Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende axicabtagene ciloleucel til andenlinjebehandling af patienter med DLBCL

Patienter, der recidiverer inden for 12 måneder efter gennemførsel af, eller er refraktær til, førstelinje kemo-immunterapi

Vers. 1.0

Bilagsoversigt

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

August 28th, 2023

Gilead response to *Medicinrådets anbefaling vedr. axicabtagene ciloleucel til andenlinje-behandling af patienter med DLBCL*

We in Gilead acknowledge the substantial work that has clearly been put into making the assessment report. We appreciate the proactivity shown from the secretariat and the expert committee's' side regarding including the newest data from ZUMA-7 in the assessment. This means that the report is based on solid evidence from a large phase 3 trial with extensive follow-up time (median 47,2 months). We would like to clarify and address four points made in the assessment report.

Point 1: ZUMA-7 is designed to provide a direct comparison of axi-cel as second line treatment for patients who are primary refractory or have failed first line chemo-immunotherapy versus salvage chemotherapy and HDT-ASCT

Medicinrådet notes on page 5 and 77 that there are no [OS] data from ZUMA-7 specifically for the subgroup of patients who achieve a response to induction therapy and undergo HDT with stem cell support. Furthermore, Medicinrådet states for this subgroup, it is therefore uncertain whether axicabtagene ciloleucel (axi-cel) is a more effective treatment than SoC.

We firmly emphasize that ZUMA-7 was designed to provide a direct comparison of axi-cel versus salvage chemotherapy and HDT-ASCT. To our knowledge, there is no evidence available determining which patients will have a response to salvage chemotherapy before initiating the treatment. Given that it is not known ex ante which patients will have a response to salvage chemoimmunotherapy, and because the majority of patients do not reach definitive therapy with HDT-ASCT, ZUMA-7 randomly assigned subjects who intended to proceed to either CAR T-cell therapy or second-line SOCT before the receipt of salvage chemoimmunotherapy by design.

The comparison of all subjects randomized to the axi-cel arm to the subgroup of subjects randomized to the SOCT arm and underwent HDT-ASCT is not a valid analysis and violates the principle of intention-to-treat analyses. The subjects in the SOCT arm who underwent HDT-ASCT represent the minority of subjects who responded to salvage chemotherapy and proceeded to HDT-ASCT (36% of the full analysis set), thus representing those with the best outcomes. However, at the time of randomization, it is not known who will respond to salvage chemotherapy, and therefore there is bias in selecting this subset of subjects randomized to the SOCT arm in comparison to all subjects in the axi-cel arm.

Moreover, the relevant positioning for axi-cel in Danish clinical practice is after the failure of first-line treatment. The EMA market authorisation indication states that axi-cel is indicated for the treatment of adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy. The subgroup that DMC refers to, i.e., patients who are not responding to salvage chemo would be treated in the 3L setting. Yescarta is also indicated for treatment in this setting supported by the ZUMA-1 data but is currently not recommended for usage in Denmark.

Point 2: Number patients eligible for axi-cel in second-line DLBCL

Medicinrådet estimates on page 67/77, that 30 patients would receive axi-cel in second-line treatment of DLBCL in Denmark if it is recommended. Gilead believes that this is a gross overestimation. Gilead has provided data on the eligible number of patients in the HTA submission that is based on the Danish Lymphoma registry (LYFO) and Danish clinical expert. Based on these data, there are 35 patients with r/r DLBCL who relapse ≤12 months. Out of these 35 patients, the Danish expert estimated that 10 patients start treatment with R-ICE DHAP GDP, while 5 patients finally receive a stem cell infusion. Our estimate of the number of patients who are intended for ASCT are thefore 10 patients per year resulting in a budget impact substantially lower than what is presented in the assessment report.

Point 3: Yescarta manufacturing excellence and turnaround times

Medicinrådet questions on page 21/22 our ability to produce and deliver axi-cel in clinical practice. We understand the concern given the fact that fast and reliable deliveries of CAR-T are of the utmost importance given the fast-progressing nature of the disease.

[redacted]

Point 4: Axi-cel is a unique CAR T-cell therapy with demonstrated higher efficacy than tisa-cel

Medicinrådet comments on page 34/77 on the discrepancies between results originating from the ZUMA-7 study and the BELINDA study and find the EFS outcomes remarkable since these two studies have comparable SOC and treatment arms. There are three similar CAR-T trials with somewhat comparable populations in 2L DLBCL. While these clinical trials target similar populations there are several differences between them that provide plausible explanations to why the outcomes in these studies vary. This is summarized in a clear manner by Bommier et al.[7]. In short, the CAR-Ts used are each unique in their design and the trials apply different designs. Two of the studies, ZUMA-7 (axi-cel) and Transform (liso-cel) met their primary endpoint while Belinda (tisa-cel) did not meet the primary endpoint. The authors conclude the methodological issues partly explain the discrepancy in the results of the three trials and taken together with the uniqueness of each CAR T-cell product and differences in manufacturing time it is not particularly remarkable that the trials show different results. Lastly, axi-cel has shown significantly improved overall survival versus tisa-cel in patients with R/R DLBCL in the real-world setting[8].

[redacted]

7 Bommier et al. Hematological Oncology. 2022;40:1090–1093
8 Bachy E. et al. A real-world comparison of tisagenlecleucel and axicabtagene ciloleucel CAR T cells in relapsed or refractory diffuse large B cell lymphoma. Nat Med. 2022 Oct;28(10):2145-2154. doi: 10.1038/s41591-022-01969-y. Epub 2022

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04.09.2023

MGK/DBS

Forhandlingsnotat

Dato for behandling i Medicinrådet	27.09.2023
Leverandør	Gilead
Lægemiddel	Yescarta (axicabtagene ciloleucel)
Ansøgt indikation	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.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel (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)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Yescarta	1 behandling	2.440.000	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

[redacted]

Informationer fra forhandlingen

[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

[redacted]

[redacted]

Medicinrådet vurderede i september 2022 Minjuvi (tafasitamab) kombination med lenalidomid til behandling af voksne patienter med kræfttypen recidiverende eller refraktær diffust storcellet B-celle lymfom, som ikke kan tåle autolog stamcelletransplantation. Medicinrådet anbefalede ikke Minjuvi.
[redacted]

Status fra andre lande

Tabel 2: Status fra andre lande

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

Konklusion

[redacted]

Application for the assessment of axicabtagene ciloleucel (Yescarta®) for adult patients with diffuse large B-cell lymphoma and high-grade B-cell lymphoma who are refractory or have relapsed within 12 months from completion of first-line therapy

Text marked with yellow is strictly confidential and should be deleted before publication

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Colour of highlighted text	**Definition of highlighted text**
	Confidential information

1. Basic information

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Overview of the pharmaceutical	
Proprietary name	Yescarta®
Generic name	Axicabtagene ciloleucel (axi-cel)
Marketing authorisation holder in Denmark	Kite Pharma EU B.V.
ATC code	L01XX70
Pharmacotherapeutic group	Other antineoplastic agents (1)
Active substance(s)	The active substance is axicabtagene ciloleucel (1).
Pharmaceutical form(s)	Dispersion for infusion. A clear to opaque, white to red dispersion (1)
Mechanism of action	Axi-cel is a CD19-directed genetically modified autologous T-cell immunotherapy product that binds to CD19-expressing cancer cells and normal B cells. Following anti-CD19 chimeric antigen receptor (CAR) T-cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells (1).
Dosage regimen	Axi-cel is intended for autologous use only. A single dose of axi-cel contains 2 x 10^6 CAR-positive viable T cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag (1).

Overview of the pharmaceutical	
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Axi-cel is expected to be indicated for adult patients with diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBCL) who have refractory disease or have relapsed within 12 months from completion of first-line (1L) chemoimmunotherapy (2).
Other approved therapeutic indications	Axi-cel is indicated for the treatment of adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy (1). In June 2022, axi-cel also obtained market authorisation for the treatment of adult patients with relapsed or refractory follicular lymphoma (FL) after three or more lines of systemic therapy.
Will dispensing be restricted to hospitals?	Yes
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).
Packaging – types, sizes/number of units, and concentrations	Yescarta® comes in packages of 1 vial per package.
Orphan drug designation	Axi-cel was designated as an orphan medicinal product (EU/3/14/1393) on 16 December 2014 in the following condition: DLBCL and HGBCL.

2. Abbreviations

aaIPI	Age-adjusted International Prognostic Index
AIC	Akaike information criterion
ASCT	Autologous stem cell transplant
Axi-cel	Axicabtagene ciloleucel
BEAM	Carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criteria
BSA	Body surface area
CAR	Chimeric antigen receptor
CEAC	Cost-effectiveness acceptability curve
CHMP	Committee for Medicinal Products for Human Use
CHOP	Cyclophosphamide, doxorubicin, vincristine and prednisone

CI	Confidence interval
CMH	Cochran-Mantel-Haenszel
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete remission
CRS	Cytokine release syndrome
CU	Cost-utility
DLG	Danish Lymphoma Group
DMC	Danish Medicines Council
DMCG	Danish Multidisciplinary Cancer Groups
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSA	Deterministic sensitivity analysis
EBMT	European Society for Blood and Marrow Transplantation
EFS	Event-free survival
EQ-5D-5L VAS	EuroQol five-dimensional five-level visual analogue scale
FAS	Full analysis set
FL	Follicular lymphoma
G-CSF	Granulocyte colony-stimulating factor
HDT	High-dose therapy
HGBCL	High-grade B-cell lymphoma
HM	Haematological malignancies
HR	Hazard ratio
HRQoL	Health related quality of life
HSUV	Health state utility value
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPCW	Inverse probability of censoring weights
IPI	International prognostic index
MCM	Mixture cure model
MMRM	Mixed effects models for repeated measure
NCCN	National Comprehensive Cancer Network
NHL	Non-Hodgkin's lymphoma
Non-GCB	Non-germinal center B-cell
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Per oral
PPP	Pharmacy purchasing price
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life years
RPSFT	Rank preserving structural failure time
R-CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone
R-DHAP	Rituximab, cisplatin, cytarabine and dexamethasone

R-GDP	Rituximab, gemcitabine, dexamethasone and cisplatin
R-GemOx	Rituximab, gemcitabine, oxaliplatin
R-IVE	Rituximab, ifosfamide, epirubicin and etoposide
RKKP	Regions' Clinical Quality Development Programme
R-ICE	Rituximab, ifosfamide, carboplatin, and etoposide
r/r	Refractory or relapse
RR	Relative risk
2L	Second-line
SAE	Serious adverse event
SC	Subcutaneous
SCT	Stem cell transplantation
SD	Stable disease
SoC	Standard of care
SPC	Summary of product characteristics
SMR	Standardised mortality ratio
3L	Third-line
TBI	Total body irradiation
TEAE	Treatment-emergent AEs
TSD	Technical Support Document
TTNT	Time to next therapy
US	United States
QoL	Quality of life
WHO	World Health Organisation
WTP	Willingness-to-pay

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4. Summary

Axicabtagene ciloleucel (axi-cel), sold under the brand name Yescarta®, is a CD19-directed genetically modified autologous T-cell immunotherapy product that binds to CD19-expressing cancer cells and normal B cells. Axi-cel is approved in the United States (US) and Europe for adult patients with relapsed or refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL) after two or more lines of systemic therapy (third-line) (3).

DLBCL is an aggressive and rare subtype of non-Hodgkin's lymphoma (NHL) (4), and CAR T-cell therapies are new innovative treatment options for patients with DLBCL. Axi-cel belongs to this new breakthrough class of CAR T-cell therapies and is already an important treatment option in DLBCL in the 3L setting in other Nordic countries and worldwide. The European Society for Blood and Marrow Transplantation (EBMT) recommends anti-CD19 CAR T therapy for patients with high-risk r/r DLBCL and unknown chemosensitivity, with these options replacing autologous stem cell transplantation (ASCT) as the standard of care in 2L treatment (5).

DLBCL progresses rapidly and has an expected survival of less than one year if untreated (6). Despite an improvement in survival outcomes since the introduction of rituximab, a third of DLBCL patients either fail to achieve remission with 1L or relapse after 1L chemo-immunotherapy and survival outcomes are particularly poor in these patients (7–10). The three-year Event Free Survival (EFS) of patients with early relapse (≤12 months) is less than half of the three-year EFS recorded in patients relapsing after 12 months (20% versus 45%, respectively). Similarly, a reduced three-year overall survival (OS) rate is seen in early relapse patients compared to those with later relapse (39% versus 64%) (11). Current Danish first-line (1L) treatment of DLBCL is the chemotherapeutic regimen cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP) (12). Although R-CHOP has improved outcomes for patients with DLBCL overall, some patients still experience disease progression, and approximately 35% of patients are refractory or experience relapse (r/r) after 1L (7,12). Standard second-line (2L) therapy for chemotherapy-sensitive r/r DLBCL patients <65 years without considerable comorbidities involves high-dose therapy (HDT) + ASCT. R-DHAP (rituximab, cisplatin, cytarabine and dexamethasone) and R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) are frequently applied salvage chemotherapy regimens in Denmark in 2L. These regimens aim at inducing complete or partial response (12). However, patients receiving 2L curative chemotherapy and ASCT incur substantial costs, and around 80% of these transplant-intended 2L r/r DLBCL patients do not achieve long-term remission with currently available treatment options (7). In addition, only around 50% of transplant-intended patients actually receive ASCT (7).

