-0.27	Multivariate normal
PFS (axicabtagene ciloleucel, PSM, mITT) - weibull, ln(p) - 24M	3.13	2.81	3.40	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - exponential theta- unadjusted	-0.44	-0.83	-0.05	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - exponential rate- unadjusted	-1.40	-1.67	-1.14	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted - theta	-0.47	-0.87	-0.07	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted- shape	0.69	0.44	0.95	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted- scale	1.09	0.91	1.27	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- theta	-0.44	-0.83	-0.05	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- shape	0.02	-0.05	0.09	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- rate	-1.47	-1.47	-1.47	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - weibull - unadjusted- theta	-0.43	-0.82	-0.05	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - weibull- unadjusted- shape	0.21	0.03	0.39	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) - weibull- unadjusted- scale	1.46	1.20	1.72	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, ITT) -	-0.46	-0.86	-0.06	Multivariate normal

lognormal- unadjusted- theta				
PFS (axicabtagene ci- loleucel, MCM, ITT) - lognormal- unadjusted- meanlog	1.06	0.84	1.28	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, ITT) - lognormal- unadjusted- sdlog	-0.08	-0.28	0.12	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, ITT) - Gen. gamma- unadjusted- theta	-0.44	-0.83	-0.05	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, ITT) - Gen. gamma- unadjusted- mu	1.21	0.89	1.52	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, ITT) - Gen. gamma- unadjusted- sigma	-0.15	-0.27	-0.03	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, ITT) - Gen. gamma- unadjusted- q	0.38	-0.32	1.08	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - ex- ponential theta- unad- justed	-0.41	-0.80	-0.01	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - ex- ponential rate- unad- justed	-1.38	-1.67	-1.10	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - log-logistic- unadjusted - theta	-0.43	-0.83	-0.02	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - log-logistic- unadjusted- shape	0.71	0.45	0.98	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - log-logistic- unadjusted- scale	1.07	0.90	1.24	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - gompertz- unadjusted- theta	-0.40	-0.79	0.00	Multivariate normal
PFS (axicabtagene ci- loleucel, MCM, mITT) - gompertz- unadjusted- shape	0.02	-0.05	0.10	Multivariate normal

PFS (axicabtagene ciloleucel, MCM, mITT) - gompertz- unadjusted- rate	-1.46	-1.49	-1.43	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - weibull - unadjusted- theta	-0.38	-0.78	0.01	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - weibull- unadjusted- shape	0.23	0.03	0.44	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - weibull- unadjusted- scale	1.42	1.19	1.66	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - lognormal- unadjusted- theta	-0.42	-0.82	-0.02	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - lognormal- unadjusted- meanlog	1.04	0.83	1.26	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - lognormal- unadjusted- sdlog	-0.10	-0.30	0.11	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - Gen. gamma- unadjusted- theta	-0.40	-0.79	0.00	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - Gen. gamma- unadjusted- mu	1.19	0.89	1.50	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - Gen. gamma- unadjusted- sigma	-0.17	-0.30	-0.04	Multivariate normal
PFS (axicabtagene ciloleucel, MCM, mITT) - Gen. gamma- unadjusted- q	0.41	-0.28	1.09	Multivariate normal
Overall survival				
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - exponential, constant - 48M	-4.09	-4.14	-4.04	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - Gen. gamma, constant -48M	2.63	1.70	3.56	Multivariate normal

OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - Gen. gamma, ln(sigma) - 48M	0.56	0.20	0.92	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - Gen. gamma, kappa - 48M	-1.52	-2.98	-0.06	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - gompertz, constant - 48M	-0.04	-0.07	-0.02	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - gompertz, gamma - 48M	-3.31	-3.28	-3.35	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - loglogistic, constant - 48M	-0.04	-0.31	0.23	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - loglogistic, ln(gamma) - 48M	3.63	3.32	3.94	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - lognormal, constant - 48M	3.67	3.20	4.15	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - lognormal, ln(sigma) - 48M	0.54	0.21	0.87	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - weibull, constant - 48M	-0.27	-0.55	0.01	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT, CORAL MAIC results) - weibull, ln(p) - 48M	4.22	3.97	4.47	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - exponential, constant - 60M	-4.04	-4.07	-4.01	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, constant -60M	2.58	1.76	3.41	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, ln(sigma) - 60M	0.73	0.49	0.97	Multivariate normal

OS (axicabtagene ciloleucel, PSM, ITT) - Gen. gamma, kappa - 60M	-1.12	-2.11	-0.12	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - gompertz, constant - 60M	-0.05	-0.07	-0.03	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - gompertz, gamma - 60M	-3.03	-3.03	-3.03	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - loglogistic, constant - 60M	-0.19	-0.40	0.02	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - loglogistic, ln(gamma) - 60M	3.44	3.12	3.75	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - lognormal, constant - 60M	3.50	3.07	3.92	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - lognormal, ln(sigma) - 60M	0.69	0.45	0.94	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - weibull, constant - 60M	-0.46	-0.67	-0.24	Multivariate normal
OS (axicabtagene ciloleucel, PSM, ITT) - weibull, ln(p) - 60M	4.18	3.91	4.46	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - exponential, constant - 48M	-4.23	-4.29	-4.17	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - Gen. gamma, constant - 48M	3.34	2.22	4.46	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - Gen. gamma, ln(sigma) - 48M	0.68	0.43	0.94	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - Gen. gamma, kappa - 48M	-0.84	-2.21	0.53	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - gompertz, constant - 48M	-0.03	-0.06	-0.01	Multivariate normal

OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - gompertz, gamma - 48M	-3.57	-3.50	-3.64	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - log-logistic, constant - 48M	-0.05	-0.35	0.25	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - log-logistic, ln(gamma) - 48M	3.85	3.54	4.16	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - lognormal, constant - 48M	3.89	3.35	4.43	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - lognormal, ln(sigma) - 48M	0.57	0.20	0.95	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - weibull, constant - 48M	-0.24	-0.56	0.08	Multivariate normal
OS (axicabtagene ciloleucel, PSM, mITT, CORAL MAIC results) - weibull, ln(p) - 48M	4.37	4.14	4.59	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - exponential, constant - 48M	-2.50	-2.51	-2.48	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - Gen. gamma, constant - 48M	1.39	0.97	1.80	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - Gen. gamma, ln(sigma) - 48M	0.47	0.35	0.59	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - Gen. gamma, kappa - 48M	-0.13	-0.69	0.43	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - gompertz, constant - 48M	-0.06	-0.08	-0.04	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - gompertz, gamma - 48M	-1.75	-1.78	-1.72	Multivariate normal

OS (BSC, PSM, mITT, CORAL MAIC results) - log-logistic, constant - 48M	0.13	-0.02	0.27	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - loglogistic, ln(gamma) - 48M	1.46	1.22	1.70	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - lognormal, constant - 48M	1.49	1.23	1.75	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - log-normal, ln(sigma) - 48M	0.47	0.34	0.59	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - weibull, constant - 48M	-0.41	-0.54	-0.29	Multivariate normal
OS (BSC, PSM, mITT, CORAL MAIC results) - weibull, ln(p) - 48M	2.24	1.92	2.56	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - exponen-tial, constant - 48M	-2.61	-2.62	-2.60	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - Gen. gamma, constant -48M	1.49	1.08	1.89	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - Gen. gamma, ln(sigma) - 48M	0.63	0.54	0.71	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - Gen. gamma, kappa - 48M	0.02	-0.43	0.46	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - gompertz, constant - 48M	-0.08	-0.10	-0.06	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - gompertz, gamma - 48M	-1.70	-1.72	-1.67	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - loglogistic, constant - 48M	-0.03	-0.16	0.09	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - loglogistic, ln(gamma) - 48M	1.46	1.22	1.69	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - lognormal, constant - 48M	1.47	1.22	1.73	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - lognormal, ln(sigma) - 48M	0.63	0.52	0.74	Multivariate normal

OS (BSC, PSM, ITT, CORAL MAIC results) - weibull, constant - 48M	-0.52	-0.64	-0.41	Multivariate normal
OS (BSC, PSM, ITT, CORAL MAIC results) - weibull, ln(p) - 48M	2.31	2.01	2.60	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - exponential theta- unadjusted	-0.23	-0.73	0.27	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - exponential rate- unadjusted	-2.79	-3.31	-2.27	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - log-logistic- unadjusted - theta	-0.26	-0.78	0.26	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - log-logistic- unadjusted-shape	0.63	0.20	1.05	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - log-logistic- unadjusted- scale	2.43	2.28	2.58	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - gompertz- unadjusted-theta	-0.19	-0.71	0.32	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - gompertz- unadjusted-shape	0.01	-0.05	0.06	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - gompertz- unadjusted-rate	-2.83	-2.89	-2.76	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - weibull - unadjusted-theta	-0.16	-0.64	0.31	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) -	0.23	-0.06	0.51	Multivariate normal

weibull- unadjusted- shape				
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - weibull- unadjusted- scale	2.76	2.47	3.05	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - lognormal- unadjusted- theta	-0.27	-0.82	0.27	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - lognormal- unadjusted- meanlog	2.44	2.20	2.68	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - lognormal- unadjusted- sdlog	-0.03	-0.30	0.24	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - Gen. gamma- unadjusted- theta	-0.24	-0.80	0.32	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - Gen. gamma- unadjusted- mu	2.48	1.99	2.96	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - Gen. gamma- unadjusted- sigma	-0.07	-0.17	0.03	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT, CORAL MAIC results) - Gen. gamma- unadjusted- q	0.15	-1.03	1.33	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - exponential theta- unadjusted - 60M	-0.40	-0.80	-0.01	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - exponential rate- unadjusted - 60M	-2.65	-2.96	-2.35	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted - theta - 60M	-0.51	-0.95	-0.07	Multivariate normal

OS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted- shape - 60M	0.42	0.10	0.75	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - log-logistic- unadjusted- scale - 60M	2.23	2.09	2.37	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- theta - 60M	-0.56	-1.36	0.24	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- shape - 60M	-0.02	-0.09	0.04	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - gompertz- unadjusted- rate - 60M	-2.55	-2.93	-2.17	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - weibull - unadjusted- theta - 60M	-0.40	-0.80	-0.01	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - weibull- unadjusted- shape - 60M	0.01	-0.21	0.23	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - weibull- unadjusted- scale - 60M	2.65	2.37	2.93	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - lognormal- unadjusted- theta - 60M	-0.53	-1.00	-0.07	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - lognormal- unadjusted- meanlog - 60M	2.25	2.03	2.48	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - lognormal- unadjusted- sdlog - 60M	0.19	-0.01	0.39	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - Gen. gamma- unadjusted- theta - 60M	-0.47	-0.91	-0.02	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - Gen. gamma- unadjusted- mu - 60M	2.34	1.92	2.76	Multivariate normal

OS (axicabtagene ciloleucel, MCM, ITT) - Gen. gamma- unadjusted- sigma - 60M	0.12	0.02	0.22	Multivariate normal
OS (axicabtagene ciloleucel, MCM, ITT) - Gen. gamma- unadjusted- q - 60M	0.26	-0.52	1.03	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - exponential theta- unadjusted	-0.15	-0.74	0.45	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - exponential rate- unadjusted	-3.01	-3.74	-2.27	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - log-logistic- unadjusted - theta	-0.21	-0.86	0.44	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - log-logistic- unadjusted- shape	0.49	-0.07	1.04	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - log-logistic- unadjusted- scale	2.61	2.59	2.64	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - gompertz- unadjusted- theta	-0.15	-1.14	0.84	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - gompertz- unadjusted- shape	0.00	-0.09	0.09	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - gompertz- unadjusted- rate	-3.01	-3.36	-2.65	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - weibull - unadjusted- theta	-0.05	-0.59	0.49	Multivariate normal

OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - weibull- unadjusted- shape	0.17	-0.22	0.56	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - weibull- unadjusted- scale	2.93	2.69	3.17	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - lognormal- unadjusted- theta	-0.30	-1.13	0.53	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - lognormal- unadjusted- meanlog	2.71	2.65	2.76	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - lognormal- unadjusted- sdlog	0.14	-0.04	0.31	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - Gen. gamma- unadjusted- theta	-0.17	-0.94	0.59	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - Gen. gamma- unadjusted- mu	2.73	2.31	3.15	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - Gen. gamma- unadjusted- sigma	0.03	0.00	0.06	Multivariate normal
OS (axicabtagene ciloleucel, MCM, mITT, CORAL MAIC results) - Gen. gamma- unadjusted- q	0.28	-0.88	1.45	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - weibull, pi	-2.14	-2.62	-1.66	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - weibull, ln(p)	-0.29	-0.41	-0.16	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - weibull, constant	1.79	1.56	2.01	Multivariate normal

OS (BSC, MCM, ITT, CORAL MAIC results) - Gen. gamma, pi	-2.23	-2.77	-1.68	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - Gen. gamma, ln(sigma)	1.49	1.18	1.80	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - Gen. gamma, kappa	0.37	0.32	0.41	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - Gen. gamma, constant	0.51	0.07	0.95	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - lognormal, pi	-2.69	-3.64	-1.73	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - lognormal, constant	1.24	1.12	1.36	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - lognormal, ln(sigma)	0.52	0.45	0.58	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - exponential, theta	-2.07	-2.51	-1.62	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - exponential, rate	-1.93	-2.09	-1.77	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - log-logistic, theta	-2.61	-3.42	-1.79	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - log-logistic, shape	0.11	-0.09	0.32	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - log-logistic, scale	1.27	1.15	1.39	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - gompertz, theta	-2.36	-3.12	-1.61	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - gompertz, shape	-0.05	-0.09	-0.02	Multivariate normal
OS (BSC, MCM, ITT, CORAL MAIC results) - gompertz, rate	-1.59	-1.72	-1.45	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - weibull, pi	-2.62	-3.31	-1.93	Multivariate normal

OS (BSC, MCM, mITT, CORAL MAIC results) - weibull, ln(p)	-0.25	-0.40	-0.10	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - weibull, constant	1.92	1.66	2.17	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - Gen. gamma, pi	-2.92	-4.04	-1.80	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - Gen. gamma, ln(sigma)	1.43	1.03	1.82	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - Gen. gamma, kappa	0.35	0.32	0.37	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - Gen. gamma, constant	0.16	-0.53	0.86	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - lognormal, pi	-3.15	-4.48	-1.81	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - lognormal, constant	1.35	1.20	1.49	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - log-normal, ln(sigma)	0.38	0.30	0.46	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - ex-ponential, theta	-2.54	-3.18	-1.90	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - ex-ponential, rate	-2.05	-2.23	-1.87	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - log-logistic, theta	-3.16	-4.45	-1.87	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - log-logistic, shape	0.22	-0.01	0.45	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - log-logistic, scale	1.36	1.22	1.50	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - gompertz, theta	-3.14	-4.82	-1.46	Multivariate normal
OS (BSC, MCM, mITT, CORAL MAIC results) - gompertz, shape	-0.05	-0.09	-0.01	Multivariate normal

OS (BSC, MCM, mITT, CORAL MAIC results) - gompertz, rate	-1.70	-1.84	-1.55	Multivariate normal
Adverse events				
Zuma-1: Cytokine release syndrome (AC-related), proportion	0.13	0.11	0.15	Beta
Zuma-1: Hypogammaglobulinemia (grade 1/2) proportion	0.11	0.09	0.13	Beta
Zuma-1: Encephalopathy (AC-related), proportion	0.21	0.18	0.24	Beta
Zuma-1: Febrile neutropenia (AC-related), proportion	0.17	0.14	0.20	Beta
Zuma-1: Hypotension (AC-related), proportion	0.11	0.09	0.13	Beta
Zuma-1: Neutropenia (AC-related), proportion	0.13	0.11	0.15	Beta
Zuma-1: Pyrexia (AC-related), proportion	0.12	0.10	0.14	Beta
Zuma-1: Anaemia (CC-related), proportion	0.41	0.35	0.47	Beta
Zuma-1: Febrile neutropenia (CC-related), proportion	0.29	0.25	0.33	Beta
Zuma-1: Hypophosphataemia (CC-related), proportion	0.11	0.09	0.13	Beta
Zuma-1: Leukopenia (CC-related), proportion	0.17	0.14	0.20	Beta
Zuma-1: Lymphocyte count decreased (CC-related), proportion	0.19	0.16	0.22	Beta
Zuma-1: Neutropenia (CC-related), proportion	0.35	0.30	0.40	Beta
Zuma-1: Neutrophil count decreased (CC-related), proportion	0.28	0.24	0.32	Beta
Zuma-1: Platelet count decreased (CC-related), proportion	0.13	0.11	0.15	Beta
Zuma-1: Thrombocytopenia (CC-related), proportion	0.23	0.20	0.26	Beta
Zuma-1: White blood cell count decreased (CC-related), proportion	0.27	0.23	0.31	Beta

Zuma-1: Cytokine release syndrome (AC-related), proportion (CSR DCO Aug 2018)	0.11	0.09	0.13	Beta
Zuma-1: Hypogammaglobulinemia (grade 1/2) proportion (CSR DCO Aug 2018)	0.16	0.14	0.18	Beta
HSUV				
Assumed non-cancer utility values month	0.72	0.66	0.78	
Utility value, progression-free disease (ZUMA-1 safety population)	0.65	0.53	0.77	Beta
Utility value, progressed disease (ZUMA-1 safety population)	0.76	0.70	0.82	Beta
Utility value, progression-free disease (NICE RCC MTA)	0.68	0.60	0.76	Beta
Utility value, progressed disease (NICE RCC MTA)	0.83	0.44	0.98	Beta
Utility value, progression-free disease (JULIET)	0.71	0.44	0.91	Beta
Utility value, progressed disease (JULIET)	0.79	0.74	0.85	Beta
Utility value, progression-free disease (DK weighted ZUMA-1 safety population)	0.71	0.49	0.92	Beta
Utility value, progressed disease (DK weighted ZUMA-1 safety population)	0.72	0.66	0.78	Beta
Utility decrements				
Anaemia, utility decrement	0.12	0.10	0.14	Beta
Encephalopathy, utility decrement	0.15	0.13	0.17	Beta
Febrile neutropenia, utility decrement	0.15	0.13	0.17	Beta
Hypophosphataemia, utility decrement	0.15	0.13	0.17	Beta
Hypotension, utility decrement	0.15	0.13	0.17	Beta
Leukopenia, utility decrement	0.15	0.13	0.17	Beta

Lymphocyte count decreased, utility decrement	0.15	0.13	0.17	Beta
Neutropenia, utility decrement	0.09	0.08	0.10	Beta
Neutrophil count decreased, utility decrement	0.15	0.13	0.17	Beta
Platelet count decreased, utility decrement	0.11	0.09	0.13	Beta
Pyrexia, utility decrement	0.11	0.09	0.13	Beta
Thrombocytopenia, utility decrement	0.11	0.09	0.13	Beta
White blood cell count decreased, utility decrement	0.15	0.13	0.17	Beta
Costs				
Multiplier for leukapheresis costs (ITT)	1.00	0.85	1.15	Gamma
Multiplier for conditioning chemotherapy/acquisition costs (ITT)	0.93	0.79	1.07	Gamma
Multiplier for leukapheresis costs (mITT)	1.10	0.87	1.17	Gamma
Multiplier for conditioning chemotherapy/acquisition costs (mITT)	1.02	0.87	1.17	Gamma
Proportion retreated	0.09	0.08	0.10	Beta
Leukapheresis cost	12059.00	10250.15	13867.85	Gamma
Hospitalisation cost for conditioning chemotherapy	52811.00	44889.35	60732.65	Gamma
Hospitalisation cost for administration of AC	55063.00	46803.55	63322.45	Gamma
Fludarabine, % <= 1.6 m^2	0.12	0.10	0.14	Beta
Cyclophosphamide, % <= 2.0 m^2	0.48	0.40	0.55	Beta
Hospitalisation cost for administration of BSC	22393.83	19034.76	25752.91	Gamma
Gemcitabine, % 1.4-2.0 m^2	0.52	0.52	0.52	Beta
Gemcitabine, % 2.0-2.2 m^2	0.29	0.29	0.29	Beta
Gemcitabine, % 2.2-2.4 m^2	0.14	0.14	0.14	Beta
Cisplatin, % 1.4-1.5 m^2	0.05	0.04	0.06	Beta
Cisplatin, % 1.5-2.0 m^2	0.48	0.40	0.55	Beta
Cisplatin, % 2.0-2.1 m^2	0.13	0.11	0.15	Beta

Cisplatin, % 2.1-2.2 m^2	0.16	0.13	0.18	Beta
Cisplatin, % 2.2-2.3 m^2	0.10	0.08	0.11	Beta
Cisplatin, % 2.3-2.5 m^2	0.07	0.06	0.08	Beta
Rituximab, % <= 1.6 m^2	0.10	0.08	0.11	Beta
Rituximab, % 1.6-1.866 m^2	0.21	0.18	0.24	Beta
Rituximab, % 1.866-2.133 m^2	0.42	0.35	0.48	Beta
Rituximab, % 2.133-2.4 m^2	0.23	0.19	0.26	Beta
Rituximab, % 2.4-2.666 m^2	0.04	0.03	0.05	Beta
GemOX, proportion	0.02	0.01	0.02	Beta
GemMono, proportion	0.02	0.01	0.02	Beta
Bendamustine, proportion	0.02	0.01	0.02	Beta
GDP, proportion	0.14	0.12	0.16	Beta
DHAP, proportion	0.57	0.48	0.65	Beta
ICE, proportion	0.24	0.20	0.27	Beta
Medical resource use (axicabtagene ciloleucel) - progression-free disease	518.27	440.53	596.01	Gamma
Medical resource use (axicabtagene ciloleucel) - progressed disease	19756.0	16792.60	22719.40	Gamma
Medical resource use (BSC) - progression-free disease	518.27	440.53	596.01	Gamma
Medical resource use (BSC) - progressed disease	19756.0	16792.60	22719.40	Gamma
Cost of CRS hospitalisation	48340.00	41089.00	55591.00	Gamma
Proportion treated with tocilizumab (CRS all grades)	0.17	0.14	0.20	Beta
Average duration of IVIG treatment	24.00	20.40	27.60	Gamma
Proportion treated with IVIG	0.55	0.47	0.63	Beta
AC proportion receiving allogeneic SCT	0.02	0.02	0.02	Beta
BSC proportion receiving allogeneic SCT (SCHOLAR-1 unadjusted all)	0.29	0.24	0.33	Beta

BSC proportion receiving allogeneic SCT (CORAL MAIC)	0.29	0.25	0.33	Beta
BSC proportion receiving allogeneic SCT (Al-Mashhadi et al)	0.08	0.07	0.09	Beta
Patient time / transport time cost, per cycle, PF - axi-cel	181.95	154.66	209.25	Gamma
Patient time / transport time cost, per cycle, PF - BSC	2664.26	2264.62	3063.90	Gamma
Patient time / transport time cost, per cycle, PD - yescarta	1448.17	1230.94	1665.39	Gamma
Patient time / transport time cost, per cycle, PD - BSC	3930.47	3340.90	4520.04	Gamma
Patient time / transport time cost, oneoff - yescarta admin	59789.00	50820.65	68757.35	Gamma
Patient time / transport time cost, oneoff - yescarta SCT	65.16	105.56	142.81	Gamma
Patient time / transport time cost, oneoff - BSC	1008.99	857.64	1160.33	Gamma
Patient time / transport time cost, HGG per cycle - yescarta	642.43	546.06	738.79	Gamma
Proportion with hypogammaglobulinemia for costing	0.25	0.21	0.29	Beta
BSC proportion receiving allogeneic SCT (conservative	0.00	0.00	0.00	Beta
Proportion treated with tocilizumab (CRS all grades) DCO Aug 2018	0.19	0.16	0.22	Beta

Appendix H. Literature searches for the clinical assessment

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

The objective of the SLR was to gather comprehensive clinical information (efficacy, safety, discontinuation and tolerability) about axi-cel and rituximab-based standard of care therapies for the management of patients with 3L DLBCL and PMBCL, and tisa-cel in 3L DLBCL.

As detailed in Table 88, Table 89, Table 90, the clinical SLR search was conducted on 14 July 2023 and 22 September 2023.

The searches were performed in the following indexed databases:

- Excerpta Medica Database (Embase®) and Medical Literature Analysis and Retrieval System Online (MEDLINE®; using Embase.com)
- MEDLINE In-Process (using PubMed.com)
- The Cochrane Library (using Wiley.com), including the following:
- The Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)*
- International HTA database (INAHTA)

Note: *, Due to recent changes introduced in the CENTRAL library, many unpublished trials registered under clinicaltrials.gov are automatically indexed and picked up using the search terms applied to identify the relevant published studies. However, clinicaltrials.gov records were only used for bibliographic searching to ensure all relevant published trials had been captured and identified. This was because it would only give unpublished results (if available), which was neither peer-reviewed nor provide a complete evidence base for the published literature.