In 2L DLBCL, the efficacy and safety of axi-cel have been demonstrated in the ZUMA-7 trial, which is a phase III, randomised, open-label, multicentre study. The trial included adult patients with r/r LBCL after 1L rituximab and anthracycline-based chemotherapy who were randomised 1:1 to axi-cel and standard of care (SoC). Thus, ZUMA-7 comprises a head-to-head comparison of axi-cel and SoC, which was used to demonstrate the value of axi-cel in the current application to the Danish Medicines Council (DMC). The head-to-head comparison included results on event-free survival (EFS); overall survival (OS); objective response rate (ORR); progression-free survival (PFS); time to next therapy (TTNT); duration of response (DOR); and EuroQol five-dimensional five-level visual analogue scale (EQ-5D-5L VAS).

The head-to-head comparison of axi-cel and SoC showed that axi-cel reduced the risk of an EFS event significantly compared to SoC by reducing the hazard for experiencing an event by 60% (hazard ratio (HR): 0.40). Axi-cel also demonstrated improvements in the interim analysis of OS and PFS was longer for axi-cel compared with SoC. DOR in the axi-cel group was numerically longer than in the SoC group and axi-cel demonstrated a significantly higher ORR compared with SoC. Axi-cel also demonstrated an acceptable safety profile with a relative risk (RR) for experiencing at least one serious adverse event (SAE) compared to SoC of 1.1 (95% CI: 0.9, 1.4) and a RR for experiencing at least one

Grade 3 or higher SAE compared to SoC of 1.1 (95% CI: 0.8, 1.4). A higher proportion of patients developed CRS in the axi-cel group compared to the SoC group (92% compared to 6%); however, none of the events were fatal.

The health economic analysis presented in the current application was a cost-utility (CU) analysis that estimated the incremental cost and quality-adjusted life years (QALY) associated with axi-cel treatment compared to SoC. The CU analysis was informed by a partitioned survival model with three health states: event-free, post-event and death. The CU analysis had a limited societal perspective in accordance with DMC guidelines and considered all relevant hospital-related costs, costs covered by public health services, treatment-related costs, municipal costs and costs related to patient time and transport costs. An incremental cost-effectiveness ratio (ICER) of DKK 501,397 was estimated in the CU analysis base case. Various deterministic sensitivity analyses (DSA) were conducted as well as a probabilistic sensitivity analysis (PSA) to assess the uncertainty in the base case result. The DSA showed that the base case ICER is most sensitive to changes in the pharmacy purchasing price (PPP) of axi-cel and the HR for SoC OS to axi-cel OS. Reducing the time horizon from 50 years to five years also showed a large impact on the base case ICER. In the cost-effectiveness plane from the PSA, 100% of the alternative ICERs were in the Northeast quadrant of the graph, where axi-cel is more effective and costly compared to the current SoC in Denmark. At a willingness-to-pay threshold of DKK 500,000, axi-cel is cost-effective in 47% of the PSA simulations. If the willingness-to-pay threshold is DKK 1,000,000, axi-cel is cost-effective in 100% of the PSA simulations.

The health economic analysis also included a budget impact analysis. The budget impact analysis estimated the budgetary implication of recommending axi-cel as standard treatment of r/r DLBCL ≤12 months in Denmark over five years. The budget impact analysis estimated that the budgetary impact will be DKK 19.8 million in year 5 and DKK 82.9 million over all five years if axi-cel is recommended in Denmark.

New effective therapies are needed in Denmark to address the high medical unmet need in DLBCL patients who are r/r ≤12 months after first-line chemoimmunotherapy. Axi-cel is already an important treatment option in DLBCL in the 3L setting in other Nordic countries and has been approved in the US for 2L DLBCL. In addition, axi-cel is the first CAR T treatment to present five-year follow-up data showing durable long-term survival (13). With the ZUMA-7 study, axi-cel has shown superiority when compared with the current SoC in 2L, bringing patients the hope of a cure in an even earlier setting. In Denmark, CAR T treatments are currently not available for lymphoma patients in 3L, underscoring the high unmet need for a curative alternative, especially for patients who are r/r <12 months after first-line therapy.

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

5.1 Diffuse large B-cell lymphoma

DLBCL is an aggressive and rare subtype of NHL. NHL is a malignancy of the lymphatic system and comprises a group of more than 90 cancers (4). These cancers primarily originate in B cells but can also originate from T cells and natural killer cells. The B cells (also called B lymphocytes) develop and mature in the bone marrow and lymph nodes (14). In DLBCL, the abnormal B-cell lymphocytes are larger than normal and have stopped responding to the signals that usually limit the growth and reproduction of cells (14). Different variants of the disease can be identified by performing advanced tests on the lymph node specimen. The centroblastic, immunoblastic and anaplastic variants are most common (15).

NHL can be broadly divided into two prognostic groups: indolent lymphomas and aggressive lymphomas (16). Aggressive NHLs, such as DLBCL, progress more rapidly and have an expected survival of less than one year if untreated (6). However, DLBCL may be cured with intensive combination chemotherapy regimens (16), ASCT (17) or with CAR T-cell therapies (18).

Until recently, the DLBCL subtype HGBCL was subsumed under DLBCL. In the updated 2016 revision of the World Health Organisation (WHO) classification of lymphoid neoplasms, HGBCL was classified as a separate entity rather than being classified under DLBCL (19). HGBCL comprises two types of lymphomas: HGBCL with MYC and BCL2 and/or BCL6 rearrangements and HGBCL, not otherwise specified (20). The pivotal phase III study for axi-cel in the present indication, the ZUMA-7 trial, included patients with histologically proven large B-cell lymphoma, as defined by WHO in 2016, including DLBCL and HGBCL with or without MYC and BCL2 and/or BCL6 rearrangement (21). Given that HGBCL was subsumed under DLBCL until recently, all DLBCL studies published prior to the 2016 change in classification of lymphoid neoplasms are presumed to cover HGBCL as well.

5.1.1 Clinical presentation of DLBCL

DLBCL manifests as a rapidly enlarging painless mass at a nodal or, in about 40% of cases, an extra-nodal site anywhere in the body (14,22). The most common site of extra-nodal involvement is the stomach or gastrointestinal tract, but the disease can arise in any organ (14). About one third of patients with DLBCL present with so-called ‘B symptoms’, which include fevers, night sweats, and unexplained weight loss (4), and some patients present with symptoms related to organ involvement (15). Additional common signs and symptoms which are similar to other less serious diseases include fatigue, coughing, itchy skin and loss of appetite (23).

5.1.2 DLBCL epidemiology

DLBCL most often appears in middle-aged or older adults and is most frequently diagnosed in people with a median age of 55-74 years (24–27). However, DLBCL can also occur in young adults and children. In Denmark, the Danish Lymphoma Group (DLG) reported a median age of DLBCL at diagnosis of 67 years in 2015, and a Danish population-based study from 2017 reported a median age of 65 in newly diagnosed DLBCL patients (28,29). Around 60% are not diagnosed with DLBCL until the disease is advanced, usually stage III or IV. In the remaining 40%, the disease is diagnosed at a localised stage (14). DLBCL is more common in men than in women (a male/female ratio of 1.20 was reported in the Danish population-based study from 2017 (29)), and more common among individuals of Hispanic or Caucasian descent (25,27).

DLBCL is the most prevalent subtype of NHL in Western countries (15,30). The prevalence of DLBCL in the EU4 (European Union 4: France, Germany, Italy, Spain) and the UK ranges from 30% to 58% of NHL cases (31), of which there were 364,500 in 2019 (32). These estimates suggest 211,410 prevalent DLBCL cases in any line of therapy (7–9,33,34). In 2018, the Danish prevalence of NHL was approximately 13,660 (35). Around 40% of NHL patients have DLBCL, resulting in a Danish prevalence of DLBCL of around 5,464 patients (36). According to the DLG, the incidence of DLBCL is 450 patients per year and the incidence has been increasing (37). Approximately one third of DLBCL patients either fail to achieve remission with 1L treatments or relapse after achieving complete remission (CR). In a Danish study using data from the Danish Lymphoma Registry (LYFO), it was found that of all DLBCL patients who received 1L treatment (n=5,412), 12.7% (n=688) were primary refractory and 15.1% (n=816) relapsed. Overall, 23.6% (n=1,276) of DLBCL patients who received 1L treatment were r/r (38). The incidence of r/r DLBCL <12 months after 1L therapy is estimated to be 1.57 per 100,000 based on 5,093 incident cases in 2019 in the EU4 and the UK (39,40). This number is based on a total EU4 and UK population of 323,975,800 in 2019 (39). HGBCL comprises around 10% of newly diagnosed DLBCL (41).

Clinical experts with extensive experience in DLBCL were consulted in the preparation of this application. The clinical experts estimated that around 20% (90 patients) of the 450 Danish DLBCL patients are refractory or experience relapse, and that around 35 patients would be refractory or have relapse within 12 months after completing 1L treatment. Moreover, the clinical experts estimated that 10 out of the 35 patients will be intended for stem cell transplantation in Denmark.

The clinical experts were also consulted in terms of the expected numbers of patients eligible for CAR T-cell therapy. The clinical experts expected that 9-10 of the incident transplant-intended patients would be eligible for CAR T-cell therapy. Table 1 presents the estimated number of transplant-intended patients being eligible for axi-cel treatment in the next five years. A gradual patient uptake is expected, as seen in Table 1, and does not take into account other future therapies within this indication. 0 patients were assumed in year 1, as it is expected, based on clinical experience, that the Danish clinics will need some time to implement axi-cel as standard of care. The patient uptake is based on the consultation with the Danish expert, who expected around 10 patients to be candidates to axi-cel. The gradual uptake is an assumption, as it is assumed, based on clinical experience, that the uptake of axi-cel will happen gradually over the first years if axi-cel has become standard of care. Furthermore, the patient access is assumed from beginning of year 2.

Table 1: Estimated number of patients eligible for treatment with axi-cel in 2L DLBCL

Year	Year 1	Year 2	Year 3	Year 4	Year 5
Number of r/r DLBCL (<12 months) transplant-intended patients in Denmark who are expected to use axi-cel in the coming years	0	4	7	9	9

Note: the patient numbers presented in the table does not consider the potential introduction of other therapies within this indication.

5.1.3 Patient populations relevant for this application

The patient population relevant for the current application is: adult patients with DLBCL and HGBCL who have refractory disease or have relapsed within 12 months from completion of 1L chemoimmunotherapy (2), and who are

intended for ASCT, as per the ZUMA-7 trial inclusion criteria. The characteristics of the patient population from ZUMA-7 are presented in Table 71 in the appendix C.

During the preparation of the current application, Danish clinical experts with vast experience in DLBCL were consulted on the characteristics of the Danish DLBCL patient population who were r/r <12 months from completing 1L therapy. The Danish clinical experts informed that the median age at relapse for all DLBCL patients in Denmark is 69 years. The median age of the total ZUMA-7 population, who all were refractory or had a relapse, was 59 years. Around 67% of those who relapse are ≥65 years in Denmark, which was 30% of the total population in the ZUMA-7 trial. The Danish study by Arboe et al. 2019 (38) presents data from LYFO and found that of all DLBCL patients who received 1L treatment, 12.7% were primary refractory and 15.1% relapsed (including both early and late relapse). Overall, 23.6% of DLBCL patients who received 1L treatment were r/r (38). According to the experts, most relapsed patients are men. In the ZUMA-7 trial, 66% of the total population were men and 74% of the total population had primary refractory disease after 1L therapy. They also informed that 97% of the Danish patient population have DLBCL as disease type compared to 69% of the total population from the ZUMA-7. The rest of the characteristics in Table 71 were similar between the Danish population and the trial population.

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

In Denmark, there is a clinical guideline for treating DLBCL which is published by the DLG (updated in 2021) in cooperation with the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Regions' Clinical Quality Development Programme (RKKP) (12). In the guideline, the choice of 1L treatment regimen is based on stage classification at diagnosis or relapse and the international prognostic index (IPI). Current 1L treatment of DLBCL is the chemotherapeutic regimen cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in combination with the anti-CD20 monoclonal antibody rituximab (R-CHOP) (12). Different R-CHOP regimens are applied depending on age and the presence of considerable comorbidities. Although R-CHOP has improved outcomes for patients with DLBCL overall, some patients still experience disease progression, and approximately 35% (i.e., one third) of patients are refractory or experience relapse after 1L (7,12).

Standard second-line (2L) therapy for chemotherapy-sensitive r/r DLBCL patients <65 years without considerable comorbidities involves HDT + ASCT. R-DHAP (rituximab, cisplatin, cytarabine and dexamethasone) and R-ICE (rituximab, ifosfamide, carboplatin, and etoposide) are frequently applied salvage chemotherapy regimens aimed at inducing complete or partial response (12). For patients with non-germinal center B-cell (non-GCB) DLBCL, no evidence exists demonstrating the superiority of R-DHAP versus R-ICE; however, for GCB DLBCL patients, R-DHAP is associated with higher PFS and higher OS (12). 2L treatment options for the DLBCL patients for whom HDT is not an option include experimental treatments, or, in patients with good performance status, platinum-based chemotherapy. R-GDP (rituximab, gemcitabine, dexamethasone and cisplatin), R-GemOx (rituximab, gemcitabine, oxaliplatin) or R-ICE are preferred in non-GCB DLBCL patients due to low toxicity. Updates in the SoC are now being implemented in international clinical guidelines as seen in the updated National Comprehensive Cancer Network (NCCN) guideline (42) where 2L DLBCL patients are accessed according to time to relapse from 1L treatment and thereafter CAR T eligibility. The updated EBMT handbook for ASCT (2022) also confirms that CAR T-cell therapy can be considered SoC in 2L DLBCL if the patients are relapsed within 12 months (43).