Searches for axi-cel and tisa-cel studies across the literature databases were conducted on 14 July 2023 and for rituximab based SoC were conducted on 22 September 2023. All databases were searched from 2010 to September 2023 to retrieve comprehensive evidence. Search strategies for Embase® and MEDLINE® were implemented using Embase.com, MEDLINE® In-Process using the PubMed platform, and the Cochrane library using Wiley platform. The search was not restricted by countries or English language. However, any articles published in German, French, and Italian languages were flagged and shared with Gilead for their review to determine whether translation was necessary.

Conference abstracts from several relevant conference websites were captured in the Embase database searches. In addition, relevant conferences or specific years that are not indexed with Embase.com were also searched for relevant abstracts from the last 5 years (as we would expect any pertinent articles to have been published in full after 5 years), as follows:

- American Society of Clinical Oncology (ASCO)
- European Society for Medical Oncology (ESMO)

- American Society of Hematology (AHS)
- European School of Haematology (ESH)
- European Hematology Association (EHA)
- International Conference on Malignant Lymphoma (ICML)
- European Society for Blood and Marrow Transplantation (EBMT)

Bibliographies of key systematic review and meta-analysis articles were screened to ensure that our initial searches captured all the relevant clinical studies. Additionally, the following clinical trials registers and clinical trials platforms were searched:

- ClinicalTrials.gov via https://clinicaltrials.gov/
- EU Clinical Trials Register via https://www.clinicaltrialsregister.eu/

Table 88 Bibliographic databases included in the literature search

Database	Platform/source	Relevant period for the search	Date of search completion
Embase	Embase.com	2010 until today	14.07.2023 and 22.09.2023
MEDLINE	Embase.com	2010 until today	14.07.2023 and 22.09.2023
MEDLINE In-Process	PubMed.com	2010 until today	14.07.2023 and 22.09.2023
The Cochrane Library	Wiley.com	2010 until today	14.07.2023 and 22.09.2023
CENTRAL	Wiley.com	2010 until today	14.07.2023 and 22.09.2023
CDSR	Wiley.com	2010 until today	14.07.2023 and 22.09.2023
International HTA database	Wiley.com	2010 until today	14.07.2023 and 22.09.2023

Abbreviations: Embase = Excerpta Medica Database, MEDLINE = Medical Literature Analysis and Retrieval System Online, CDSR = The Cochrane Database of Systematic Reviews, Central = Cochrane Central Register of Controlled Trials, HTA = Health Technology Assessment.

Table 89 Other sources included in the literature search

Source name	Location/source	Search strategy	Date of search
ClinicalTrials.gov	www.clinicaltrials.gov	Kymriah Yescarta	14.07.2023
EU Clinical Trials Register	www.clinicaltrialsregister.eu	Axicabtagene Tisagenlecleucel Axi-cel Tisa-cel Rituximab	14.07.2023

Abbreviations: EU = European Union

Table 90 Conference material included in the literature search

Conference	Source of abstracts	Search strategy	Words/terms searched	Date of search
ESMO	https://oncology.esmo.org/meeting-resources/esmo-2018-congress	Manual search	Kymriah Yescarta Axicabtagene Tisagenlecleucel Axi-cel Tisa-cel Rituximab	
ASH	https://oncology.esmo.org/meeting-resources/esmo-2019-congress	Manual search		
EHA	https://ashpublications.org/blood/issue/140/Supplement%201	Manual search		
ICML	https://www.lymphcon.ch/icml/website/doc/15-ICML_Abstract_Book.pdf	Manual search		
EBMT	Abstract book	Manual search		

Abbreviations: ESMO = European Society for Medical Oncology, ASH = American Society of Hematology, EHA = European Hematology Association, ICML = International Conference on Malignant Lymphoma, EBMT = European Society for Blood and Marrow Transplantation

H.1.1 Search strategies

The SLR was conducted based on PRISMA, Table 97, and generated from the research question pertinent to each section.

Relevant studies were selected based on a two-step process: (1) title/abstract screening and (2) full-text screening.

Two investigators working independently screened all citations identified in the literature search. The same two investigators independently reviewed the full texts. In case any discrepancies occurred between the studies selected by the two investigators, a third investigator provided the arbitration.

Data extraction was performed in the following steps:

3. Information for the study population of interest for the final list of selected eligible studies was extracted independently into data extraction form by two investigators.
4. Data extractions were extracted in the form of report-ready tables. Any discrepancies observed between the data extracted by the two data extractors were resolved by discussion and coming to a consensus.

Table 91 Search strategy table for MEDLINE including MEDLINE In-process for axi-cel and tisa-cel

	Query	Results
#1	'nonhodgkin lymphoma'/syn OR 'b cell lymphoma'/syn	299,857
#2	(('non-hodgkin*' OR nonhodgkin* OR 'b-cell' OR 'b cell' OR 'non hodgkin*') NEAR/3 lymphoma*):ab,ti	117,298

#3	nhl:ab,ti	27,601
#4	#1 OR #2 OR #3	306,968
#5	aggressive:ab,ti OR highgrad*:ab,ti OR 'high-grad*':ab,ti OR 'high grade*':ab,ti OR 'fast-grow*':ab,ti OR 'fast grow*':ab,ti	423,846
#6	#4 AND #5	29,039
#7	'diffuse large b cell lymphoma'/syn OR 'dlbcl':ab,ti OR 'diffuse large b-cell lymphoma*':ab,ti OR 'double-hit lymphoma':ab,ti OR dhl:ab,ti OR tfl:ab,ti	47,666
#8	(((diffus* OR 'large cell' OR anaplas* OR aggress* OR 'high grade' OR 'large b-cell' OR 'large b cell' OR histiocytic OR transform*) NEAR/3 (lympho* OR nhl OR 'non-hodgkin lymphoma' OR 'non hodgkin lymphoma')):ab,ti) OR tfl:ab,ti	82,481
#9	'primary mediastinal large b-cell lymphoma'/syn OR 'primary mediastinal b-cell lymphoma*':ab,ti OR ((mediastinal* NEAR/5 lympho*):ab,ti) OR pmbcl:ab,ti OR pbcl:ab,ti OR mpmbcl:ab,ti	4,755
#10	#6 OR #7 OR #8 OR #9	104,749
#11	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR random*:ab,ti OR ((random* NEAR/2 (alloca* OR assign* OR distribut* OR group*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple blind procedure'/exp OR ('controlled study'/exp NOT 'case control study'/exp) OR 'comparative study'/exp OR (((clinical OR control*) NEAR/3 (study OR studies OR trial* OR group* OR random*)):ab,ti)	13,245,329
#12	'clinical study'/de OR 'clinical article'/exp OR 'clinical trial'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'family study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti OR 'medical record review'/exp OR 'intervention study'/exp OR 'major clinical study'/exp OR 'open study'/exp OR registr*:ab,ti OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'non-rct':ab,ti OR 'non rct':ab,ti OR nrct:ab,ti OR 'single group*':ab,ti OR 'non-random*':ab,ti OR 'non random*':ab,ti OR 'single arm*':ab,ti OR 'observational study'/exp OR 'observational method'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti OR 'real-world*':ab,ti OR 'real life*':ab,ti OR 'real-life*':ab,ti OR claim*:ab,ti OR 'compassionate use'/exp OR 'compassionate use':ab,ti OR 'expanded access*':ab,ti OR 'register'/exp	12,577,705
#13	#11 OR #12	18,626,647
#14	'chimeric antigen receptor immunotherapy'/syn OR 'chimeric antigen receptor t-cell'/syn OR 'chimeric antigen receptor t-cell immunotherapy'/syn	20,382

#15	'axicabtagene ciloleucel'/syn OR 'axi cel':ab,ti OR 'axi-cel':ab,ti OR 'fkc 876':ab,ti OR 'fkc876':ab,ti OR 'kte c19':ab,ti OR 'kte c19 car':ab,ti OR 'ktec19':ab,ti OR 'yescarta':ab,ti OR axicabtagene*:ab,ti	2,249
#16	'tisagenlecleucel t'/syn OR 'cart 19':ab,ti OR 'cart19':ab,ti OR car19:ab,ti OR 'ctl 019':ab,ti OR 'ctl019':ab,ti OR 'kymriah':ab,ti OR 'lg 740':ab,ti OR 'lg740':ab,ti OR tisagenlecleucel*:ab,ti OR 'tisa cel':ab,ti	2,997
#17	#14 OR #15 OR #16	21,214
#18	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti,kw OR 'meta analysis':ab,ti,kw)	2,953,156
#19	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	5,743,400
#20	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	5,983,615
#21	#18 OR #19 OR #20	14,357,680
#22	#10 AND #13 AND #17	3,364
#23	#22 NOT #21	2,295
#24	#22 NOT #21 AND [2010-2023]/py	2,295

Table 92 Search strategy for MEDLINE including MEDLINE In-process for axi-cel and tisa-cel

	Query	Results
#1	non hodgkin lymphoma OR b cell lymphoma	153,093
#2	('non-hodgkin' OR nonhodgkin OR 'b-cell' OR 'b cell' OR 'non hodgkin' OR non hodgkin) AND lymphoma	126,442
#3	nhl	15,623
#4	#1 OR #2 OR #3	160,422
#5	aggressive OR highgrad* OR 'high-grade' OR 'high grade' OR 'fast-grow' OR 'fast grow' OR high grade	458,156
#6	#4 AND #5	17,344
#7	'diffuse large b cell lymphoma' OR dlbcl OR 'diffuse large b-cell lymphoma' OR 'double-hit lymphoma' OR dhl OR tfl	34,752
#8	(diffuse OR 'large cell' OR anaplastic OR aggressive OR 'high grade' OR 'large b-cell' OR 'large b cell' OR histiocytic OR transformed) AND (lymphoma OR nhl OR 'non-hodgkin lymphoma' OR 'non hodgkin lymphoma')	85,958
#9	'primary mediastinal large b-cell lymphoma' OR (mediastinal AND lymphoma) OR pmbcl OR pbcl OR mpmbcl	7,301
#10	#6 OR #7 OR #8 OR #9	93,113
#11	randomization OR controlled clinical trial OR placebo effect OR placebo OR clinical trial OR control group OR randomized controlled trial OR (random*[Title/Abstract] OR placebo*[Title/Abstract] OR ((clinical[Title/Abstract] OR control*[Title/Abstract] OR compar*[Title/Abstract]) AND (study[Title/Abstract] OR studies[Title/Abstract] OR trial*[Title/Abstract] OR group*[Title/Abstract] OR random*[Title/Abstract])) OR RCT[Title/Abstract] OR ((single[Title/Abstract] OR double[Title/Abstract] OR	8,703,063

	triple[Title/Abstract] OR treble[Title/Abstract]) AND (blind*[Title/Abstract] OR mask*[Title/Abstract]))	
#12	'clinical study' OR 'clinical article' OR 'clinical trial' OR 'case control study' OR 'longitudinal study' OR 'family study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR ((cohort AND (study OR studies OR trial*))) OR (('case control' AND (study OR studies OR trial*))) OR (('follow up' NEAR/1 (study OR studies OR trial*))) OR ((observational AND (study OR studies OR trial*))) OR (('cross sectional' AND (study OR studies OR trial*))) OR 'comparative study' OR 'follow up' OR retrospectiv* OR 'medical record review' OR 'intervention study' OR 'major clinical study' OR 'open study' OR registr* OR (((hospital OR medical OR electronic) AND (record OR chart))) OR 'community trial' OR 'cross-sectional study' OR 'non-rct' OR 'non rct' OR nrct OR 'single group*' OR 'non-random*' OR 'non random*' OR 'single arm*' OR 'observational study' OR 'observational method' OR 'cancer registry' OR 'real world*' OR 'real-world*' OR 'real life*' OR 'real-life*' OR claim* OR 'compassionate use' OR 'compassionate use' OR 'expanded access*' OR 'register'	11,997,230
#13	#11 OR #12	14,548,196
#14	'chimeric antigen receptor immunotherapy' OR 'chimeric antigen receptor t-cell' OR 'chimeric antigen receptor t-cell immunotherapy'	10,990
#15	'axicabtagene ciloleucel' OR 'axi cel' OR 'axi-cel' OR 'fkc 876' OR 'fkc876' OR 'kte c19' OR 'kte c19 car' OR 'ktec19' OR 'yescarta' OR axicabtagene	483
#16	'tisagenlecleucel t' OR 'cart 19' OR 'cart19' OR car19 OR 'ctl 019' OR 'ctl019' OR 'kymriah' OR 'lg 740' OR 'lg740' OR tisagenlecleucel OR 'tisa cel'	806
#17	#14 OR #15 OR #16	11,243
#18	#10 AND #13 AND #17	1,016
#19	#10 AND #13 AND #17, case reports	83
#20	#10 AND #13 AND #17, systematic reviews	26
#21	#10 AND #13 AND #17, reviews	335
#22	#24 NOT #25 (Reviews NOT systematic reviews)	327
#23	#23 or #26 (case reports or literature reviews)	402
#24	#18 NOT #27 (excluding case reports and literature reviews)	614
#25	#18 NOT #27, 2010 onwards	604

Table 93 Search strategy for Cochrane for axi-cel and tisa-cel

	Query	Results
#1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees	2,652
#2	MeSH descriptor: [Lymphoma, B-Cell] explode all trees	982
#3	(('non-hodgkin*' OR nonhodgkin* OR 'b-cell' OR 'b cell' OR 'non hodgkin*') NEAR/3 lymphoma*):ab,ti	7,466
#4	nhl:ab,ti	1,850
#5	#1 OR #2 OR #3 OR #4	8,546
#6	aggressive:ab,ti OR highgrad*:ab,ti OR 'high-grad*':ab,ti OR 'high grade*':ab,ti OR 'fast-grow*':ab,ti OR 'fast grow*':ab,ti	32,888

#7	#5 AND #6	1,994
#8	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees	589
#9	'dlbcl':ab,ti OR dhl:ab,ti OR tfl:ab,ti OR 'diffuse large b cell lymphoma':ab,ti	2,079
#10	(((diffus* OR 'large cell' OR anaplas* OR aggress* OR 'high grade' OR 'large b-cell' OR 'large b cell' OR histiocytic OR transform*) NEAR/3 (lympho* OR nhl OR 'non-hodgkin lymphoma' OR 'non hodgkin lymphoma')):ab,ti) OR tfl:ab,ti	26,725
#11	'primary mediastinal large b cell lymphoma':ab,ti OR 'primary mediastinal b cell lymphoma*':ab,ti OR ((mediastinal* NEAR/5 lympho*):ab,ti) OR pmbcl:ab,ti OR pbcl:ab,ti OR mpmbcl:ab,ti	183
#12	#7 OR #8 OR #9 OR #10 OR #11	27,161
#13	MeSH descriptor: [Receptors, Chimeric Antigen] explode all trees	19
#14	(chimeric NEAR/3 receptor*):ab,ti	247
#15	'axicabtagene ciloleucel':ab,ti OR 'axi cel':ab,ti OR 'axi-cel':ab,ti OR 'fkc 876':ab,ti OR 'fkc876':ab,ti OR 'kte c19':ab,ti OR 'kte c19 car':ab,ti OR 'ktec19':ab,ti OR 'yescarta':ab,ti OR axicabtagene*:ab,ti	72
#16	'tisagenlecleucel t':ab,ti OR 'cart 19':ab,ti OR 'cart19':ab,ti OR car19:ab,ti OR 'ctl 019':ab,ti OR 'ctl019':ab,ti OR 'kymriah':ab,ti OR 'lg 740':ab,ti OR 'lg740':ab,ti OR tisagenlecleucel*:ab,ti OR 'tisa cel':ab,ti	232
#17	#13 OR #14 OR #15 OR #16	461
#18	#12 AND #17 in Cochrane Reviews, Trials	192

Table 94 Search strategy for Embase and MEDLINE for rituximab based SoC

	Query	Results
#1	'b-r':ab,ti OR 'r-b':ab,ti OR 'b/r':ab,ti OR 'r/b':ab,ti OR (bendamustine:ab,ti AND rituximab:ab,ti)	11,505
#2	'chop r*':ab,ti OR 'chop-r*':ab,ti OR 'r chop*':ab,ti OR 'r-chop*':ab,ti OR rchop*:ab,ti OR rpoch*:ab,ti OR 'r-poch':ab,ti OR 'r poch':ab,ti OR 'r±chop':ab,ti OR 'chop±r':ab,ti OR 'r ± chop':ab,ti OR 'chop ± r':ab,ti OR 'chop protocol'/exp OR 'cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus rituximab plus vincristine'/syn OR 'cyclophosphamide plus doxorubicin plus prednisolone plus rituximab plus vincristine'/syn OR (rituximab:ab,ti AND cyclophosphamide AND (hydroxydaunorubicin:ab,ti OR doxorubicin:ab,ti) AND vincristine:ab,ti AND prednison*:ab,ti)	14,429
#3	'r-dhap':ab,ti OR 'r dhap':ab,ti OR 'dhap r':ab,ti OR 'r±dhap':ab,ti OR 'r ± dhap':ab,ti OR 'dhap±r':ab,ti OR 'dhap ± r':ab,ti OR (rituximab:ab,ti AND dexamethasone:ab,ti AND cytarabine:ab,ti AND cisplatin:ab,ti)	575
#4	'r eshap':ab,ti OR reshap:ab,ti OR 'r-eshap':ab,ti OR 'eshap r':ab,ti OR 'eshap-r':ab,ti OR 'r±eshap':ab,ti OR 'r ± eshap':ab,ti OR 'eshap±r':ab,ti OR 'eshap ± r':ab,ti OR (rituximab:ab,ti AND etoposide:ab,ti AND methylpredniso*:ab,ti AND cytarabin*:ab,ti AND cisplatin:ab,ti) OR 'r ehap':ab,ti OR 'ehap r':ab,ti	182
#5	'r-gemox':ab,ti OR 'r gemox':ab,ti OR 'r-gem ox':ab,ti OR 'r-gem-ox':ab,ti OR 'gemox r':ab,ti OR 'gemox-r':ab,ti OR 'gem ox r':ab,ti OR 'gem-ox-r':ab,ti OR 'gem-ox r':ab,ti OR 'r±gemox':ab,ti OR 'r ± gemox':ab,ti OR 'r±gem ox':ab,ti OR 'r ± gem ox':ab,ti OR 'r±gem-ox':ab,ti OR 'r ± gem-	261

	Query	Results
	ox':ab,ti OR 'gemox±r':ab,ti OR 'gemox ± r':ab,ti OR 'gem ox±r':ab,ti OR 'gem ox ± r':ab,ti OR 'gem-ox±r':ab,ti OR 'gem-ox ± r':ab,ti OR (rituximab:ab,ti AND gemcitabine:ab,ti AND oxaliplatin:ab,ti)	
#6	'r-gdp':ab,ti OR 'r gdp':ab,ti OR 'gdp-r':ab,ti OR 'gdp r':ab,ti OR r±gdp:ab,ti OR 'r ± gdp':ab,ti OR gdp±r:ab,ti OR 'gdp ± r':ab,ti OR (rituximab:ab,ti AND gemcitabine:ab,ti AND cisplatin:ab,ti AND dexamethasone:ab,ti)	1,314
#7	'r-ice':ab,ti OR 'r ice':ab,ti OR 'ice r':ab,ti OR 'r±ice':ab,ti OR 'r ± ice':ab,ti OR ice±r:ab,ti OR 'ice ± r':ab,ti OR (rituximab:ab,ti AND ifosfamid:ab,ti AND carboplatin:ab,ti AND etoposide:ab,ti)	2,540
#8	'dose adjusted epoch-r':ab,ti OR 'da-r-epoch':ab,ti OR 'dose-adjusted epoch-r':ab,ti OR 'da epoch r':ab,ti OR 'r epoch':ab,ti OR 'epoch r':ab,ti OR 'da epoch±r':ab,ti OR 'da epoch ± r':ab,ti OR 'r ± epoch':ab,ti OR r±epoch:ab,ti OR 'epoch ± r':ab,ti OR epoch±r:ab,ti OR 'cyclophosphamide plus doxorubicin plus etoposide plus prednisolone plus rituximab plus vincristine'/syn OR (cyclophosphamide:ab,ti AND doxorubicin:ab,ti AND etoposide:ab,ti AND prednisolone:ab,ti AND rituximab:ab,ti AND vincristine:ab,ti) OR ((salvage NEXT/1 (chemotherapy OR regimen OR treatment OR therapy)):ab,ti)	24,333
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	50,782
#10	'nonhodgkin lymphoma'/syn OR 'b cell lymphoma'/syn	256,701
#11	(('non-hodgkin*' OR nonhodgkin* OR 'b-cell' OR 'b cell' OR 'non hodgkin*') NEAR/3 lymphoma*):ab,ti	118,230
#12	nhl:ab,ti	27,722
#13	#10 OR #11 OR #12	264,361
#14	aggressive:ab,ti OR highgrad*:ab,ti OR 'high-grad*':ab,ti OR 'high grade*':ab,ti OR 'fast-grow*':ab,ti OR 'fast grow*':ab,ti	428,166
#15	#13 AND #14	27,883
#16	'diffuse large b cell lymphoma'/syn OR 'dlbcl':ab,ti OR 'diffuse large b-cell lymphoma*':ab,ti OR 'double-hit lymphoma':ab,ti OR dhl:ab,ti OR tfl:ab,ti	50,446
#17	(((diffus* OR 'large cell' OR anaplas* OR aggress* OR 'high grade' OR 'large b-cell' OR 'large b cell' OR histiocytic OR transform*) NEAR/3 (lympho* OR nhl OR 'non-hodgkin lymphoma' OR 'non hodgkin lymphoma')):ab,ti) OR tfl:ab,ti	83,156
#18	'primary mediastinal large b-cell lymphoma'/syn OR 'primary mediastinal b-cell lymphoma*':ab,ti OR ((mediastinal* NEAR/5 lympho*):ab,ti) OR pmbcl:ab,ti OR pbcl:ab,ti OR mpmbcl:ab,ti	4,808
#19	#15 OR #16 OR #17 OR #18	104,987
#20	'randomization'/exp OR 'controlled clinical trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'placebo effect'/exp OR 'placebo'/exp OR 'clinical trial'/exp OR 'clinical trial (topic)'/exp OR 'control group'/exp OR 'randomized controlled trial'/exp OR 'randomized controlled trial (topic)'/exp OR 'controlled clinical trial':ab,ti OR 'controlled clinical trials':ab,ti OR 'randomised controlled trial':ab,ti OR 'randomized controlled trial':ab,ti OR 'randomised controlled trials':ab,ti OR 'randomized controlled trials':ab,ti OR 'randomi?ed controlled trial*' OR rct:ab,ti OR random*:ab,ti OR ((random* NEAR/2 (alloca* OR assign* OR distribut* OR group*)):ab,ti) OR (((single OR double OR triple OR treble) NEAR/2 (blind* OR mask*)):ab,ti) OR placebo*:ab,ti OR 'single blind procedure'/exp OR 'crossover procedure'/exp OR 'double blind procedure'/exp OR 'triple	13,419,166