No specific regimen is recommended as third-line (3L) for DLBCL in Denmark. 3L treatment options involve inclusion in clinical trials (if feasible), radiation therapy for localised relapse and allogenic transplantation to consolidate treatment of relapse after an ASCT and if the disease is chemo-sensitive (12). The treatment recommendations for r/r DLBCL also apply to r/r HGBCL.

Prognosis with current treatment options

The prognosis for r/r DLBCL patients is generally poor (12,44,45), especially for DLBCL patients with r/r within 12 months, for whom the median OS is less than one year (11). In a systematic literature review, the median survival was 9.9 to 44.0 months for r/r DLBCL patients eligible for stem cell transplantation (SCT) and from 3.4 to 9.0 months in patients not eligible for SCT (46). The current SoC is salvage chemotherapy followed by HDT + ASCT (47); however, only half of the patients with r/r DLBCL are intended for HDT + ASCT, and 8 out of 10 of these patients do not achieve a long-term remission (7). Of the 50% of the patients with r/r DLBCL intended for HDT + ASCT, only around 50% actually proceed to HDT + ASCT (7). Furthermore, a recent Swedish lymphoma registry study found the proportion of DLBCL patients who receive ASCT to be even lower: 34% were reported in the Swedish study (48).

5.2.2 Choice of comparator(s)

Current SoC for patients with r/r DLBCL intended for ASCT is salvage chemotherapy followed by HDT and ASCT. The initial goal of salvage chemotherapy is to determine chemosensitivity before proceeding to HDT + ASCT. Salvage chemotherapy regimens generally consist of drugs demonstrating minimal cross-resistance with 1L R-CHOP. Common regimens include R-ICE, R-ESHAP, R-GDP and R-DHAP/R-DHAX. No regimen has demonstrated superiority in randomised studies (11,49), and institutional preference and AE profile often dictate which treatment regimen is used. We consulted the Danish clinical expert on the current SoC for the patient population of interest, and they confirmed that the R-ICE, R-GDP and R-DHAP/R-DHAX regimens are relevant in Danish clinical practice. Traditionally, R-ESHAP is not used in Denmark, and therefore, R-ESHAP was excluded from the comparator regimens. The choice of comparator regimens was also discussed with the DMC at the dialogue meeting at which the DMC found the suggested comparators to align with Danish clinical practice. Descriptions of each chemotherapy regimen are provided in section 5.2.3.

5.2.3 Description of the comparator(s)

Table 2: Description of R-ICE

Description of R-ICE	
Proprietary name	R-ICE
Generic name	Rituximab, ifosfamide, carboplatin and etoposide
ATC code	Rituximab: L01FA01 Ifosfamide: L01AA06 Carboplatin: L01XA02 Etoposide: L01CB01

Description of R-ICE	
Pharmaceutical form(s)	Rituximab: concentrate for infusion Ifosfamide: powder for concentrate for solution for infusion Carboplatin: concentrate for infusion Etoposide: concentrate for infusion
Packaging	**Rituximab** Rituximab comes in packages with 1 or 2 vials. **Ifosfamide** Ifosfamide comes in a package with 1 vial. **Carboplatin** Carboplatin comes in packages of 1 x 15 ml vial and 1 x 45 ml vial. **Etoposide** Etoposide comes in packages of 1 x 5 ml, 20 ml and 25 ml vials and a package with 5 x 5 ml vials. Etoposide is also available as capsules and comes in packages with 20 capsules.
Mode of action	Ifosfamide, carboplatin and etoposide are chemotherapy drugs. They destroy quickly dividing cells such as cancer cells. Rituximab is a type of targeted drug called a monoclonal antibody. Monoclonal antibodies target proteins on the surface of cells. Rituximab targets a protein known as CD20. CD20 is found on white blood cells called B cells. It is the B cells that are cancerous in the most common types of lymphoma. Rituximab attaches itself to the B cells and marks them. The cells of the immune system then recognise the marked cells and kill them (50).

Description of R-ICE	
Dosage regimen/posology	**Rituximab** Induction therapy: 375 mg/m² as an IV infusion on day 1 in the first chemotherapy cycle after administration of glycocorticosteroid. In the following cycles, patients can continue to receive 375 mg/m² IV or receive 1400 mg subcutaneously (SC) per cycle for up to 8 cycles (51). Maintenance therapy: 375 mg/m² as an IV infusion or 1400 mg SC once every second month in treatment-naïve patients who have responded to induction therapy. In r/r patients who have responded to induction therapy, rituximab should be given every third month (51). **Ifosfamide** The dose is individual, and the dose, treatment duration and frequency depend on the indication, the combination therapy regimen, the general health of the patient and laboratory values (52). A guide to the dosage regimens used for most indications is 8-12 g/m² equally fractionated as single daily doses over 3-5 days every 2-4 weeks or 5-6 g/m² (maximum 10 g) given as a 24-hour infusion every 3–4 weeks. The frequency of dosage is determined by the degree of myelosuppression and the time it takes to recover adequate bone marrow function. The usual number of courses given is 4, but up to 7 (6 by 24-hour infusion) courses have been given (53). **Carboplatin** The recommended dose of carboplatin for patients that have not previously received treatment with normal kidney function (creatinine clearance >60 ml/min) is 400 mg/m² IV over 15 to 60 minutes. Alternatively, the dose can be calculated with the Calvert formula (area under the curve) (52). **Etoposide** The dose of etoposide depends on the type of cancer and the other cytostatic drugs that etoposide is used in combination with (54). The recommended dose of etoposide in adult patients is 50-100 mg/m²/day on days 1 to 5 or 100 to 120 mg/m² on days 1, 3, and 5 every 3 to 4 weeks in combination with other drugs indicated in the disease to be treated (55).
Combination therapy and/or co-medication	Antiemetic treatments can be co-administrated. In addition, mesna can be administrated to protect the bladder mucosa. Granulocyte colony-stimulating factor (G-CSF) can be administrated to stimulate the bone marrow to produce leucocytes (56).
Treatment duration/criteria for end of treatment	The duration of R-ICE therapy is determined by the type of cancer, patient age, the spread of the disease, the general health of the patient and how the patient responds to the treatment (56). Typically, patients receive 3 to 4 cycles of R-ICE with 2 or 3 weeks between each cycle (56).
Necessary monitoring, both during administration and during the treatment period	Blood samples should be collected once or twice per week (56).

Description of R-ICE	
Need for diagnostics or other tests (i.e. companion diagnostics)	None

Table 3: Description of R-GDP

Description of R-GDP	
Proprietary name	R-GDP
Generic name	Rituximab, gemcitabine, dexamethasone, platinol/cisplatin
ATC code	Rituximab: L01FA01 Gemcitabine: L01BC05 Dexamethasone: H02AB02 Platinol/cisplatin: L01XA01
Pharmaceutical form(s)	Rituximab: concentrate for infusion Gemcitabine: solution for injection Dexamethasone: tablets Platinol/cisplatin: concentrate for infusion
Packaging	**Rituximab** Rituximab comes in packages with 1 or 2 vials. **Gemcitabine** Gemcitabine comes in packages of 1 x 25, 50, 120, 140, 160, 180, 200 and 220 ml vials. In addition, gemcitabine is available in a package with 5 x 5 ml vials and a 1 x 26.3 ml vial package. **Dexamethasone** Many different packages of dexamethasone are available on www.medicinpriser.dk. Dexamethasone is available as eye drops, vials and tablets. **Platinol/cisplatin** Cisplatin comes in packages of 1 x 50 ml and 1 x 100 ml packages.
Mode of action	GDP destroys quickly dividing cells such as cancer cells. Rituximab is a type of targeted drug called a monoclonal antibody. Monoclonal antibodies target proteins on the surface of cells. Rituximab targets a protein known as CD20. CD20 is found on white blood cells called B cells. It is the B cells that are cancerous in the most common types of lymphoma. Rituximab attaches itself to the B cells and marks them. The cells of immune system then recognise the marked cells and kill them (50).

Description of R-GDP	
Dosage regimen/posology	**Rituximab** Induction therapy: 375 mg/m² as an IV infusion on day 1 in the first chemotherapy cycle after administration of glycocorticosteroid. In the following cycles, patients can continue to receive 375 mg/m² IV or receive 1400 mg SC per cycle for up to 8 cycles (51). Maintenance therapy: 375 mg/m² as an IV infusion or 1400 mg SC once every second month in treatment-naïve patients who have responded to induction therapy. In r/r patients who have responded to induction therapy, rituximab should be given every third month (51). **Gemcitabine** 1,000-1,250 mg/m² IV over 30 minutes once weekly for 7 weeks followed by a one-week break, or 2 to 3 times over 3 to 4 weeks (57). **Dexamethasone** In DLBCL, patients usually receive 40 mg or 20 mg once daily (58). **Platinol/cisplatin** Cisplatin is administrated IV over 6 to 8 hours either as 50-100 mg/m² once every 3 to 4 weeks, or 15-20 mg/m² daily for 5 days every 3 to 4 weeks. When used in combination with other cytostatic treatments, dose reductions may be necessary (59).
Combination therapy and/or co-medication	Patients should receive hydration treatment during treatment, as chemotherapy can cause kidney damage. Antiemetic treatments can be co-administrated to ease nausea, and anti-diuretic drugs and allopurinol can be administrated to avoid oedema and accumulation of waste products from the broken cancer cells (60).
Treatment duration/criteria for end of treatment	R-GDP is typically given for 6 cycles with 3 weeks between each cycle. The exact number of cycles varies between patients (60).
Necessary monitoring, both during administration and during the treatment period	Blood samples should be taken prior to initiating R-GDP, on days with infusions and 2 weeks after the first treatment day. A kidney function test should be performed before initiating treatment to assess the kidney function (60).
Need for diagnostics or other tests (i.e. companion diagnostics)	None

Table 4: Description of R-DHAP

Description of R-DHAP	
Proprietary name	R-DHAP
Generic name	Rituximab, dexamethasone, arabine/cytarabine and platinum/cisplatin

Description of R-DHAP	
ATC code	Rituximab: L01FA01 Dexamethasone: H02AB02 Cytarabine: L01BC01 Cisplatin: L01XA01
Pharmaceutical form(s)	Rituximab: concentrate for infusion Dexamethasone: tablets Cytarabine: solution for injection Platinol/cisplatin: concentrate for infusion
Packaging	**Rituximab** Rituximab comes in packages with 1 or 2 vials. **Cytarabine** Cytarabine comes in packages of 1 x 10 ml, 20 ml and 5 ml vials. Cytarabine also comes in packages with 1 vial with powder for solution. **Dexamethasone** Many different packages of dexamethasone are available on www.medicinpriser.dk. Dexamethasone is available as eye drops, vials and tablets. **Platinol/cisplatin** Cisplatin comes in packages of 1 x 50 ml and 1 x 100 ml packages.
Mode of action	DHAP destroys quickly dividing cells such as cancer cells. The glucocorticosteroid slows down the cancer and has antiemetic properties.

Description of R-DHAP	
Dosage regimen/posology	**Rituximab** Induction therapy: 375 mg/m^2 as an IV infusion on day 1 in the first chemotherapy cycle after administration of glycocorticosteroid. In the following cycles, patients can continue to receive 375 mg/m^2 IV or receive 1400 mg SC per cycle for up to 8 cycles (51). Maintenance therapy: 375 mg/m^2 as an IV infusion or 1400 mg SC once every second month in treatment-naïve patients who have responded to induction therapy. In r/r patients who have responded to induction therapy, rituximab should be given every third month (51). **Cytarabine (high-dose)** Cytarabine can be administrated as 100-200 mg/m^2 per day continuously or every twelfth hour for 5 to 7 days. High-dose therapy consists of 1000 mg/m^2 every twelfth hour for 2 to 3 days (61). **Dexamethasone** In DLBCL, patients usually receive 40 mg or 20 mg once daily (58). **Platinol/cisplatin** Cisplatin is administrated IV over 6 to 8 hours either as 50-100 mg/m^2 once every 3 to 4 weeks, or 15-20 mg/m^2 daily for 5 days every 3 to 4 weeks. When used in combination with other cytostatic treatments, dose reductions may be necessary (59).
Combination therapy and/or co-medication	Eye drops can be administered to prevent inflammation of the eye, which can be caused by cytarabine. In addition, G-CSF can be administrated to stimulate the bone marrow to produce leucocytes as well as antiemetics to prevent nausea and vomiting (62).
Treatment duration/criteria for end of treatment	Patients typically receive 3 cycles of treatment with 3 weeks between each cycle.
Necessary monitoring, both during administration and during the treatment period	Prior to treatment with R-DHAP, patients should receive a PET-CT or CT scan, a bone marrow examination, a kidney function test and a blood sample. Patients should have blood samples done once or twice a week between the treatment cycles.
Need for diagnostics or other tests (i.e. companion diagnostics)	None

5.3 The intervention: axi-cel

Axi-cel belongs to the breakthrough class of CAR T-cell therapies and represents an innovative treatment in adult patients with DLBCL who have refractory disease or have relapsed within 12 months from 1L chemo-immunotherapy treatment. Treatment with axi-cel consists of a single infusion of CAR-transduced autologous T cells administered intravenously at a target dose of 2 x 10^6 anti-CD19 CAR T-cell/kg body weight.

Table 5: **Description of axi-cel. Source: summary of product characteristics (SPC) of Yescarta®.**

Description of axi-cel	
Proprietary name	Yescarta®
Generic name	Axicabtagene ciloleucel
ATC code	L01XX70
Pharmaceutical form(s)	Dispersion for infusion. A clear to opaque, white to red dispersion (1).
Packaging	Yescarta® comes in packages of one vial per package.
Mode of action	Axi-cel is a CD19-directed genetically modified autologous T-cell immunotherapy product that binds to CD19-expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19-expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells (1).
Dosage regimen/posology	Axi-cel is intended for autologous use only. A single dose of axi-cel contains 2 x 10^6 CAR-positive viable T-cells per kg of body weight (or maximum of 2 x 10^8 CAR-positive viable T-cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag (1).
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 Yescarta® (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).
Treatment duration/criteria for end of treatment	Axi-cel is only administered once. According to the SPC, patients should be hospitalised for 10 days after the infusion of axi-cel (1).
Necessary monitoring, both during administration and during the treatment period	In accordance with the SPC on axi-cel, patients should be monitored daily for 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 should be monitored at the physician's discretion. Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion (1).

Description of axi-cel	
Need for diagnostics or other tests (i.e. companion diagnostics)	None

6. Literature search and identification of efficacy and safety studies

The efficacy and safety of axi-cel have been assessed in the ZUMA-7 trial (63). The ZUMA-7 trial is a phase III randomised, open-label, multicentre international study of axi-cel compared to SoC in adult DLBCL patients who have refractory disease or have relapsed within 12 months from 1L therapy with an anti-CD20 monoclonal antibody and an anthracycline-containing chemotherapy regimen, and who intend to proceed to HDT + ASCT (63).

Since the ZUMA-7 trial is a head-to-head trial of axi-cel and DLBCL SoC, no literature search was conducted in accordance with the DMC method guideline (64). This approach was discussed with the DMC at a dialogue meeting on 17 May 2022. Based on this, the headings in this section have been deleted.

7. Efficacy and safety

7.1 Relevant study

The efficacy and safety of axi-cel is being evaluated in ZUMA-7, the largest (359 patients enrolled) phase III randomised controlled trial comparing CAR T-cell therapy to SoC in 2L DLBCL for r/r patients who are intended for transplant with a median follow-up of approximately two years. A brief description of the trial will be provided in the following. Please see Appendix B for a detailed presentation of the main study characteristics and Appendix C for baseline characteristics of patients included in the ZUMA-7 trial.

The ZUMA-7 trial is a phase III, randomised, open-label, multicentre study. 437 patients were assessed for eligibility and 78 were excluded (69 did not meet eligibility criteria, 4 were withdrawn by investigator and 5 had other reasons) i.e., 359 patients were enrolled and randomised. Patients were randomised 1:1 to axi-cel and SoC with randomisation being stratified by response to 1L therapy (primary refractory, relapse ≤6 months of 1L therapy, or relapse >6 and ≤12 months of 1L therapy) and 2L age-adjusted International Prognostic Index (aaIPI) (0 to 1, or 2 to 3, indicating high risk), as assessed at the time of screening. For subjects randomised to axi-cel, treatment consisted of lymphodepleting chemotherapy followed by a single IV infusion of axi-cel. Bridging therapy using corticosteroids was allowed prior to lymphodepleting chemotherapy for subjects with high disease burden, at the investigator's discretion. For subjects randomised to SoC, treatment consisted of a single protocol-defined, platinum-based salvage chemotherapy regimen as selected by the treating investigator. Subjects who responded to salvage chemotherapy were to proceed to HDT with or without total body irradiation (TBI), followed by ASCT.

Subsequent therapy (3L and beyond) was recorded for all randomised subjects until one of the following occurred: the subject completed the long-term follow-up period, was considered lost to follow-up, withdrew full consent or died. Subsequent therapies were administered to treat a subject's progressive disease (PD), and included chemotherapy, immunotherapy (including CAR T-cell therapies), targeted agents, as well as allo- or ASCT and radiation therapy. Nineteen subjects (11%) in the axi-cel arm received subsequent SCT, including 11 subjects who received ASCT and eight subjects who received allo-SCT. Although crossover between the treatment groups was not planned, patients who did not have a response to SoC could receive cellular immunotherapy outside the protocol (treatment switching) (63). Patients in the SoC group who relapsed or did not respond to treatment were permitted to switch onto CAR T-cell therapy (e.g., tisagenlecleucel or axi-cel). Therefore, crossover adjustment analyses were required to reflect a Danish healthcare setting and provide efficacy estimates for OS if patients in the ZUMA-7 trial were not permitted to switch. Two crossover adjustment methods were explored, and results are presented in section 7.2.2.1.

Subjects in both treatment arms were assessed for response and progression at the same times relative to randomisation: study day 0, study days 50, 100, 150, and month 9, then every 3 months thereafter until month 24, and then every 6 months from months 30 to 60. For a subject who completed the long-term follow-up period, the study was to take approximately 5 or 15 years to complete as determined by randomisation to the SoC or axi-cel groups, respectively.

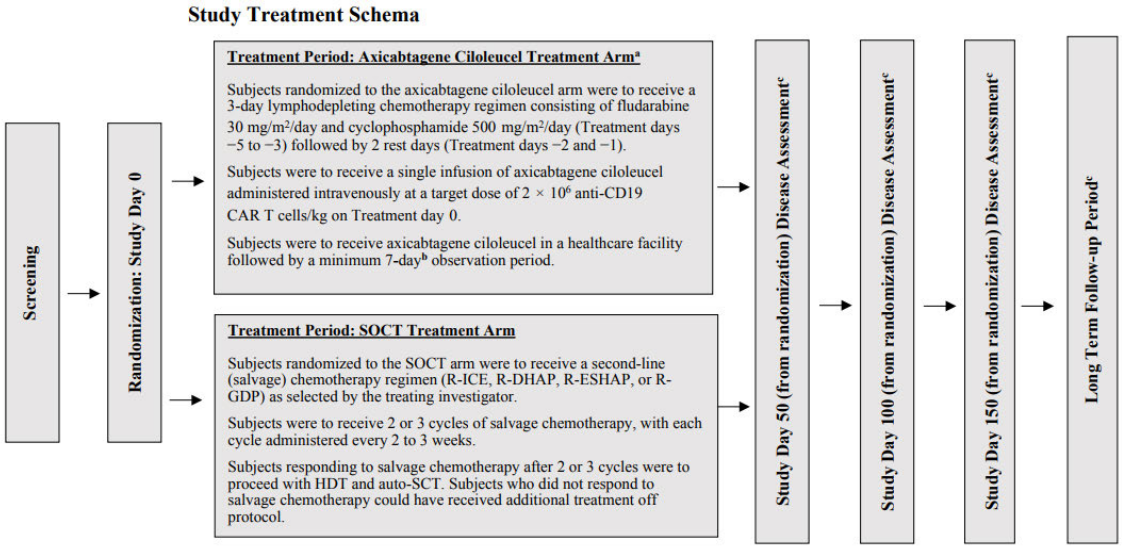

Figure 1: ZUMA-7 schema

Abbreviations: auto-SCT, autologous stem cell transplant; CAR, chimeric antigen receptor; HDT, high-dose therapy; R-DHAP, rituximab + dexamethasone, high-dose cytarabine and cisplatin; R-ESHAP, rituximab + etoposide, methylprednisolone, cytarabine, cisplatin; R-GDP, rituximab + gemcitabine, dexamethasone and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOCT, standard of care therapy; Study Day, number of days from the day of randomisation; Treatment day, number of days from the day of axicabtagene ciloleucel treatment.

[a]At the discretion of the investigator, corticosteroid bridging therapy could have been considered for subjects with high disease burden at screening.

[b]Minimum observation period: 7 days unless otherwise required by country regulatory agencies (e.g., 10 days for subjects treated in Germany, Switzerland, and France)

[c]Disease assessments were to be calculated from the date of randomisation and not the date of dosing with axicabtagene ciloleucel or SOCT. Independent of the treatment arm, study procedures and disease assessments were to occur at the same protocol-defined timepoints.

7.2 Efficacy results from the ZUMA-7 trial

The ZUMA-7 trial is a head-to-head trial of axi-cel and SoC; thus, direct comparative analyses are presented for all the outcomes presented in section 7.2. Information on the analyses and results is also provided in Appendix F. Gilead Sciences found it relevant to present results on the following outcomes:

- EFS;
- OS;
- ORR;
- PFS;
- TTNT;
- DOR; and
- EQ-5D-5L VAS.

7.2.1 Results on event-free survival

EFS is a widely accepted, robust and early efficacy outcome in clinical trials involving patients with DLBCL, on the basis of retrospective analyses of randomised trials that have shown a correlation between improvements in EFS and OS

(see Appendix D) (63). The primary endpoint in ZUMA-7 was EFS defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification (65), commencement of new lymphoma therapy, death from any cause, or a best response of SD up to and including the response at the day 150 assessment after randomisation, according to blinded central review.

EFS was analysed on the full analysis set (FAS) population. Kaplan–Meier estimates were provided for EFS and a HR with 95% confidence interval (CI) was calculated from a Cox proportional-hazards model with stratification according to the randomisation stratification factors (response to 1L therapy (primary refractory versus relapse ≤6 months of 1L therapy versus relapse >6 and ≤12 months of 1L therapy) and 2L age-adjusted IPI (0 to 1 versus 2 to 3) as collected via interactive voice/web response system (63)). Nonproportionality among the treatment groups was assessed by comparing the standardised martingale residuals over time to a normal distribution at the 5% level (see Figure 2) (66). A plot of the standardised residuals over time was provided. If the comparison of the standardised martingale residuals over time was significant, a piece-wise Cox model was used for the analysis. For the stratified piece-wise Cox model, 2 or more equal-length intervals of 12 weeks were considered (67). This was to include 1 scheduled tumour assessment in each interval. These models allowed estimation of the overall as well as within-interval treatment HR (21).

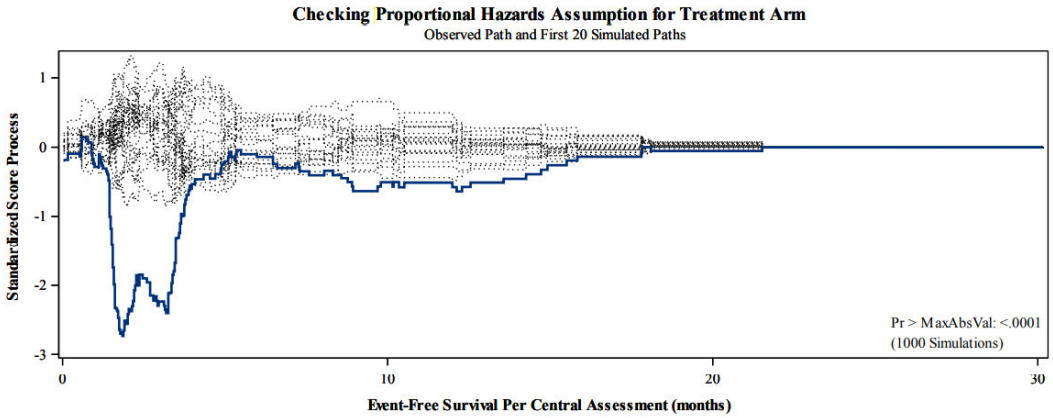

Figure 2: Standardised score process plot for EFS per central assessment (FAS population)

Event/censoring time was calculated as event/censoring date – randomisation date +1 (= days) / 30.4375 (= months). The absolute difference in EFS is presented as the difference in EFS rates at 24 months and difference in median EFS. The absolute differences were calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68).

Median EFS (according to blinded central review) was significantly longer in the axi-cel group: the median EFS was 8.3 months (95% CI: 4.5, 15.8) in the axi-cel group compared to 2.0 months (95% CI: 1.6, 2.8) in the SoC group. The estimated EFS at 24 months was 41% (95% CI: 33%, 48%) in the axi-cel group compared to 16% (95% CI: 11%, 22%) in the SoC group (63). Results are summarised in Table 6.

Table 6: Median EFS and EFS at 24 months from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

	Axi-cel (N=180)	SoC (N=179)
Median EFS	8.3 months (95% CI: 4.5, 15.8)	2.0 months (95% CI: 1.6, 2.8)
EFS at 24 months	41% (95% CI: 33%, 48%)	16% (95% CI: 11%, 22%)

The Kaplan-Meier EFS curves for axi-cel and SoC are presented in Figure 3. Axi-cel was superior to SoC in EFS, and the HR for event or death was 0.40 (95% CI: 0.31, 0.51 and log-rank p-value: <0.001) (63), showing that the hazard for an event or death was statistically significantly lower in the axi-cel group compared to the SoC group. Table 7 presents the absolute difference and relative difference in EFS between axi-cel and SoC.