	Query	Results
	blind procedure'/exp OR ('controlled study'/exp NOT 'case control study'/exp) OR 'comparative study'/exp OR (((clinical OR control*) NEAR/3 (study OR studies OR trial* OR group* OR random*)):ab,ti)	
#21	'clinical study'/de OR 'clinical article'/exp OR 'clinical trial'/exp OR 'case control study'/exp OR 'longitudinal study'/exp OR 'family study'/exp OR 'retrospective study'/exp OR 'prospective study'/exp OR 'cohort analysis'/exp OR ((cohort NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR (('case control' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR (('follow up' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR ((observational NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR (('cross sectional' NEAR/1 (study OR studies OR trial*)):ab,ti,kw) OR 'comparative study'/exp OR 'follow up'/exp OR retrospectiv*:ab,ti,kw OR 'medical record review'/exp OR 'intervention study'/exp OR 'major clinical study'/exp OR 'open study'/exp OR registr*:ab,ti,kw OR (((hospital OR medical OR electronic) NEAR/2 (record OR chart)):ab,ti,kw) OR 'community trial'/exp OR 'cross-sectional study'/exp OR 'non-rct':ab,ti,kw OR 'non rct':ab,ti,kw OR nrct:ab,ti,kw OR 'single group*':ab,ti,kw OR 'non-random*':ab,ti,kw OR 'non random*':ab,ti,kw OR 'single arm*':ab,ti,kw OR 'observational study'/exp OR 'observational method'/exp OR 'cancer registry'/exp OR 'real world*':ab,ti,kw OR 'real-world*':ab,ti,kw OR 'real life*':ab,ti,kw OR 'real-life*':ab,ti,kw OR claim*:ab,ti,kw OR 'compassionate use'/exp OR 'compassionate use':ab,ti,kw OR 'expanded access*':ab,ti,kw OR 'register'/exp	12,745,083
#22	#20 OR #21	18,864,420
#23	'second line chemotherapy' OR 'third line chemotherapy' OR 'second-line' OR 'second line' OR 'third-line' OR 'third line' OR '2nd line' OR '2nd-line' OR '3rd line' OR '3rd-line' OR 'second or later*' OR 'third or later*' OR 'fourth or later*' OR 'second- or later*' OR 'second and later*' OR 'second- and later*' OR '2 l' OR '3 l' OR '2l' OR '3l' OR '2-l' OR '3-l' OR '2 line*' OR '2-line*' OR '3 line*' OR '3-line*' OR 'previously treated' OR 'previously-treated' OR 'pre-treated' OR 'pretreated' OR 'prior treatment' OR 'prior-treatment' OR 'prior treated' OR 'prior-treated' OR 'prior therap*' OR 'prior-therap*' OR relaps* OR refrac* OR resist* OR 'cancer recurrence'/exp OR 'relapse'/exp OR 'therapy resistance'/exp OR 'recurrence risk'/exp OR 'leukemia relapse'/exp OR 'recurrent disease'/exp OR 'treatment failure'/exp OR reocur* OR 're occur' OR 're ocur' OR (((pre* OR prior* OR prev*) NEAR/2 (treat* OR therap* OR regim* OR progress* OR fail* OR relaps* OR resis* OR refract* OR line* OR chemo*)):ab,ti) OR (((lack* OR inadequa*) NEAR/2 respon*):ab,ti)	4,029,431
#24	#9 AND #19 AND #22 AND #23	6,586
#25	(review:it OR 'literature review':it) NOT ('meta-analysis':it OR 'meta-analysis as topic'/mj OR 'systematic review':ti OR 'systematic literature review':ti OR 'meta-analysis':ab,ti,kw OR 'meta analysis':ab,ti,kw)	2,978,122
#26	'case study':it OR 'case report':it OR 'abstract report':it OR editorial:it OR letter:it OR comment:it OR note:it OR 'case report'/exp OR 'case study'/exp OR 'editorial'/exp	5,789,759
#27	'animal'/exp NOT ('animal'/exp AND 'human'/exp)	6,016,348
#28	#25 OR #26 OR #27	14,460,079
#29	#24 NOT #28	5,210
#30	#24 NOT #28 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim)	3,579

	Query	Results
#31	#24 NOT #28 AND ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim) AND [2018-2023]/py	1,729
#32	#30 NOT #31	1,850
#33	#29 NOT #32	3,360
#34	#29 NOT #32 AND [english]/lim	3,271
#35	#29 NOT #32 AND ([english]/lim OR [french]/lim OR [german]/lim OR [italian]/lim)	3,285

Table 95 Search strategy for MEDLINE including MEDLINE In-Processs for rituximab based SoC

	Query	Results
#1	non hodgkin lymphoma OR b cell lymphoma	154,137
#2	('non-hodgkin' OR nonhodgkin OR 'b-cell' OR 'b cell' OR 'non hodgkin' OR non hodgkin) AND lymphoma	127,352
#3	nhl	15,736
#4	#1 OR #2 OR #3	161,515
#5	aggressive OR highgrad* OR 'high-grade' OR 'high grade' OR 'fast-grow' OR 'fast grow' OR high grade	463,394
#6	#4 AND #5	17,487
#7	'diffuse large b cell lymphoma' OR dlbcl OR 'diffuse large b-cell lymphoma' OR 'double-hit lymphoma' OR dhl OR tfl	35,142
#8	(diffuse OR 'large cell' OR anaplastic OR aggressive OR 'high grade' OR 'large b-cell' OR 'large b cell' OR histiocytic OR transformed) AND (lymphoma OR nhl OR 'non-hodgkin lymphoma' OR 'non hodgkin lymphoma')	86,734
#9	'primary mediastinal large b-cell lymphoma' OR (mediastinal AND lymphoma) OR pmbcl OR pbcl OR mpmbcl	7,366
#10	#6 OR #7 OR #8 OR #9	93,976
#11	randomization OR controlled clinical trial OR placebo effect OR placebo OR clinical trial OR control group OR randomized controlled trial OR (random*[Title/Abstract] OR placebo*[Title/Abstract] OR ((clinical[Title/Abstract] OR control*[Title/Abstract] OR compar*[Title/Abstract]) AND (study[Title/Abstract] OR studies[Title/Abstract] OR trial*[Title/Abstract] OR group*[Title/Abstract] OR random*[Title/Abstract])) OR RCT[Title/Abstract] OR ((single[Title/Abstract] OR double[Title/Abstract] OR triple[Title/Abstract] OR treble[Title/Abstract]) AND (blind*[Title/Abstract] OR mask*[Title/Abstract])))	8,808,033
#12	'clinical study' OR 'clinical article' OR 'clinical trial' OR 'case control study' OR 'longitudinal study' OR 'family study' OR 'retrospective study' OR 'prospective study' OR 'cohort analysis' OR ((cohort AND (study OR studies OR trial*))) OR (('case control' AND (study OR studies OR trial*))) OR (('follow up' NEAR/1 (study OR studies OR trial*))) OR ((observational AND (study OR studies OR trial*))) OR (('cross sectional' AND (study OR studies OR trial*))) OR 'comparative study' OR 'follow up' OR retrospectiv* OR 'medical record review' OR 'intervention study' OR 'major clinical study' OR 'open study' OR registr* OR (((hospital OR medical OR electronic) AND (record OR chart))) OR 'community trial' OR 'cross-sectional study' OR 'non-rct' OR 'non rct' OR nrct OR 'single group*' OR 'non-random*' OR 'non random*' OR 'single arm*' OR 'observational study' OR	12,125,106

	Query	Results
	'observational method' OR 'cancer registry' OR 'real world*' OR 'real-world*' OR 'real life*' OR 'real-life*' OR claim* OR 'compassionate use' OR 'compassionate use' OR 'expanded access*' OR 'register'	
#13	#11 OR #12	14,706,429
#14	"b-r" OR "r-b" OR "b/r" OR "r/b" OR (bendamustine AND rituximab)	18,281
#15	"chop r" OR "chop-r" OR "r chop" OR "r-chop" OR rchop OR rpoch OR "r-poch" OR "r poch" OR "r±chop" OR "chop±r" OR "r ± chop" OR "chop ± r" OR (rituximab AND cyclophosphamide AND (hydroxydaunorubicin OR doxorubicin) AND vincristine AND prednison*)	4,820
#16	"r-dhap" OR "r dhap" OR "dhap r" OR "r±dhap" OR "r ± dhap" OR "dhap±r" OR "dhap ± r" OR (rituximab AND dexamethasone AND cytarabine AND cisplatin)	258
#17	"r eshap" OR reshap OR "r-eshap" OR "eshap r" OR "eshap-r" OR "r±eshap" OR "r ± eshap" OR "eshap±r" OR "eshap ± r" OR (rituximab AND etoposide AND methylpredniso* AND cytarabin* AND cisplatin) OR "r ehap" OR "ehap r"	51
#18	r-gemox OR "r gemox" OR "r gem ox" OR "r-gem-ox" OR "gemox r" OR "gemox-r" OR "gem ox r" OR "gem-ox-r" OR "gem-ox r" OR "r±gemox" OR "r ± gemox" OR "r±gem ox" OR "r ± gem ox" OR "r±gem-ox" OR "r ± gem-ox" OR "gemox±r" OR "gemox ± r" OR "gem ox±r" OR "gem ox ± r" OR "gem-ox±r" OR "gem-ox ± r" OR (rituximab AND gemcitabine AND oxaliplatin)	38
#19	r-gdp OR "r gdp" OR "gdp-r" OR "gdp r" OR "r±gdp" OR "r ± gdp" OR "gdp±r" OR "gdp ± r" OR (rituximab AND gemcitabine AND cisplatin AND dexamethasone)	490
#20	"r-ice" OR "r ice" OR "r ± ice" OR "ice r" OR "ice ± r" OR (rituximab AND ifosfamid AND carboplatin AND etoposide)	189
#21	"dose adjusted epoch-r" OR "da-r-epoch" OR "dose-adjusted epoch-r" OR "da epoch r" OR "r epoch" OR "epoch r" OR "da epoch±r" OR "da epoch ± r" OR "r ± epoch" OR "r±epoch" OR "epoch ± r" OR "epoch±r" OR (cyclophosphamide AND doxorubicin AND etoposide AND prednisolone AND rituximab AND vincristine) OR ((salvage NEXT/1 (chemotherapy OR regimen OR treatment OR therapy)))	336
#22	#14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	23,874
#23	"second line chemotherapy" OR "third line chemotherapy" OR "second-line" OR "second line" OR "third-line" OR "third line" OR "2nd line" OR "2nd-line" OR "3rd line" OR "3rd-line" OR "second or later" OR "third or later" OR "second- or later" OR "third- or later" OR "second and later" OR "third and later" OR "second- and later" OR "third- and later" OR "2 l" OR "3 l" OR "2l" OR "3l" OR "2-l" OR "3-l" OR "2 line" OR "2-line" OR "3 line" OR "3-line" OR "previously treated" OR "previously-treated" OR "pre-treated" OR "pretreated" OR "failed" OR "prior treatment" OR "prior-treatment" OR "prior treated" OR "prior-treated" OR "prior therap" OR "prior-therap" OR relapse OR refractory OR resistant OR recurrence OR reocurrence OR "re occur" OR "re ocur" OR (((pre OR prior OR previous) AND (treatment OR therapy OR regimen OR progress OR fail OR relapse OR resistant OR refractory OR line OR chemotherapy))) OR (((lack OR inadequate) AND response))	4,012,718
#24	(publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook) OR (pubstatusaheadofprint) OR (inprocess[sb])	329,989

	Query	Results
#25	#10 AND #13 AND #22 AND #23 AND #24	20

Table 96 Search strategy for Cochrane for rituximab based SoC

	Query	Results
#1	MeSH descriptor: [Lymphoma, Non-Hodgkin] explode all trees	2,664
#2	MeSH descriptor: [Lymphoma, B-Cell] explode all trees	987
#3	(('non-hodgkin*' OR nonhodgkin* OR "b-cell" OR "b cell" OR 'non hodgkin*') NEAR/3 lymphoma*):ab,ti	6,286
#4	nhl:ab,ti	1,853
#5	#1 OR #2 OR #3 OR #4	7,740
#6	aggressive:ab,ti OR highgrade:ab,ti OR "high-grade":ab,ti OR "high grade":ab,ti OR "fast-grow":ab,ti OR "fast grow":ab,ti	13,839
#7	#5 AND #6	1,370
#8	MeSH descriptor: [Lymphoma, Large B-Cell, Diffuse] explode all trees	593
#9	dlbcl:ab,ti OR dhl:ab,ti OR tfl:ab,ti OR "diffuse large b cell lymphoma":ab,ti	1,793
#10	(((diffus* OR "large cell" OR anaplas* OR aggress* OR "high grade" OR "large b-cell" OR "large b cell" OR histiocytic OR transform*) NEAR/3 (lympho* OR nhl OR "non-hodgkin lymphoma" OR "non hodgkin lymphoma")):ab,ti) OR tfl:ab,ti	3,557
#11	primary mediastinal large b cell lymphoma:ab,ti OR 'primary mediastinal b cell lymphoma*':ab,ti OR ((mediastinal* NEAR/5 lympho*):ab,ti) OR pmbcl:ab,ti OR pbcl:ab,ti OR mpmbcl:ab,ti	185
#12	#7 OR #8 OR #9 OR #10 OR #11	3,977
#13	b-r:ab,ti OR "r-b":ab,ti OR "b/r":ab,ti OR "r/b":ab,ti OR (bendamustine:ab,ti AND rituximab:ab,ti)	1,039
#14	'chop r*':ab,ti OR 'chop-r*':ab,ti OR 'r chop*':ab,ti OR 'r-chop*':ab,ti OR rchop*:ab,ti OR rpoch*:ab,ti OR "r-poch":ab,ti OR "r poch":ab,ti OR "r±chop":ab,ti OR "chop±r":ab,ti OR "r ± chop":ab,ti OR "chop ± r":ab,ti OR (rituximab:ab,ti AND cyclophosphamide AND (hydroxydaunorubicin:ab,ti OR doxorubicin:ab,ti) AND vincristine:ab,ti AND prednison*:ab,ti)	2,514
#15	r-dhap:ab,ti OR "r dhap":ab,ti OR "dhap r":ab,ti OR "r±dhap":ab,ti OR "r ± dhap":ab,ti OR "dhap±r":ab,ti OR "dhap ± r":ab,ti OR (rituximab:ab,ti AND dexamethasone:ab,ti AND cytarabine:ab,ti AND cisplatin:ab,ti)	94
#16	r eshap:ab,ti OR reshap:ab,ti OR "r-eshap":ab,ti OR "eshap r":ab,ti OR "eshap-r":ab,ti OR "r±eshap":ab,ti OR "r ± eshap":ab,ti OR "eshap±r":ab,ti OR "eshap ± r":ab,ti OR (rituximab:ab,ti AND etoposide:ab,ti AND methylpredniso*:ab,ti AND cytarabin*:ab,ti AND cisplatin:ab,ti) OR "r ehap":ab,ti OR "ehap r":ab,ti	19
#17	r-gemox:ab,ti OR "r gemox":ab,ti OR "r-gem ox":ab,ti OR "r-gem-ox":ab,ti OR "gemox r":ab,ti OR "gemox-r":ab,ti OR "gem ox r":ab,ti OR "gem-ox-r":ab,ti OR "gem-ox r":ab,ti OR "r±gemox":ab,ti OR "r ± gemox":ab,ti OR "r±gem ox":ab,ti OR "r ± gem ox":ab,ti OR "r±gem-ox":ab,ti OR "r ± gem-ox":ab,ti OR "gemox±r":ab,ti OR "gemox ± r":ab,ti OR "gem ox±r":ab,ti OR	81