Table 7: Absolute difference and relative difference in EFS from the ZUMA-7 trial (FAS population)

	Absolute difference in EFS	Relative difference in EFS
Axi-cel vs SoC	Difference in EFS rates: 32% (95% CI: 23%, 41%) Median difference in EFS: 3.0 (95% CI: 1.9, 4.5)	HR: 0.40 (95% CI: 0.31, 0.51)

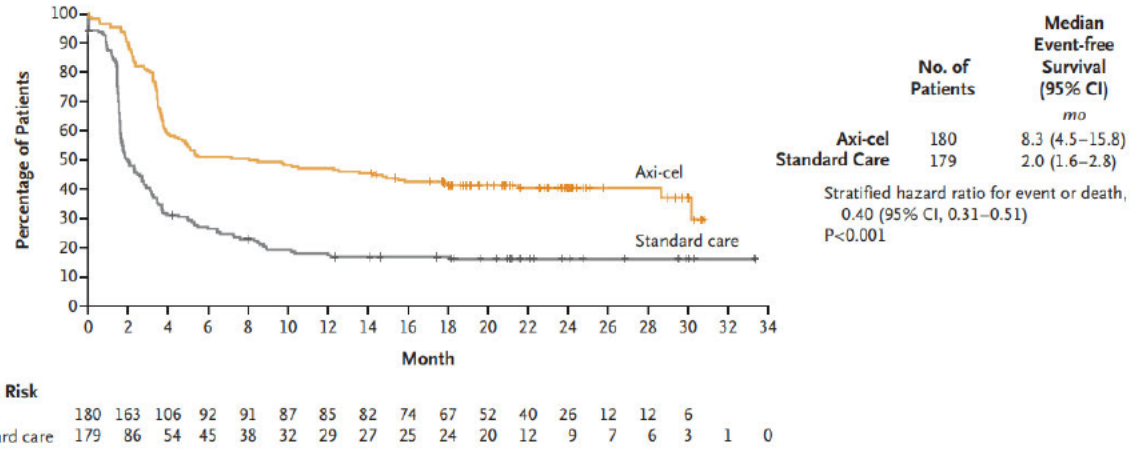

Figure 3: Kaplan-Meier plot of EFS from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

7.2.2 Results on overall survival

OS is a critical outcome for demonstrating efficacy in cancer studies. OS was a key secondary outcome in the ZUMA-7 trial and defined as the time from randomisation to death from any cause. OS was evaluated as an interim analysis on the FAS population and analysed the same way as the primary outcome (see section 7.2.1). Subjects who had not died by the analysis data cut-off date (18 March 2021) were censored at their last contact date prior to the data cut-off date, with the exception that subjects known to be alive or determined to have died after the data cut-off date were censored at the data cut-off date. By the data cut-off date, 14 subjects had discontinued from ZUMA-7 and were

either lost to follow-up, had withdrawn consent, or had been withdrawn by the investigator. A subsequent search of public records identified additional survival data for 8 of the discontinued subjects, including 4 subjects (all in the SoC group) who had died before the primary analysis data cut-off date, and 4 subjects (3 in the SoC group and 1 in the axi-cel group) confirmed as being alive at the primary analysis data cut-off date. Additional survival data for the remaining 6 discontinued subjects (5 in the SoC group and 1 in the axi-cel group) could not be obtained. The interim OS analysis data presented in Locke et al. 2021 (63) was updated (with the same data cut-off date of 18 March 2021) to include the updated information for these 8 subjects. Stratified Cox regression models were used to provide the estimated OS HR and 95% CIs. For the stratification factors, please see section 7.2.1. The absolute difference was calculated based on the HR using the method suggested in Appendix 6 in the DMC guideline (68) and presented as the difference in OS rates at 24 months.

In the updated interim analysis, the estimated OS at 24 months was 61% (95% CI: 53%, 68%) in the axi-cel group and 51.3% (95% CI: 43.4%, 58.7%) in the SoC group. The median OS was not reached in the axi-cel group and was 25.7 months (95% CI: 17.6, not estimable) in the SoC group (63). Results are summarised in Table 8.

Table 8: Median OS and OS at 24 months from the ZUMA-7 trial (FAS population). Source: Locke et al. 2021 (63).

	Axi-cel (N=180)	SoC (N=179)
Median OS	Not reached	25.7 months (95% CI: 17.6, not estimable)
OS at 24 months	61% (95% CI: 53%, 68%)	51.3% (95% CI: 43.4%, 58.7%)

Kaplan-Meier curves on OS are presented in Figure 4. The stratified HR for death was 0.71 (95% CI: 0.52, 0.97, p-value: 0.0159) for the axi-cel group compared to the SoC group (63). Table 9 presents the absolute difference and relative difference in OS between axi-cel and SoC.

Table 9: Absolute difference and relative difference in OS from the FAS population in the ZUMA-7 trial at 24 months

	Absolute difference in OS	Relative difference in OS
Axi-cel vs SoC	11% (95% CI: 1%, 19%)	HR: 0.71 (95% CI: 0.52, 0.97)

[redacted]

7.2.2.1 OS sensitivity analysis

Although there was no planned study crossover between treatment arms in the ZUMA-7 trial, 100 of 179 subjects (56%) in the SoC group later received off-protocol cell therapy at some time after SoC. A sensitivity analysis of OS was included in the interim analysis of OS to address the confounding effects of this treatment switching in the SoC group. Two crossover adjustment methods are explored in the NICE Technical Support Document (TSD) 16 (69) using the rank preserving structural failure time (RPSFT) model with g-estimation by Robins et al. 1991 (70) and inverse probability of censoring weights (IPCW) (71) adjustment methods. These sensitivity analyses were also updated to include the additional survival data for discontinued subjects. The RPSFT method estimates survival times that would have been observed had treatment switching not occurred (i.e., counterfactual survival times) (72). The method relies on two key assumptions: 1) the 'common treatment effect' assumption, and 2) the 'randomisation' assumption. The 'common treatment effect' assumption requires that the effect of the intervention treatment in switching patients is equal to the effect of the intervention treatment in those initially randomised to receive the treatment. The 'randomisation' assumption assumes that if no patients in either trial group had received the experimental treatment, the average survival time in the two groups would have been equal, because the two groups were created through randomisation (72).

The IPCW method artificially censors patients that switch treatments, and to remove the selection bias resulting from the artificial censoring, all remaining uncensored observations are weighted based on their baseline and time-dependent covariate values in relation to the characteristics associated with patients that were artificially censored. The IPCW method requires that data must be available at baseline and over time on all prognostic factors that influence the probability of treatment switching and death; this is known as the 'no unmeasured confounders' assumption (72).

[redacted]

[redacted]

Figure note: RPSFT (70) was used to adjust treatment drop in from SoC to CAR T-cell therapy. OS is defined as the time from the randomisation date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date (March 2021) was censored at their last contact date prior to the data cutoff date with the exception that subjects known to be alive or determined to have died after the data cutoff date was censored at the data cutoff date. The stratification factors were response to first-line therapy (primary refractory versus relapse ≤ 6 months of first-line therapy versus relapse >6 and ≤12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models were used to provide the estimated HR and 95% CIs for axi-cel relative to SoC.

7.2.3 Results on progression-free survival

PFS can be used as a measure for the degree and length of disease control after patients have received a treatment. In the ZUMA-7 trial, PFS was a secondary outcome and defined as the time from randomisation to disease progression per the Lugano Classification (65) as determined by investigator assessment or death from any cause. Censoring was based on the following criteria:

Subjects alive who did not meet the criteria for progression at the analysis data cut-off date (18 March 2021) had PFS time censored at the last evaluable disease assessment.

Subjects who received subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and ASCT while in a protocol therapy-induced response) in the absence of documented disease progression had their last evaluable disease assessment date censored before the commencement of the subsequent new lymphoma therapy.

Auto/allo-SCT that occurred while a subject was in response from a protocol-specified therapy was not considered a PFS event, and such subjects were censored for PFS at the last evaluable disease assessment before the auto/allo-SCT for subjects in the axi-cel group and were censored at the last evaluable disease assessment date for subjects in the SoC group for the primary analysis of PFS.

The analysis of PFS was conducted on the FAS population and analysed with the same methods as the analysis of EFS. Disease outcomes were based on investigator assessment. Stratified Cox regression models were used to provide the estimated HR and 95% CIs for axi-cel relative to SoC. The absolute difference was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68), and the absolute difference in PFS rates at 24 months and absolute difference in median PFS are presented.

At the data cut-off from 18 March 2021, the median PFS time was longer in the axi-cel group compared to the SoC group: 14.7 months (95% CI: 5.4, not estimable) compared to 3.7 months (95% CI: 2.9, 5.3) (63). The Kaplan-Meier

estimates of the percentage of subjects who remained progression-free and alive at 24 months from randomisation were 46% (95% CI: 38%, 53%) in the axi-cel group and 27% (95% CI: 20%, 35%) in the SoC group. Results are summarised in Table 10.

Table 10: Median PFS and PFS at 24 months from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

	Axi-cel (N=180)	SoC (N=179)
Median PFS	14.7 (95% CI: 5.4, not estimable)	3.7 (95% CI: 2.9, 5.3)
PFS at 24 months	46% (95% CI: 38%, 53%)	27% (95% CI: 20%, 35%)

The Kaplan-Meier PFS curves for axi-cel and SoC are presented in Figure 6. The stratified HR was 0.49 (95% CI: 0.37, 0.65) and log-rank p-value <.0001, demonstrating a statistically significantly lower hazard for progression with axi-cel compared to SoC. Table 11 presents the absolute difference and relative difference in PFS between axi-cel and SoC.

Table 11: Absolute difference and relative difference in PFS from the FAS population in the ZUMA-7 trial at 24 months

	Absolute difference in PFS	Relative difference in PFS
Axi-cel vs SoC	Difference in PFS rates: 26% (95% CI: 16%, 35%) Median difference in PFS: 3.9 (95% CI: 2.0, 6.3)	HR: 0.49 (95% CI: 0.37, 0.65)

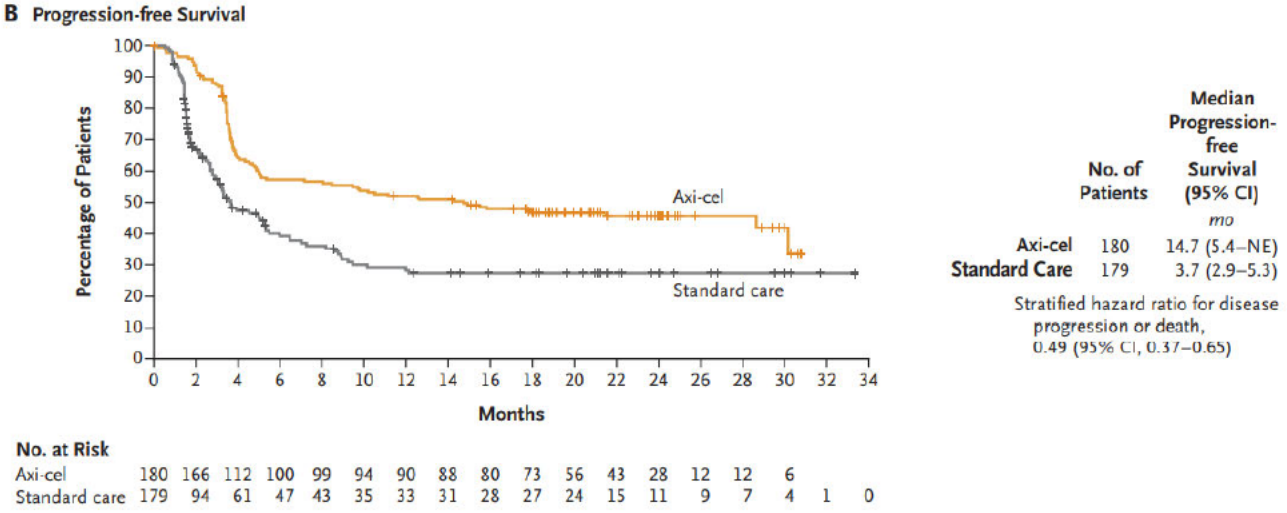

Figure 6: Kaplan-Meier plot of PFS (investigator assessed) from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

7.2.4 Results on objective response rate

ORR was a key secondary outcome in the ZUMA-7 trial and defined as the incidence of either a CR or a PR by the Lugano Classification (65). Subjects who did not meet the criteria for an objective response by the analysis cut-off date (18 March 2021) were considered non-responders. The primary analysis of ORR included disease assessments up to an EFS event. The analysis of ORR was conducted on the FAS population and based on disease responses determined by blinded central assessment.

A stratified Cochran-Mantel-Haenszel (CMH) test was performed, and the odds ratio (OR) from the CMH test was used to calculate the RR according to the method suggested in Appendix 2 in the DMC guideline (68). The absolute difference was estimated based on the calculated RR according to the method suggested in Appendix 5 in the DMC guideline (68). The stratification factors in the CMH test were the same as for EFS (see section 7.2.1).

The number of objective responders (CR+PR) was 150 out of 180 subjects (83%, 95% CI: 77.1%, 88.5%) in the axi-cel group and 90 out of 179 subjects (50%, 95% CI: 42.7%, 57.8%) in the SoC group (63). 117 out of 180 subjects (65%, 95% CI: 57.6%, 71.9%) achieved CR in the axi-cel group compared to 58 out of 179 subjects (32%, 95% CI: 25.6%, 39.8%) in the SoC group (63). Results are summarised in Table 12.

The absolute difference in objective responders was 34.0% (95% CI: 25.4%, 39.7%), and the RR was 1.7 (95% CI: 1.5, 1.8), demonstrating a significant improvement in ORR associated with axi-cel (see Table 13).

Table 12: Results on ORR from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

	Axi-cel (N=180)	SoC (N=179)
Objective responders (CR + PR)	83% (95% CI: 77.1%, 88.5%)	50% (95% CI: 42.7%, 57.8%)
Subjects with CR	65% (95% CI: 57.6%, 71.9%)	32% (95% CI: 25.6%, 39.8%)
OR from stratified CMH test*	5.31 (95% CI: 3.08, 8.90, p-value: <0.0001)	

*OR was defined as the ratio of odds of objective response in the axi-cel group to odds of objective response in the SoC group per Lugano Classification (65).

Table 13: Absolute difference and relative difference in ORR from the FAS population in the ZUMA-7 trial at 24 months

	Absolute difference	Relative difference in ORR
Axi-cel vs SoC	34.0% (95% CI: 25.4%, 39.7%)	RR: 1.7 (95% CI: 1.5, 1.8)

7.2.5 Results on duration of response

DOR was a secondary outcome in the ZUMA-7 trial and defined as the time from first response to disease progression as per the Lugano Classification (65) or death from any cause. DOR was only derived among subjects who experienced an objective response per the Lugano Classification as determined by blinded central assessment. Censoring was performed the following way:

Subjects not meeting the criteria for progression or death by the analysis data cut-off date were to have DOR censored at their last evaluable disease assessment date.