	Query	Results
	"gem ox ± r":ab,ti OR "gem-ox±r":ab,ti OR "gem-ox ± r":ab,ti OR (rituximab:ab,ti AND gemcitabine:ab,ti AND oxaliplatin:ab,ti)	
#18	r-gdp:ab,ti OR "r gdp":ab,ti OR "gdp-r":ab,ti OR "gdp r":ab,ti OR "r±gdp":ab,ti OR "r ± gdp":ab,ti OR "gdp±r":ab,ti OR "gdp ± r":ab,ti OR (rituximab:ab,ti AND gemcitabine:ab,ti AND cisplatin:ab,ti AND dexamethasone:ab,ti)	35
#19	r-ice:ab,ti OR "r ice":ab,ti OR "ice r":ab,ti OR "r±ice":ab,ti OR "r ± ice":ab,ti OR "ice±r":ab,ti OR "ice ± r":ab,ti OR (rituximab:ab,ti AND ifosfamid:ab,ti AND carboplatin:ab,ti AND etoposide:ab,ti)	51
#20	dose adjusted epoch-r:ab,ti OR "da-r-epoch":ab,ti OR "dose-adjusted epoch-r":ab,ti OR "da epoch r":ab,ti OR "r epoch":ab,ti OR "epoch r":ab,ti OR "da epoch±r":ab,ti OR "da epoch ± r":ab,ti OR "r ± epoch":ab,ti OR "r±epoch":ab,ti OR "epoch ± r":ab,ti OR "epoch±r":ab,ti OR (cyclophosphamide:ab,ti AND doxorubicin:ab,ti AND etoposide:ab,ti AND prednisolone:ab,ti AND rituximab:ab,ti AND vincristine:ab,ti) OR ((salvage NEXT/1 (chemotherapy OR regimen OR treatment OR therapy)):ab,ti)	1,722
#21	#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20	5,079
#22	second line chemotherapy OR "third line chemotherapy" OR "second-line" OR "second line" OR "third-line" OR "third line" OR "2nd line" OR "2nd-line" OR "3rd line" OR "3rd-line" OR "second or later" OR "third or later" OR "second- or later" OR "third- or later" OR "second and later" OR "third and later" OR "second- and later" OR "third- and later" OR "2 l" OR "3 l" OR "2l" OR "3l" OR "2-l" OR "3-l" OR "2 line" OR "2-line" OR "3 line" OR "3-line" OR "previously treated" OR "previously-treated" OR "pre-treated" OR "pretreated" OR "failed" OR "prior treatment" OR "prior-treatment" OR "prior treated" OR "prior-treated" OR "prior therap" OR "prior-therap" OR relapse OR refractory OR resistant OR recurrence OR [mh "Salvage Therapy"] OR [mh "Treatment Failure"] OR [mh "Drug Resistance"] OR [mh Recurrence] OR [mh "Relapse"] OR reocurrence OR "re occur" OR "re ocur" OR (((pre OR prior OR previous) NEAR/2 (treatment OR therapy OR regimen OR progress OR fail OR relapse OR resistant OR refractory OR line OR chemotherapy)):ab,ti) OR (((lack OR inadequate) NEAR/2 response):ab,ti)	212,297
#23	#12 AND #21 AND #22	777

H.1.2 Systematic selection of studies

Table 97 Inclusion and exclusion criteria used for assessment of studies

Clinical effectiveness	Inclusion criteria	Exclusion criteria
Population	Adults with R/R DLBCL and PMBCL (according to WHO classification of hematopoietic and lymphatic neoplasms, 2008) after at least two lines of therapy	• 2L or earlier treatment therapy for R/R DLBCL • Patients with disease other than DLBCL and PMBCL • Paediatric population • Healthy volunteers
Intervention	• Axi-cel • Tisa-cel • Rituximab-based SoC: B-R, R-CHOP, R-DHAP, R-ESHAP, R-EHAP, R-Gemox, R-GDP, R-ICE, and R-EPOCH	• Non-pharmacological interventions • Interventions not included in the list
Comparators	• Placebo • Best supportive care (author-defined) • No comparator limit for single-arm trials	• No exclusion on comparator
Outcomes	• Overall survival • Progression-free survival • Complete response rate • Overall response rate • Treatment-free interval • Event-free survival • Quality of life (EQ-5D questionnaire, FACT-Lym, FACT-G, EORTC QLQ-C30) • Treatment discontinuation • Adverse events	• Studies assessing outcomes not relevant to the review
Study design/publication type	• Randomized controlled trials • Non-randomized controlled trials • Single-arm studies • Prospective and retrospective observational studies • Systematic reviews (to identify relevant unique studies)* • Relevant high-quality meta-analysis	• Case series and case reports • Non-comparative observational studies • Literature reviews • Animal/in vitro studies
Language restrictions	English, German, French, Italian languages	

Abbreviations: 2L = second-line, B-R = bendamustine-rituximab, DLBCL = diffuse large B-cell lymphoma, EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (30 items), FACT-G = Functional Assessment of Cancer Therapy – General, FACT-Lym = Functional Assessment of Cancer Therapy – Lymphoma, PMBCL = primary mediastinal large B-cell lymphoma, R-CHOP = rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone, R-DHAP = rituximab + dexamethasone + cytarabine + cisplatin, R-ESHAP = rituximab + etoposide + methylprednisone + cytarabine + cisplatin, R-ICE = rituximab + ifosfamide + carboplatin + etoposide, R-GDP = rituximab + gemcitabine + dexamethasone + cisplatin, R-Gemox = rituximab + gemcitabine + oxaliplatin, R/R = relapsed or refractory, SLR = systematic literature review, SoC = standard of care, WHO = World Health Organization.

The PRISMA flow diagram of the clinical SLR is presented in Section H.1.3 below. From the searches a total of 7,173 potentially relevant titles or abstracts were identified from the literature databases. Following the removal of duplicates 5,728 records were screened based on the information reported in their titles and/or abstracts. Following the primary screening, a total of 1,066 citations were included and all these were assessed in full for further evaluation. Of these, 914 were excluded due to the following reasons: animal/in vitro (n = 1), review/editorial (n = 42), line of therapy (n = 393), age (<18 years) (n = 2), disease (n = 111), intervention (n = 173), outcomes (n = 42), study design (n = 99), language (n = 4) and Duplicate (n = 47). In addition, 18 publications were identified from the bibliographic/conference/registry searches.

Therefore, meeting the predefined inclusion criteria provided in Table 97, a total of 170 records were included in the review. As some studies were associated with multiple publications, secondary publications were linked to the primary publication and all the relevant data were extracted in a single row. Therefore, a total of 27 studies of the 170 publications were extracted. The details of these publications are provided in the data extraction workbook.

Of these 27 studies, 3 were relevant for use in this submission in the comparison of axi-cel to salvage therapy (which consists of R-DHAP, R-ICE, R-GDP, R-GemOx, R-Gemcitabine and R-Bendamustine), and provided the richest data to 3L DLBCL patients. The studies are described in Table 98.

The 24 studies that were excluded from the health technology assessment are presented in Table 99 below.

H.1.3 PRISMA diagram of systematic selection of studies for clinical efficacy and safety

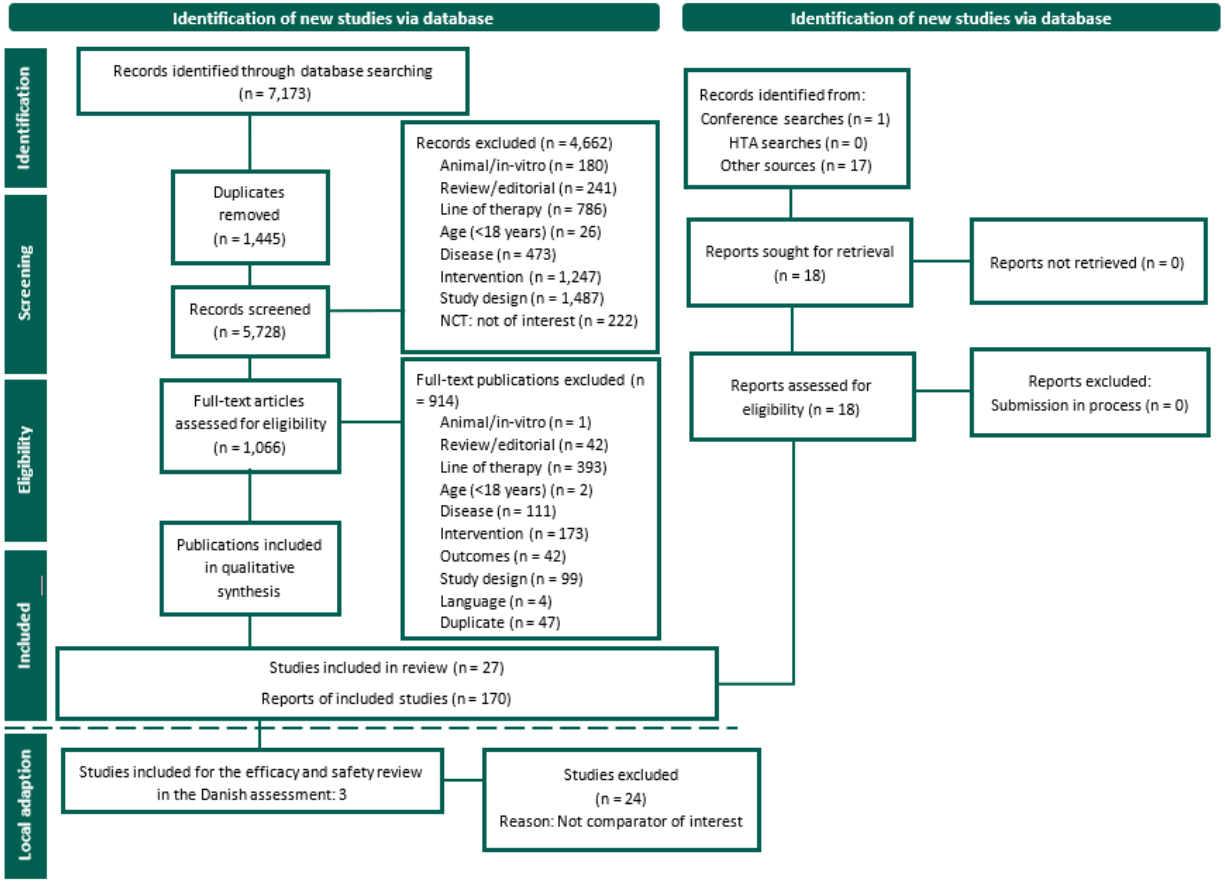


Table 98 Overview of study design for studies included in the technology assessment