Subjects who received subsequent new lymphoma therapy (with the exception of HDT, TBI for HDT, and ASCT while in a protocol therapy-induced response) in the absence of documented progression had DOR censored at the last evaluable disease assessment before the commencement of the new lymphoma therapy.

For the primary analysis of DOR, DOR was censored at the last evaluable disease assessment date before allo/ASCT for subjects undergoing allo/ASCT while in protocol-specified therapy-induced response in the axi-cel group and was censored at the last evaluable disease assessment date (including assessments after ASCT) for subjects in the SoC group.

The analysis of DOR was conducted on the FAS population with the exceptions noted in the definition of DOR stated above, i.e., DOR was analysed for the 150 subjects in the axi-cel group and the 90 subjects in the SoC group who achieved an objective response of CR or PR. The analysis of DOR included fewer patients in the SoC group, as most of the patients in the SoC group did not respond to salvage chemotherapy and received 3L treatment (i.e., they were not part of DOR analysis). The analysis of DOR was performed using the same methods as the analysis of EFS. Stratified Cox regression models were used to provide the estimated HR and 95% Cis for axi-cel relative to SoC (see stratification factors in section 7.2.1). The absolute difference was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68), and the absolute difference in DOR rates at 24 months is presented.

The Kaplan-Meier estimate of the percentage of subjects who remained in response at 24 months from first objective response was 54% (95% CI: 45.1%, 62.0%) in the axi-cel group and 46% (95% CI: 33.2%, 57.1%) in the SoC group (63). The Kaplan-Meier median DOR for the axi-cel group was 26.9 months (95% CI: 13.6, not estimable) compared with 8.9 months (95% CI: 5.7, not estimable) in the SoC group (63). Results are summarised in Table 14.

Table 14: Median DOR and DOR at 24 months from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

	Axi-cel (N=180)	SoC (N=179)
Number of objective responders (CR+PR)	150	90
DOR rates at 24 months	54% (95% CI: 45.1%, 62.0%)	46% (95% CI: 33.2%, 57.1%)
Median DOR	26.9 months (95% CI: 13.6, not estimable)	8.9 months (95% CI: 5.7, not estimable)

The Kaplan-Meier DOR curves for axi-cel and SoC are presented in Figure 7. The stratified HR was 0.74 (95% CI: 0.49, 1.12 and log-rank p-value of 0.0695), demonstrating that the hazard for disease progression or death was lower in the axi-cel group compared to the SoC group, i.e., patients maintained their objective response longer with axi-cel than with SoC (63). Table 15 presents the absolute difference and relative difference in DOR between axi-cel and SoC.

Table 15: Absolute difference and relative difference in DOR from the FAS population in the ZUMA-7 trial at 24 months

	Absolute difference in DOR	Relative difference in DOR
Axi-cel vs SoC	Difference in DOR rates: 10% (-0.3%, 22%) Median difference in DOR: 3.1 (-1.0, 9.3)	HR: 0.74 (95% CI: 0.49, 1.12)

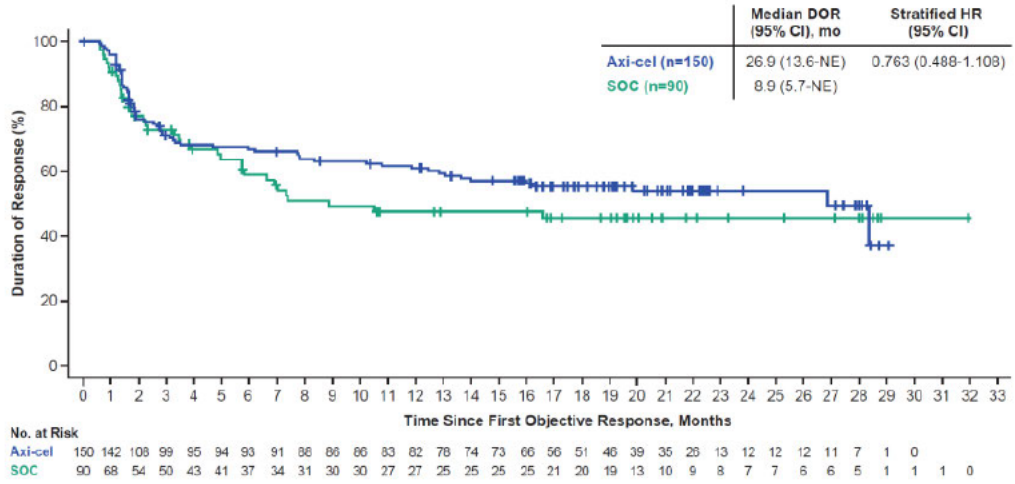

Figure 7: Kaplan-Meier plot of DOR (per central review) from the ZUMA-7 trial (FAS population, data cut-off 18 March 2021). Source: Locke et al. 2021 (63).

7.2.6 Results on time to next therapy

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7.2.7 Results on patient-reported outcomes

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	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

7.2.8 Summary of efficacy results

The primary objective of the ZUMA-7 trial was to determine whether axi-cel is superior to SoC, as measured by central assessment of EFS. As demonstrated in section 7.2.1, the primary objective was met, and at the time of data cut-off (March 2021), the median study duration was 24.9 months, and the risk of an EFS event for subjects in the axi-cel group was significantly reduced compared with the SoC group: The hazard for experiencing an event was reduced by 60% (HR: 0.40) in the axi-cel group compared to the SoC group. Axi-cel also demonstrated efficacy in the updated interim analysis of OS that favoured axi-cel over SoC where the hazard was reduced by 29% (HR: 0.71), but statistical significance was not reached based on the alpha spent at this interim analysis. Other secondary outcomes were also consistent with the primary outcome in favouring axi-cel over SoC: PFS was longer for axi-cel compared with SoC, and DOR in the axi-cel group was numerically longer than in the SoC group. In terms of ORR, axi-cel demonstrated a significantly higher ORR compared with SoC (RR: 1.7).

7.3 Safety results from the ZUMA-7 trial

A secondary objective of the ZUMA-7 trial was to evaluate the safety of axi-cel compared to SoC. In the following, proportions of patients with AEs and SAEs are presented for the safety analysis set, i.e., subjects in the axi-cel group who received a single infusion of axi-cel and subjects in the SoC group who received at least one dose of salvage chemotherapy. In addition, discontinuation data is presented. All-cause discontinuation data was analysed on the FAS population and presented separately for subjects who received axi-cel or SoC and subjects who did not receive axi-cel or SoC. Discontinuation due to TEAEs was analysed in the safety analysis set. Common AEs observed with CAR T-cell therapy are CRS and neutropaenia, which are also reported in the following. Neurologic toxicities are often reported for CAR T-cell therapies and therefore also reported.

7.3.1 Adverse events and serious adverse events

In the ZUMA-7 trial, an adverse event (AE) was defined as any untoward medical occurrence in a study subject, and treatment-emergent AEs (TEAEs) were defined as any AE with onset on or after the axi-cel infusion for the axi-cel arm and as any AE with onset on or after the first dose of salvage chemotherapy for the SoC group. The event was not necessarily related to the study treatment. Investigators were responsible for ensuring that any AEs observed by the

investigator or reported by the subject were recorded in the subject's medical record. A SAE was defined as an event that met at least one of the following serious criteria:

- The event was fatal.
- The event was life-threatening (i.e., an event that placed the subject at immediate risk of death; it does not refer to an event that hypothetically might have caused death if it was more severe).
- The event required inpatient hospitalisation or prolongation of planned hospitalisation:
    - An AE met the criterion of "requires hospitalisation" if the event necessitated an admission to a healthcare facility (e.g., overnight stay).
- Events that required an escalation of care when the subject was already hospitalised, e.g., movement from routine care in the hospital to the intensive care unit, or resulted in a prolongation of the planned hospitalisation
- The event resulted in persistent or significant disability/incapacity.
- The event resulted in congenital anomaly/birth defect.

Other medically serious event: If an investigator considered an event to be clinically important, but it did not meet any of the serious criteria, the event could be classified as an SAE with the criterion of "other medically important serious event".

The severity of AEs and SAEs was graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The investigator assessed and recorded whether the AE or SAE was possibly related to axi-cel, leukapheresis or lymphodepleting chemotherapy (axi-cel group), salvage chemotherapy, HDT, CD34+ leukapheresis, or CD34+ infusion (SoC group), disease progression, concurrent disease, concomitant medication or other possible reasons.

All subjects in the axi-cel group and the SoC group had at least one TEAE: 170 out of the 170 subjects in the safety analysis set (100%, 95% CI: 98%, 100%) in the axi-cel group, and 168 out of the 168 subjects in the SoC group (100%, 95% CI: 98%, 100%). 155 subjects (91%, 95% CI: 86.9%, 95.4%) in the axi-cel group and 140 subjects (83%, 95% CI: 77.7%, 89.0%) in the SoC group had a Grade 3 or higher TEAE.

85 out of 170 subjects (50%, 95% CI: 42.5%, 57.5%) in the axi-cel group and 77 out of 168 subjects (46%, 95% CI: 38.3%, 53.4%) in the SoC group had at least one SAE. 72 subjects (42%, 95% CI: 34.9%, 49.8%) in the axi-cel group had a Grade 3 or higher SAE compared to 67 subjects (40%, 95% CI: 32.5%, 47.3%) in the SoC group. Results are summarised in Table 20, while Table 21 presents the absolute and relative differences (expressed in risk ratios (RR)) between the axi-cel group and the SoC group in the safety outcomes.

Table 20: Summary of safety data from the ZUMA-7 trial (safety population). Source: Locke et al. 2021 (63) and data on file (21).

	Axi-cel (N=170)	SoC (N=168)
Proportion of subjects with at least one TEAE	100% (95% CI: 98%, 100%)*	100% (95% CI: 98%, 100%)*
Proportion of subjects with at least one Grade 3 or higher TEAE	91% (95% CI: 86.9%, 95.4%)	83% (95% CI: 77.7%, 89.0%)
Proportion of subjects with at least one SAE	50% (95% CI: 42.5%, 57.5%)	46% (95% CI: 38.3%, 53.4%)

	Axi-cel (N=170)	SoC (N=168)
Proportion of subjects with at least one Grade 3 or higher SAE	[redacted]	[redacted]

*95% CI calculated with Clopper-Pearson's exact method.

Table 21: Absolute and relative differences in safety outcomes between the axi-cel group and the SoC group (safety population)

	Absolute differences	Relative differences
Proportion of subjects with at least one TEAE	0% (95% CI: -2.0%, 2.0%)	RR: 1.0 (95% CI: 1.0, 1.0)
Proportion of subjects with at least one Grade 3 or higher TEAE	7.8% (95% CI: 0.8%, 14.9%)	RR: 1.1 (95% CI: 1.0, 1.2)
Proportion of subjects with at least one SAE	4.2% (-6.5%, 14.8%)	RR: 1.1 (95% CI: 0.9, 1.4)
Proportion of subjects with at least one Grade 3 or higher SAE	[redacted]	[redacted]

7.3.2 CRS, neutropaenia and neurologic toxicities

The most common AE of Grade 3 or higher was neutropaenia (combined preferred terms of neutropaenia and neutrophil count decreased), which was experienced by 118 out of 170 subjects (69%, 95% CI: 62.5%, 76.3%) in the axi-cel group and 69 out of 168 subjects (41%, 95% CI: 33.6%, 48.5%) in the SoC group (63).

CRS only occurred in patients treated with axi-cel and occurred in 157 subjects (92%, 95% CI: 88.4%, 96.3%). 76 (45%) subjects experienced a Grade 2 CRS (corresponding to 48% of all subjects experiencing CRS) and Grade 3 or higher CRS events occurred in 11 subjects (6%, 95% CI: 2.8%, 10.3%) (corresponding to 7% of the subhects with CRS. No deaths related to CRS occurred. The median time to the onset of CRS was three days (range, 1 to 10) after the infusion, and the median duration was seven days (range, 2 to 43). All the events were resolved (63).

Results are summarised in Table 22, and Table 23 presents the absolute and relative differences (expressed as RR) between the axi-cel group and the SoC group.

Table 22: CRS and neutropaenia from the ZUMA-7 trial (safety population). Source: Locke et al. 2021 (63).

	Axi-cel (N=170)	SoC (N=168)
Proportion of subjects with Grade 3+ neutropaenia	69% (95% CI: 62.5%, 76.3%)	41% (95% CI: 33.6%, 48.5%)
Proportion of subjects with CRS	92% (95% CI: 88.4%, 96.3%)	NA
Proportion of subjects with Grade 3+ CRS	6% (95% CI: 2.8%, 10.3%)	NA

Table 23: Absolute and relative differences in proportions experiencing neutropaenia between the axi-cel group and the SoC group (safety population)

	Absolute differences	Relative differences
Proportion of subjects with neutropaenia	28.3% (95% CI: 18.2%, 38.5%)	RR: 1.7 (95% CI: 1.4, 2.1)

Neurotoxicity is another prominent AE associated with axi-cel, and cases of serious and fatal cerebral oedema have occurred in treated patients. Patients who experience Grade 2+ neurological toxicities should be monitored with continuous cardiac telemetry and pulse oximetry, with intensive care supportive therapy provided for severe or life-threatening neurological toxicities. Supportive care may be sufficient in mild cases, although more severe cases require tocilizumab and/or corticosteroid administration. Neurotoxicity may occur concurrently with CRS or following CRS resolution; it may also be present without CRS.

102 out of 170 subjects (60%, 95% CI: 52.6%, 67.4%) in the axi-cel group experienced any TE neurologic event compared to 33 out of 168 subjects (20%, 95% CI: 13.6%, 25.7%) in the SoC group (63). Grade 3+ TE neurological events were observed in 36 out of 170 subjects (21%, 95% CI: 15.0%, 27.3%) in the axi-cel group and 1 out of 168 subjects (1%, 95% CI: 0.0%, 3.3%) in the SoC group (63).

[redacted]

The most common symptoms in the axi-cel group were tremor and confusional state. Tremor was experienced by 44 out of 170 subjects (26%, 95% CI: 19.3%, 32.5%) in the axi-cel group and 1 out of 168 subjects (1%, 95% CI: 0.0%, 3.3%) in the SoC group (63). Confusional state was experienced by 40 subjects (24%, 95% CI:) in the axi-cel group and 4 (2%, 95% CI:) in the SoC group (63).

[redacted]

Median time to onset (Q1, Q3) was 7.0 days (5.0, 9.0) in the axi-cel group and 23.0 (3.0, 75.0) days in the SoC group. Median duration of events (range) was 8.5 days (4.0, 25.5) and 23.0 days (4.5, 51.0) in the axi-cel group and SoC group, respectively. Time to onset was estimated as the onset date minus the first dose + 1. First dose date is the date of axi-cel infusion in the axi-cel arm or date of first dose for salvage chemotherapy in the SoC arm. Duration is calculated from patients whose events were resolved i.e., last ending date of all qualified events minus first onset date of all qualified events + 1.

Results are summarised in Table 24, and the absolute and relative differences are presented in Table 25.

Table 24: Neurologic toxicities observed in ZUMA-7 (safety population). Source: Locke et al. 2021 (63).

	Axi-cel (N=170)	SoC (N=168)
Proportion with any TE neurological event	60% (95% CI: 52.6%, 67.4%)	20% (95% CI: 13.6%, 25.7%)
Proportion with Grade 3+ TE neurological events	21% (95% CI: 15.0%, 27.3%)	1% (95% CI: 0.0%, 3.3%)[a]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Most common symptoms		
Tremor	26% (95% CI: 19.3%, 32.5%)	1% (95% CI: 0.0%, 3.3%)[a]
Confusional state	24% (95% CI: 17.2%, 29.9%)	2% (95% CI: 0.1%, 4.7%)
[redacted]	[redacted]	[redacted]

[a]*Confidence interval calculated with the Clopper-Pearson's exact method.*

[b]*Upper limit of confidence interval calculated by dividing 3 with n (3/n) as suggested by the Cochrane handbook (version 5.1.0* (73)*).*

Note: TEAE includes all AEs with an onset on or after the axi-cel infusion date in the axi-cel group or the first dose of salvage chemotherapy in the SoC group. Patients were summarised at their worst CTCAE grade or Lee Grade for CRS, and AEs are graded per CTCAE version 4.03, and CRS events are graded according to a modified grading system proposed by Lee and colleagues (Lee et al., 2014 (74)*).*

Table 25: Absolute and relative differences in neurologic events between the axi-cel group and the SoC group (safety population)

	Absolute differences	Relative differences
Proportion with any TE neurological event	40.4% (95% CI: 30.9%, 49.9%	3.1 (95% CI: 2.2, 4.2)
Proportion with Grade 3+ TE neurological events	20.6% (95% CI: 14.4%, 26.8%)	35.6 (95% CI: 4.9, 256.5)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Tremor	25.3% (95% CI: 18.7%, 31.9%)	43.5 (95% CI: 6.1, 312.0)
Confusional state	21.1% (95% CI: 14.4%, 27.9%)	9.9 (95% CI: 3.6, 27.0)
[redacted]	[redacted]	[redacted]

*Calculated by adding 0.5 to the SoC arm due to zero events.

7.3.3 Discontinuation

[redacted]

Table 26: Discontinuation results. All-cause discontinuation in the FAS population and discontinuation due to AEs in the safety population. Source: data on file (21).

	Axi-cel (N=180)	SoC (N=179)
All-cause discontinuation in the subjects who received axi-cel or SoC	[redacted]	[redacted]
All-cause discontinuation in the subjects who did not receive axi-cel or SoC	[redacted]	[redacted]
Discontinuation due to AEs	[redacted]	[redacted]

*95% CI calculated with Clopper-Pearson's exact method.**Upper limit of confidence interval calculated by dividing 3 with n (3/n), as suggested by the Cochrane handbook (version 5.1.0 (73)).

Table 27: Absolute and relative differences in discontinuation between the axi-cel group and the SoC group (safety population)

	Absolute differences	Relative differences
All-cause discontinuation in the subjects who received axi-cel or SoC	[redacted]	[redacted]
All-cause discontinuation in the subjects who did not receive axi-cel or SoC	[redacted]	[redacted]
Discontinuation due to AEs	[redacted]	[redacted]

*Calculated by adding 0.5 to axi-cel due to zero events.

8. Health economic analysis

The health economic analysis conducted in the present application is a cost-utility analysis. The purpose of the health economic analysis was to estimate the cost-effectiveness of treating adult patients with r/r DLBCL who are intended for ASCT (referred to as transplant-intended throughout this application) with axi-cel versus SoC. The analysis was based on a global CU model adjusted to a Danish setting. The global model was designed to accommodate as much of the available evidence as possible and accurately reflect the condition of DLBCL patients with r/r within 12 months.

8.1 Model

The health economic model is a three-state partitioned survival model estimating the costs and QALYs of treating transplant-intended adult DLBCL patients who have refractory disease or have relapsed within 12 months from 1L chemo-immunotherapy with axi-cel compared to SoC. The model also estimates the incremental cost-effectiveness ratio (ICER). A budget impact model is also included, and both models have been developed in Excel.

A Danish clinical expert in DLBCL was consulted in the preparation of this application. The Danish clinical expert validated country-specific inputs in the model to ensure alignment with Danish clinical practice. In addition, all applied extrapolations were validated by clinical experts on an international advisory board. The health economic model was reviewed and quality checked by an in-house team member experienced in model quality assurance who was not directly involved in the development of the model.

8.1.1 Model structure

The model consists of three mutually exclusive health states: event-free, post-event and death. Figure 11 illustrates the model structure.

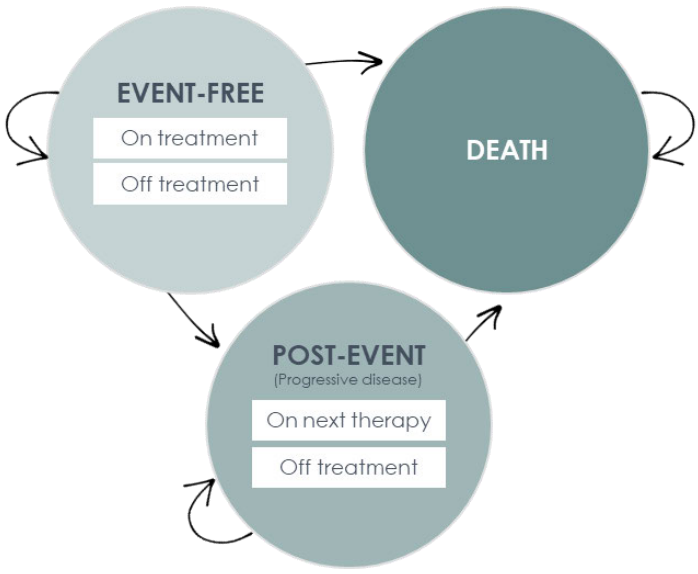

Figure 11: Model structure

8.1.2 Patient flow in the model

The patient cohort enters the model in the event-free health state. After each model cycle, patients can either stay in the same state, have an event and therefore proceed to the post-event state, or they can die. Once a patient reaches the post-event health state, they can stay in that state or die, but they cannot transition back to the event-free health state.

In the model, an event is defined as either disease progression, initiation of the next line of therapy or death. However, patients do not need to have disease progression to receive the next line of treatment. If patients have SD as best response from 2L therapy, they are moved to the next line of treatment, given the severe nature of the condition.

The proportion of the cohort remaining in the event-free health state over time is derived directly from the extrapolated EFS curves (see section 8.3.2). State membership for the death health state is calculated as 1 minus the OS curve, and state membership for the post-event health state is calculated as the difference between the OS curve and the EFS curve (the proportion of patients who are still alive but are no longer event-free). The post-event subsequent therapy is determined by the TTNT curve. This is illustrated in Figure 12. It should be noted that Figure 12 is purely illustrative and not based on any efficacy data reported elsewhere in this document.

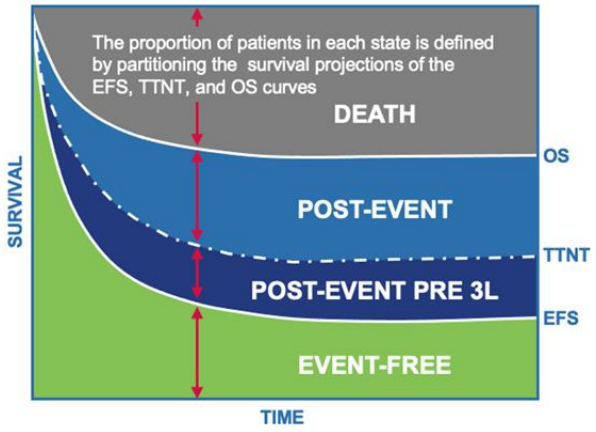

Figure 12: Implementation method of the partitioned survival model, estimating health state occupancy through the disaggregation of sequential event curves

Note: The figure is purely illustrative and is not based on any efficacy data reported elsewhere in this document.

The choice to capture EFS in the model structure rather than PFS was driven by two factors. First, EFS is the primary endpoint of the ZUMA-7 trial informing the model and the endpoint for which the trial is powered. Second, EFS as primary endpoint is considered clinically valid, and an EFS event is associated with decrements in QoL and therefore appropriate for use in the modelling. Compared to OS and PFS, EFS has the added value of capturing the burden of disease because treatment failure, PR or relapse signify a reduced QoL and substantial morbidity or mortality associated with disease progression, use of toxic salvage therapies or both (75). For patients achieving a durable CR, EFS captures the clinical relevance of delaying or preventing relapse, which is known to increase the likelihood of long-term survival or cure. EFS therefore enables a holistic evaluation of disease-related outcomes of a treatment that may fail to achieve statistical significance on OS (75).

Furthermore, due to the severe nature of DLBCL, it is common practice to move patients to the next line of therapy if their best response is SD. In discussions with clinicians in the development phase of the model, the clinicians believed

that QoL for patients with SD may be as poor as for patients with PD in this setting, as both SD and PD patients initiate yet another treatment pathway with similar challenges, expectations and health effects. In addition, the Danish clinical expert who was consulted during the preparation of the present health economic analysis informed that due to the aggressiveness of DLBCL, SD as best response is not satisfactory, and in that situation, treatment should be changed. Thus, from a clinical perspective, it makes sense to use EFS rather than PFS.

8.1.3 Applied perspective

In the base case, a restricted societal perspective was applied in accordance with the DMC guidelines (76). This means that all relevant hospital-related costs, costs covered by public health services, treatment-related costs incurred by the patient, municipal costs, costs related to patient time and transport costs were considered in the analysis. Indirect costs, such as productivity loss, were not included. The health effects for patients were estimated based on the expected lifetime of patients and HRQoL.

8.1.4 Time horizon

In the base case, the health economic model applied a lifetime time horizon, which was set to 50 years. This time horizon was deemed acceptable as the mean age of patients in the ZUMA-7 trial was 57.2 years, i.e., patients in the model had a mean age of 57.2 years in cycle 0. Scenario analyses were conducted with shorter time horizons.

8.1.5 Cycle length and half-cycle correction

The model has a cycle length of one month (365.25 days/12 months = 30.44 days per month), which was deemed a sufficient length of time to account for changes in EFS and OS. The monthly cycle length allows for ease of interpretation of model engine outputs, and it also enables accurate modelling of outcomes without impairing computational efficiency by having many cycles in the model engines. The cycle length allows alignment with chemotherapy treatment regimens, which are applied in cycles measured in weeks.

Since endpoints from ZUMA-7 are included based on the observation of patients at the end of each month, half-cycle correction was used.

8.1.6 Discounting

Both costs and QALYs were discounted at a rate of 3.5% starting from year one, in line with the Danish Ministry of Finance (77) and DMC guidelines (76). In the model, the discount was applied per year. By default, the discount rates were not varied in the PSA. For the purposes of calculating life years in each health state, the undiscounted values were used. In the fully incremental results, discounted life years were considered.

8.1.7 General mortality

Survival estimates were corrected for all-cause mortality in the Danish general population. This ensures that the rate of death observed in the model for patients with r/r DLBCL (regardless of response or long-term response) will not drop below that expected in the general Danish population. The most recent National Life Tables for Denmark (78) were sourced and matched to the ZUMA-7 trial population based on age and gender. This is to ensure that the extrapolated OS better matches expected long-term mortality rates due to causes other than R/R DLBCL.

Evidence shows that long-term survivors with DLBCL who do not relapse within five years have a long-term survival similar to that of the general population, with a standardised mortality ratio (SMR) of 0.99 (95% CI: 0.88 to 1.10, not statistically different) (79). However, a previous analysis in DLBCL reported that the SMR for patients who were event-free at 24 months in American and French cohorts showed a trend for a higher mortality rate than the age- and

gender-matched general population (US SMR: 1.18, 95% CI: 0.89 to 1.57 P= 0.25; French SMR: 1.09, 95% CI: 0.69 to 1.74 P=0.71) (80). This suggests that long-term survivors may have a slightly higher mortality than the general population. [redacted]

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

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

In Table 28, we present input data on clinical efficacy, adverse reactions and health state utility values (HSUVs) applied in the model and describe how these input data were obtained.