Study/ID	Aim	Study design	Patient population	Intervention and comparator (sample size (n))	Primary outcome and follow-up period	Secondary outcome and follow-up period
ZUMA-1	The primary objective of phase 2 was to evaluate the efficacy of KTE-C19, as measured by objective response rate in subjects with DLBCL, primary PMBCL, and TFL. Secondary objectives included assessing the safety and tolerability of KTE-C19 and additional efficacy endpoints as outlined below	Single arm trial	Patients with refractory aggressive NHL (≥80% DLBCL)	Axicabtagene Ciloleucel 2×10^6 CAR T/Kg. (101)	ORR (CR + PR) (Up to 16 months)	
CORAL EXT 1	To evaluate the response to third line treatment in patients who relapsed after BEAM/ASCT either before or after randomisation between rituximab maintenance and observation.	Randomised controlled trial	Patient with DLBCL in 1st relapse after CR, less than PR or partial response to first line treatment; aged from 18 to 65 years.	Addition of rituximab to SoC (75)	OO and RR. Median follow up: 32.8 months (range 24.3–45.8 months).	
CORAL EXT 2	To analyse the characteristics and survival of patients included in the CORAL study, who did not fulfill the protocol strategy at the time of evaluation before transplant.	Randomised controlled trial	Patient with histologically proven, CD 20+ diffuse large B cell lymphoma in 1st relapse after CR, less than PR or partial response to first line treatment; aged from 18 to 65 years.	Addition of rituximab to SoC (203)	OS, CR/CrU, PR, SD, PD, ORR and subsequent treatment. Median follow-up: 30.1 months	

Table 99 Overview of studies excluded in the technology assessment

Publication	Exclusion reason
Long-term clinical outcomes of tisagenlecleucel in patients with relapsed or refractory aggressive B-cell lymphomas (JULIET): a multicentre, open-label, single-arm, phase 2 study. Schuster SJ, Tam CS, Borchmann P, Worel N, McGuirk JP, Holte H, Waller EK, Jaglowski S, Bishop MR, Damon LE, Foley SR, Westin JR, Fleury I, Ho PJ, Mielke S, Teshima T, Janakiram M, Hsu JM, Izutsu K, Kersten MJ, Ghosh M, Wagner-Johnston N, Kato K, Corradini P, Martinez-Prieto M, Han X, Tiwari R, Salles G, Maziarz RT. Lancet Oncol. 2021 Oct;22(10):1403-1415.	Wrong comparator
Outcomes of Patients (Pts) in ZUMA-9, a Multicenter, Open-Label Study of Axicabtagene Ciloleucel (Axi-Cel) in Relapsed/Refractory Large B Cell Lymphoma (R/R LBCL) for Expanded Access (EA) and Commercial out-of-Specification (OOS) Product. Caron A. Jacobson, Frederick L. Locke, David B. Miklos, Julie M. Vose, Yi Lin, Lihua E. Budde, David G. Maloney, Samantha Jaglowski, Peter A. Riedell, Lazaros J. Lekakis, et al. Transplantation and Cellular Therapy. 27. S408. 10.1016/S2666-6367(21)00524-8.	Wrong comparator
Phase 1/2 primary analysis of ZUMA-6:Axicabtagene ciloleucel (Axi-Cel) in combination With atezolizumab (Atezo) for the treatment of patients (Pts) with refractory diffuse large B cell lymphoma (DLBCL). Caron A. Jacobson; Jason R. Westin; David B. Miklos; Alex F. Herrera; Jennifer Lee; Judy Seng; John M. Rossi; Jennifer Sun; Jinghui Dong; Zachary J. Roberts; Remus Vezan; Mauro P. Avanzi; Frederick L. Locke. (2020) Cancer Research. |Volume 80, Issue 16	Wrong comparator
Real-Life CAR-T Cell Treatment in Large B-Cell Lymphomas Indicates That Axi-Cel and Tisa-Cel Have Similar Outcomes, but Long-Term Cytopenia Is an Emerging Problem. A. Chiappella, A. Guidetti, A. Dodero, S. Bramanti, P. Zinzani, A. Santoro, B. Casadei, A. Di Rocco, M. Carrabba, P. Chiusolo, M. Martino, A. Barbui, M. Tisi, R. Saccardi, V. Perriello, E. Orciuolo, B. Botto, D. Russo, R. Miceli, S. Ljevar, C. Carniti, P. Corradini. Blood 2021; 138 (Supplement 1): 3867	Wrong study design
Commercial anti-CD19 CAR T cell therapy for patients with relapsed/refractory aggressive B cell lymphoma in a European center. Sesques P, Ferrant E, Safar V, Wallet F, Tordo J, Dhomps A, Karlin L, Brisou G, Vercasson M, Hospital-Gustem C, Schwiertz V, Ranchon F, Rioufol C, Choquet M, Sujobert P, Ghergus D, Bouafia F, Golfier C, Lequeu H, Lazareth A, Novelli S, Devic P, Traverse Glehen A, Viel S, Venet F, Mialou V, Hequet O, Chauchet A, Arkam Y, Nicolas-Virelizier E, Peyrade F, Cavalieri D, Ader F, Ghesquières H, Salles G, Bachy E. Am J Hematol. 2020 Nov;95(11):1324-1333.	Wrong study design
Patterns of Use, Outcomes, and Resource Utilization among Recipients of Commercial Axicabtagene Ciloleucel and Tisagenlecleucel for Relapsed/Refractory Aggressive B Cell Lymphomas. Riedell PA, Hwang WT, Nastoupil LJ, Pennisi M, McGuirk JP, Maziarz RT, Bachanova V, Oluwole OO, Brower J, Flores OA, Ahmed N, Schachter	Wrong study design

L, Bharucha K, Dholaria BR, Schuster SJ, Perales MA, Bishop MR, Porter DL. Transplant Cell Ther. 2022 Oct; 28(10): 669-676	
Impact of CD19 CAR T-cell product type on outcomes in relapsed or refractory aggressive B-NHL. Gauthier J, Gazeau N, Hirayama AV, Hill JA, Wu V, Cearley A, Perkins P, Kirk A, Shadman M, Chow VA, Gopal AK, Hodges Dwinal A, Williamson S, Myers J, Chen A, Nagle S, Hayes-Lattin B, Schachter L, Maloney DG, Turtle CJ, Sorror ML, Maziarz RT. Blood. 2022 Jun 30;139(26):3722-3731. doi: 10.1182/blood.2021014497.	Wrong study design
Current Challenges in Providing Good Leukapheresis Products for Manufacturing of CAR-T Cells for Patients with Relapsed/Refractory NHL or ALL. Cells. Korell F, Laier S, Sauer S, Veelken K, Hennemann H, Schubert ML, Sauer T, Pavel P, Mueller-Tidow C, Dreger P, Schmitt M, Schmitt A. 2020 May 15;9(5):1225. doi: 10.3390/cells9051225. PMID: 32429189; PMCID: PMC7290830.	Wrong study design
Single-center experience with axicabtagene-ciloleucel (axi-cel) and tisagenlecleucel (tisa-cel) for relapsed/refractory diffuse large B-cell lymphoma: comparable response rates and manageable toxicity. Veit Buecklein, Viktoria Blumenberg, Josephine Ackermann, Christian Schmidt, Kai Rejeski, Niklas Mueller, Anna Reischer, Louisa von Baumgarten, Florian Schoeberl, Andreas Humpe, Michael von Bergwelt, Marion Subklewe. Blood, 136, 34-35.	Wrong study design
CAR T-Cells for the Treatment of Refractory or Relapsed Large B-Cell Lymphoma: A Single-Center Retrospective Canadian Study. Benoit A, B Boies MH, Déry N, M Garcia L, Simard M, Poirier M, Delage R, Lortal Canguilhem B, Doyle C, Larouche JF, Couture F, Lemieux C. Clin Lymphoma Myeloma Leuk. 2023;23(3):203-210. doi:10.1016/j.clml.2022.12.015	Wrong study design
Axicabtagene ciloleucel compared to tisagenlecleucel for the treatment of aggressive B-cell lymphoma. Kwon M, Iacoboni G, Reguera JL, Corral LL, Morales RH, Ortiz-Maldonado V, Guerreiro M, Caballero AC, Domínguez MLG, Pina JMS, Mussetti A, Sancho JM, Bastos-Oreiro M, Catala E, Delgado J, Henriquez HL, Sanz J, Calbacho M, Bailén R, Carpio C, Ribera JM, Sureda A, Briones J, Hernandez-Boluda JC, Cebrián NM, Martin JLD, Martín A, Barba P. Haematologica. 2023;108(1):110-121. Published 2023 Jan 1. doi:10.3324/haematol.2022.280805	Wrong comparator
Safety and efficacy of tisagenlecleucel plus pembrolizumab in patients with r/r DLBCL: phase 1b PORTIA study results. Jaeger U, Worel N, McGuirk JP, Riedell PA, Fleury I, Du Y, Han X, Pearson D, Redondo S, Waller EK. Blood Adv. 2023 Jun 13;7(11):2283-2286. doi: 10.1182/bloodadvances.2022007779.	Wrong comparator
Multicenter phase II study of bendamustine plus rituximab in patients with relapsed or refractory diffuse large B-cell lymphoma. Ohmachi K, Niitsu N, Uchida T, Kim SJ, Ando K, Takahashi N, Takahashi N, Uike N, Eom HS, Chae YS, Terauchi T, Tateishi U, Tatsumi M, Kim WS, Tobinai K, Suh C, Ogura M. American Society of	Wrong population

Clinical Oncology. J Clin Oncol. 2013 Jun 10;31(17):2103-9. doi: 10.1200/JCO.2012.46.5203.	
GEMOX-R regimen is a highly effective salvage regimen in patients with refractory/relapsing diffuse large-cell lymphoma: A phase II study. López A, Gutiérrez A, Palacios A, Blancas I, Navarrete M, Morey M, Perelló A, Alarcón J, Martínez J, Rodríguez J. Eur J Haematol. 2008 Feb;80(2):127-32. doi: 10.1111/j.1600-0609.2007.00996.x."	Wrong population
Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy. El Gnaoui T, Dupuis J, Belhadj K, Jais JP, Rahmouni A, Copie-Bergman C, Gaillard I, Diviné M, Tabah-Fisch I, Reyes F, Haioun C. Ann Oncol. 2007 Aug;18(8):1363-8. doi: 10.1093/annonc/mdm133. Epub 2007 May 11. PMID: 17496309.	Wrong population
Randomized phase 2 trial of polatuzumab vedotin (pola) with bendamustine and rituximab (BR)in relapsed/refractory (r/r) FL and DLBCL. Laurie Helen Sehn, Manali Kamdar, Alex Francisco Herrera, Andrew McMillan, Christopher Flowers, Won Seog Kim, Tae Min Kim, Muhit Özcan, Judit Demeter, Mark Hertzberg, Marek Trněný, Gilles A. Salles, Andrew Davies, Jamie H. Hirata, Ji Cheng, Grace Ku, and Matthew J. Matasar. DOI: 10.1200/JCO.2018.36.15_suppl.7507, Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018), 7507-7507	Wrong population
Bendamustine plus rituximab in Japanese patients with relapsed or refractory diffuse large B-cell lymphoma. Murayama K, Kiguchi T, Izutsu K, Kameoka Y, Hidaka M, Kato H, Rai S, Kuroda J, Ishizawa K, Ichikawa S, Ando K, Ogura M, Fukushima K, Terui Y. Ann Hematol 101, 979–989 (2022). https://doi.org/10.1007/s00277-022-04801-2	Wrong population
Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, Link BK, Hay A, Cerhan JR, Zhu L, Boussetta S, Feng L, Maurer MJ, Navale L, Wiezorek J, Go WY, Gisselbrecht C. Blood. 2017 Oct 19;130(16):1800-1808. doi: 10.1182/blood-2017-03-769620. Epub 2017 Aug 3. Erratum in: Blood. 2018 Feb 1;131(5):587-588. PMID: 28774879; PMCID: PMC5649550.	Wrong population
Rituximab plus gemcitabine and oxaliplatin (R-GemOx) in refractory/relapsed diffuse large B-cell lymphoma: a real-life study in patients ineligible for autologous stem-cell transplantation. Cazelles C., Belhadj K., Vellemans H., Camus V., Poullot E., Gaulard P., Veresezan L., Itti E., Becker S., Carvalho M., Dupuis J., Le Bras F., Lemonnier F., Roulin L., El Gnaoui T., Jardin F., Mounier N., Tilly H., Haioun C. Leuk Lymphoma. 2021 Sep;62(9):2161-2168. doi: 10.1080/10428194.2021.1901090.	Wrong population
Bendamustine plus rituximab for relapsed or refractory diffuse large B cell lymphoma: a retrospective analysis. Merchionne F., Quintana G., Gaudio F., Minoia C., Specchia G., Guarini A., Quarta G., Pavone	Wrong population

V., Melpignano A. Leuk Res . 2014 Dec;38(12):1446-50. doi: 10.1016/j.leukres.2014.10.001. Epub 2014 Oct 22.	
Bendamustine with or without rituximab for the treatment of heavily pretreated non-Hodgkin's lymphoma patients : A multicenter retrospective study on behalf of the Italian Lymphoma Foundation (FIL). Rigacci L., Puccini B., Cortelazzo S., Gaidano G., Piccin A., D'Arco A., Freilone R., Storti S., Orciuolo E., Zinzani P.L., Zaja F., Bongarzoni V., Balzarotti M., Rota-Scalabrini D., Patti C., Gobbi M., Carpaneto A., Liberati A.M., Bosi A., Iannitto E. Ann Hematol . 2012 Jul;91(7):1013-22. doi: 10.1007/s00277-012-1422-5.	Wrong population
Comparative Effectiveness of Bendamustine Plus Rituximab (BR) and Rituximab Plus Gemcitabine and Oxaliplatin (R-GemOx) in Relapsed/Refractory Diffuse Large B-Cell Lymphoma. Castro F., Surinach A., Launonen A., Thuresson P.-O., Felizzi F. Blood (2020) 136 (Supplement 1): 41. doi.org/10.1182/blood-2020-137529	Wrong population
Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. Crump M, Kuruvilla J, Couban S, MacDonald DA, Kukreti V, Kouroukis CT, Rubinger M, Buckstein R, Imrie KR, Federico M, Di Renzo N, Howson-Jan K, Baetz T, Kaizer L, Voralia M, Olney HJ, Turner AR, Sussman J, Hay AE, Djurfeldt MS, Meyer RM, Chen BE, Shepherd LE. J Clin Oncol. 2014 Nov 1;32(31):3490-6. doi: 10.1200/JCO.2013.53.9593. Epub 2014 Sep 29. PMID: 25267740.	Wrong population
Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. Gisselbrecht C, Schmitz N, Mounier N, Singh Gill D, Linch DC, Trneny M, Bosly A, Milpied NJ, Radford J, Ketterer N, Shpilberg O, Dührsen U, Hagberg H, Ma DD, Viardot A, Lowenthal R, Brière J, Salles G, Moskowitz CH, Glass B. J Clin Oncol. 2012 Dec 20;30(36):4462-9. doi: 10.1200/JCO.2012.41.9416. Epub 2012 Oct 22. PMID: 23091101; PMCID: PMC3646314.	Wrong population

H.1.4 Quality assessment

The quality assessment of non-RCTs and single-arm studies were performed using the Cochrane Risk of Bias in Non-Randomized Studies – of Interventions (ROBINS-I) tool(115) presented in Table 100.

Table 100 ROBINS-I checklist for nRCTs

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study?	Y / PY / PN / N	N	PN	PN
	If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	Y / PY / PN / N	PY	PY	PY
	If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding:				
	1.2. Was the analysis based on splitting participants' follow up time according to intervention received?	N/A / Y / PY / PN / N / NI	N	NA	NA
	If N/PN, answer questions relating to baseline confounding (1.4 to 1.6)	N/A / Y / PY / PN / N / NI			
	If Y/PY, proceed to question 1.3.	N/A / Y / PY / PN / N / NI			
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome?	N/A / Y / PY / PN / N / NI	NA	NI	NI
	If N/PN, answer questions relating to baseline confounding (1.4 to 1.6)	N/A / Y / PY / PN / N / NI			

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
	If Y/PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	N/A / Y / PY / PN / N / NI			
	Questions relating to baseline confounding only				
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	N/A / Y / PY / PN / N / NI	Y	NA	NA
	1.5. If Y/PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	N/A / Y / PY / PN / N / NI	Y	NA	NA
	1.6. Did the authors control for any post-intervention variables that could have been affected by the intervention?	N/A / Y / PY / PN / N / NI	Y	NA	NA
	Questions relating to baseline and time-varying confounding				
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding domains and for time-varying confounding?	N/A / Y / PY / PN / N / NI	Y	NA	NA
	1.8. If Y/PY to 1.7: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	N/A / Y / PY / PN / N / NI			
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	NI	Low
	Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable	Favours experimental	Unpredictable	Unpredictable

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	Y / PY / PN / N / NI	N	N	N
	If N/PN to 2.1: go to 2.4	Y / PY / PN / N / NI			
	2.2. If Y/PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention?	N/A / Y / PY / PN / N / NI	NA		
	2.3 If Y/PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	N/A / Y / PY / PN / N / NI	NA		
	2.4. Do start of follow-up and start of intervention coincide for most participants?	Y / PY / PN / N / NI	Y	NI	Y
	2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	N/A / Y / PY / PN / N / NI	Y	NA	Y
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	Moderate	Moderate
	Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours	Unpredictable	Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	Y / PY / PN / N / NI	Y	Y	Y
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y / PY / PN / N / NI	Y	PY	Y

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Y / PY / PN / N / NI	Y	PN	Y
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	Low	Low
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Favours	Unpredictable	Unredictable
Bias due to deviations from intended interventions	If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2				
	4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Y / PY / PN / N / NI	N	N	N
	4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	N/A / Y / PY / PN / N / NI	NA	NA	NA
	If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6				
	4.3. Were important co-interventions balanced across intervention groups?	Y / PY / PN / N / NI	N	NA	N
	4.4. Was the intervention implemented successfully for most participants?	Y / PY / PN / N / NI	PY	NA	PY
	4.5. Did study participants adhere to the assigned intervention regimen?	Y / PY / PN / N / NI	Y	NA	Y

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
	4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	N/A / Y / PY / PN / N / NI	N	NA	N
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	NI	NI	NI
	Optional: What is the predicted direction of bias due to deviations from the intended interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable	Unpredictable	Unpredictable	Unpredictable
Bias due to missing data	5.1 Were outcome data available for all, or nearly all, participants?	Y / PY / PN / N / NI	Y	Y	Y
	5.2 Were participants excluded due to missing data on intervention status?	Y / PY / PN / N / NI	N	N	N
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y / PY / PN / N / NI	N	N	N
	5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	N/A / Y / PY / PN / N / NI		NA	NA
	5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	N/A / Y / PY / PN / N / NI		NA	NA
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	Low	Low
	Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards null /Away	Unpredictable	Unpredictable	Unpredictable

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Y / PY / PN / N / NI	Y	NI	Y
	6.2 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	Y	PY	Y
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Y / PY / PN / N / NI	NI	NI	NI
	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	Y / PY / PN / N / NI	NI	NI	NI
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Moderate	NI	NI
	Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental / Favours comparator / Towards null /Away	Unpredictable	Unpredictable	Unpredictable
Bias in selection of the reported result	Is the reported effect estimate likely to be selected, on the basis of the results, from...				
	7.1. ... multiple outcome *measurements* within the outcome domain?	Y / PY / PN / N / NI	Y	PY	Y
	7.2 ... multiple *analyses* of the intervention-outcome relationship?	Y / PY / PN / N / NI	Y	PY	Y
	7.3 ... different *subgroups*?	Y / PY / PN / N / NI	Y	PY	Y

ROBINS-I checklist for nRCTs					
Bias domain	**Signalling questions**	**Response options**	**ZUMA-1**	**CORAL 1**	**CORAL 2**
	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	Low	Low
	Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away	Favours	Unpredictable	Unpredictable
Overall bias	Risk of bias judgement	Low / Moderate / Serious / Critical / NI	Low	Moderate	Moderate
	Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null /Away	Favours	Unpredictable	Unpredictable

Abbreviations: N = no, N/A= not available, NI = no information, PN = partially no, PY = partially yes, Y = yes.

H.1.5 Unpublished data

N/A

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

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

The HRQoL SLR was conducted together with the clinical SLR described in Appendix H as part of the outcomes in the PICO criteria. The same methods and search strategies apply.

2 HRQoL studies were identified in the SLR for this patient population, both of which were included in the health technology assessment.

I.1.1 Search strategies

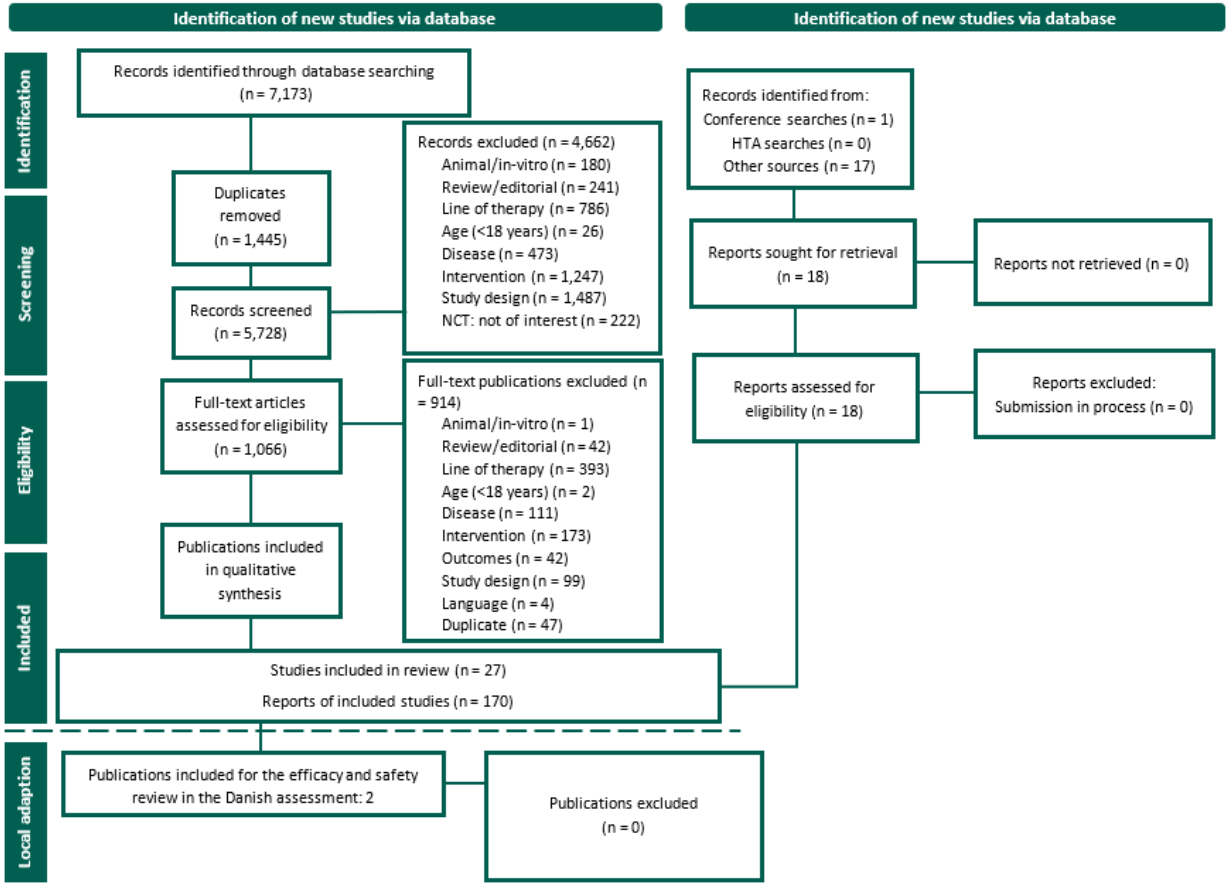
The search strategies for health-related quality-of-life follow the methods described in Appendix H.

The selection process is described in appendix H.1.2 meaning that the same eligibility criteria apply here as those described in Table 97.

From the searches a total of 7,173 potentially relevant titles or abstracts were identified from the literature databases. Following the removal of duplicates 5,728 records were screened based on the information reported in their titles and/or abstracts. Following the primary screening, a total of 1,066 citations were included and all these were assessed in full for further evaluation. Of these, 914 were excluded due to the following reasons: animal/in vitro (n = 1), review/editorial (n = 42), line of therapy (n = 393), age (<18 years) (n = 2), disease (n = 111), intervention (n = 173), outcomes (n = 42), study design (n = 99), language (n = 4) and duplicate (n = 47). In addition, 18 publications were identified from the bibliographic/conference/registry searches.

Therefore, meeting the predefined inclusion criteria provided in Table 97, a total of 170 records were included in the review. As some studies were associated with multiple publications, secondary publications were linked to the primary publication and all the relevant data were extracted in a single row. Therefore, a total of 27 studies of the 170 publications were extracted. Among the 27 included studies, two studies reported HRQoL data.

I.1.2 PRISMA diagram of systematic selection of studies for health-related quality of life



I.1.3 Quality assessment

A quality assessment for health-related quality-of-life was not undertaken.

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

An SLR for inputs into the health economic model was not performed for the submission.

Appendix K. Cost components for axi-cel and comparator arm

As requested, Figure 47 below provides graphical description, e.g. a separate flow chart for the intervention and comparator, depicting the different treatment components you have included in the HE-model along with relevant assumptions regarding the different components.

Figure 47: Chart for treatment components - axi-cel and comparator arm

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