Table 28: Input data used in the model

Name of estimates*	Results from ZUMA-7	Input value used in the model	How is the input value obtained/estimated?
EFS	HR: 0.40 (95% CI: 0.31, 0.51). Relative difference from ZUMA-7 (63)	Axi-cel: Gompertz extrapolation as favoured by the Danish clinical expert. SoC: Exponential extrapolation as best statistical fit from clinical plausible curves.	Extrapolated ZUMA-7 data
OS	HR: 0.71 (95% CI: 0.52, 0.97). Relative difference from ZUMA-7 (63)	Axi-cel: Gamma extrapolation as favoured by the Danish clinical expert. SoC: Treatment switching adjusted curve (HR: 2.40, the reciprocal of the 0.416 HR, see Table 38)	Extrapolated ZUMA-7 data
TTNT	[redacted] Relative difference from ZUMA-7 (63)	Axi-cel: Loglogistic extrapolation, which was the best statistical fit of the clinically plausible curves. SoC: Gamma extrapolation which was best statistical fit of the clinical plausible curves.	Extrapolated ZUMA-7 data
Adverse reactions (measured in costs)	NA	CRS: 52,166 Neurologic events: 26,440 Hypoxia: 52,166	Based on DRG 2022 tariffs

<table>
<tr><th>Name of estimates*</th><th>Results from ZUMA-7</th><th>Input value used in the model</th><th>How is the input value obtained/estimated?</th></tr>
<tr><td>Adverse reactions (measured as occurrence)</td><td>The following AEs from ZUMA-7 were included in the model (63). Only Grade 3+ AEs were included, and only AEs that required treatment were included.
<table><tr><th></th><th>Axi-cel</th><th>SoC</th></tr><tr><td>CRS</td><td>11 (6%)</td><td>0%</td></tr><tr><td>Neurologic events</td><td>36 (21%)</td><td>1 (1%)</td></tr><tr><td>Hypoxia</td><td>16 (9%)</td><td>7 (4%)</td></tr></table>Occurrence of AEs are based on data from the safety population in ZUMA-7.</td><td>The treatment requiring AEs with ≥5 percentage points of difference between axi-cel and SoC. Risk of AEs:
<table><tr><th></th><th>Axi-cel</th><th>SoC</th></tr><tr><td>CRS</td><td>11 (6%)</td><td>0%</td></tr><tr><td>Neurologic events</td><td>36 (21%)</td><td>1 (1%)</td></tr><tr><td>Hypoxia</td><td>16 (9%)</td><td>7 (4%)</td></tr></table></td><td>AEs from ZUMA-7 were validated by the clinical expert who informed which AEs would be treatment-requiring and cost-triggering.</td></tr>
<tr><td>Adverse reactions (measured as utility loss)</td><td>Disutilities for AEs are assumed to be captured in the on-treatment HRQoL measurement in the ZUMA-7 trial.</td><td>Disutilities for AEs were assumed to be captured by the HRQoL measurement; therefore, no additional disutility was used.</td><td>NA</td></tr>
<tr><td>Axi-cel, on-treatment utility</td><td rowspan="3">In the ZUMA-7 QoL analysis set, there was a statistically significant and clinically meaningful difference in mean change of scores for the EQ-5D-5L VAS from screening in favour of axi-cel at day 100 (13.7, 95% CI: 8.5, 18.8, adjusted p-value < 0.0001) and day 150 (11.3, 95% CI: 5.4, 17.1, adjusted p-value = 0.0004) (82).</td><td>0.848 (SE: 0.016)</td><td>ZUMA-7 data and Danish weights</td></tr>
<tr><td>SoC, on-treatment utility</td><td>0.841 (SE: 0.017)</td><td>ZUMA-7 data and Danish weights</td></tr>
<tr><td>Event-free, off-treatment utility</td><td>0.858 (0.011)</td><td>ZUMA-7 data and Danish weights</td></tr>
</table>

Name of estimates*	Results from ZUMA-7	Input value used in the model	How is the input value obtained/estimated?
Post-event utility	The pre-progression utility from ZUMA-1 (3L treatment) was assumed to reflect the post-event state in ZUMA-7 (2L treatment) (83). The EQ-5D-5L data from ZUMA-1 was indexed with the Danish preference weights from Jensen et al. 2021 (91). In ZUMA-7, it was not mandated to collect post-event utilities, resulting in too few observations to inform the post-event state.	0.788 (0.039)	Estimated based on ZUMA-1 data and Danish weights.

*Some of these estimates will be presented in other tables in the document. This table is a summary.

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

8.2.2.1 Patient population

The Danish patient population

The clinical expert was consulted on the characteristics of the Danish patient population within the expected EMA indication. The Danish expert informed that the median age at relapse in Danish patients is 69 years with a share of 67% being ≥65 years old. Additionally, among Danish patients, 40% have primary refractory disease, and 97% relapse ≤12 months after the initiation or completion of 1L therapy. The majority of Danish relapsed patients are men (62%). Moreover, the Danish clinical expert informed that in Denmark, high-dose treatment is not provided to patients above the age of 70 years.

Patient population in the clinical documentation submitted

The characteristics of the patient population in the ZUMA-7 trial are presented in Appendix C. As seen in Appendix C, the total patient population in the ZUMA-7 trial had a median age of 59 years with a share of 30% being ≥65 years old and a slight overweight of male participants (66%) (63). 74% of the patient population in ZUMA-7 had primary refractory disease, and 26% had relapse at ≤12 months after the initiation or completion of 1L therapy.

Patient population in the health economic analysis submitted

The population in the model has been parameterised with information that is important to survival and/or costs. While most baseline characteristics have not been directly modelled, age and gender distributions from ZUMA-7 have been included to determine the influence of background mortality. This includes age, gender distribution, body surface area (BSA), body weight and country-specific background mortality rates.

The patient population in the model was based on the ZUMA-7 trial. According to the Danish clinical expert, the median age and the share of patients above 65 are higher in Denmark compared to the population in ZUMA-7. The proportion of patients in ZUMA-7 that were primary refractory is higher than what would typically be observed in Denmark. On the contrary, the proportion of patients who relapse ≤12 months after the initiation or completion of 1L therapy are expectedly higher in Denmark than in ZUMA-7. Table 29 summarises characteristics of the patient population from ZUMA-7, the model and Danish clinical practice.

Table 29: Patient population

Patient population Important baseline characteristics	Clinical documentation (ZUMA-7)	Used in the model (based on ZUMA-7)	Danish clinical practice
Female	34.0%	34.0%	38.0%
Mean age (years)	57.2	57.2	Not stated
Mean bodyweight (kg)	84.26 (SD: 22.01)	84.3	Not stated
Mean height (cm)	172.43 (SD: 10.05)	172.4	Not stated
Mean BSA (m^2)	Not reported	1.97	Not stated

8.2.2.2 Intervention

The intervention in the health economic analysis is the CAR T-cell therapy axi-cel. Axi-cel is a recombinant receptor which, when present on the host's T-cells, causes the T-cells to target specific cell surface antigens. Eligible patients undergo leukapheresis to obtain peripheral blood mononuclear cells for CAR T-cell production. Whilst waiting for manufacturing and infusion of the T-cells, patients with high disease burden will receive bridging therapy. After manufacturing of the T-cells, patients receive conditioning chemotherapy consisting of intravenous fludarabine (30 mg/m^2 BSA per day) and cyclophosphamide (500 mg/m^2 BSA per day) on days −5, −4, and −3, before receiving a single intravenous infusion of axi-cel on day 0 at a target dose of 2×10^6 CAR T-cells per kg of bodyweight.

Table 30: Intervention

Intervention	Clinical documentation (63)	Used in the model	Expected Danish clinical practice
Posology	Stem cell harvest for three to four hours to obtain peripheral blood mononuclear cells for CAR T-cell production. Optional bridging therapy was limited to glucocorticoids only. Conditioning therapy with cyclophosphamide (at a dose of 500 mg per square metre of body-surface area per day) and fludarabine (30 mg per square metre per day) at −5,	Stem cell harvest for three to four hours to obtain peripheral blood mononuclear cells for CAR T-cell production. Optional bridging therapy was limited to dexamethasone only. Conditioning therapy with cyclophosphamide (at a dose of 500 mg per square metre of body-surface area per day) and fludarabine (30 mg per	Stem cell harvest for three to four hours to obtain peripheral blood mononuclear cells for CAR T-cell production. Since axi-cel is not currently recommended in Denmark, no standard practice for bridging therapy has been established. Conditioning therapy with cyclophosphamide (at a dose of 500 mg per square metre of body-surface area per day)

<table>
<tr><th>Intervention</th><th>Clinical documentation (63)</th><th>Used in the model</th><th>Expected Danish clinical practice</th></tr>
<tr><td></td><td>–4, and –3 days before receiving a single infusion of axi-cel (target dose, 2×106 CAR T-cells per kg of body weight).
Axi-cel was administered as a single intravenous infusion on day 0 at a target dose of 2 × 10^6 CAR T-cells per kg of bodyweight.</td><td>square metre per day) at –5, –4, and –3 days before receiving a single infusion of axi-cel (target dose, 2×106 CAR T-cells per kg of body weight). Optional bridging therapy was limited to glucocorticoids only. Axi-cel was administered as a single intravenous infusion on day 0 at a target dose of 2 × 10^6 CAR T-cells per kg of bodyweight.</td><td>and fludarabine (30 mg per square metre per day) at –5, –4, and –3 days before receiving a single infusion of axi-cel (target dose, 2×106 CAR T-cells per kg of body weight). Axi-cel should be administered as a single intravenous infusion on day 0 at a target dose of 2 × 10^6 CAR T-cells per kg of bodyweight.</td></tr>
<tr><td>Criteria for discontinuation</td><td>Unable to receive an infusion of axi-cel due to experiencing an AE while receiving bridging therapy or conditioning chemotherapy, progression or death.</td><td>Unable to receive an infusion of axi-cel due to experiencing an AE while receiving bridging therapy or conditioning chemotherapy, progression or death.</td><td>Unable to receive an infusion of axi-cel due to experiencing an AE while receiving bridging therapy or conditioning chemotherapy, progression or death.</td></tr>
<tr><td>The pharmaceutical's position in Danish clinical practice</td><td>2L</td><td>2L</td><td>2L</td></tr>
<tr><td>Subsequent treatment basket</td><td>The following is based on the safety population from ZUMA-7.
<table><tr><th></th><th>% of patients</th><th># of cycles</th></tr><tr><td>Chemotherapy</td><td>97%</td><td>3</td></tr><tr><td>Nivolumab</td><td>16%</td><td>2</td></tr><tr><td>Pembrolizumab</td><td>7%</td><td>5</td></tr><tr><td>Pola-BR</td><td>17%</td><td>6</td></tr><tr><td>R-Lenalidomide</td><td>9%</td><td>4</td></tr><tr><td>R-benda</td><td>0%</td><td>-</td></tr><tr><td>Prednisone</td><td>0%</td><td>-</td></tr><tr><td>Radiotherapy</td><td>29%</td><td>-</td></tr><tr><td>Palliative radiation</td><td>0%</td><td>-</td></tr><tr><td>Allogenic SCT</td><td>11%</td><td>-</td></tr><tr><td>CAR T-cell therapy</td><td>0%</td><td>-</td></tr><tr><td>ASCT</td><td>16%</td><td>-</td></tr></table></td><td>In the model, we applied the subsequent therapies and number of cycles informed by the consulted clinical expert.
<table><tr><th></th><th>% of patients</th><th># of cycles</th></tr><tr><td>Chemotherapy</td><td>89%</td><td>4.5</td></tr><tr><td>Nivolumab</td><td>3%</td><td>4.5</td></tr><tr><td>Pembrolizumab</td><td>3%</td><td>4.5</td></tr><tr><td>Pola-BR</td><td>0%</td><td>-</td></tr><tr><td>R-Lenalidomide</td><td>0%</td><td>-</td></tr><tr><td>R-benda</td><td>0%</td><td>-</td></tr><tr><td>Prednisone</td><td>0%</td><td>-</td></tr><tr><td>Radiotherapy</td><td>27%</td><td>4.5</td></tr><tr><td>Palliative radiation</td><td>0%</td><td>-</td></tr><tr><td>Allogeneic SCT</td><td>0%</td><td>-</td></tr><tr><td>CAR T-cell therapy</td><td>0%</td><td>-</td></tr><tr><td>ASCT</td><td>5%</td><td>-</td></tr></table></td><td>The clinical expert was consulted in terms of which subsequent therapies patients who have been treated with axi-cel would receive. Please see the table below.</td></tr>
</table>

Intervention	Clinical documentation (63)	Used in the model	Expected Danish clinical practice

	% of patients	# of cycles
Chemotherapy	89%	4.5
Nivolumab	3%	4.5
Pembrolizumab	3%	4.5
Pola-BR	0%	-
R-Lenalidomide	0%	-
R-benda	0%	-
Prednisone	0%	-
Radiotherapy	27%	4.5
Palliative radiation	0%	-
Allogenic SCT	0%	-
CAR T-cell therapy	0%	-
ASCT	5%	-

8.2.2.3 Comparators

The comparator arm comprises a basket of treatments representing SoC for transplant-intended r/r DLBCL patients in Denmark followed by ASCT in responders. In ZUMA-7, SoC comprised the salvage chemotherapy regimens R-ICE, R-GDP, R-ESHAP and R-DHAP/R-DHAX. According to the Danish clinical expert, R-ESHAP is traditionally not used in Denmark, and R-GDP is used in patients who are not transplant-intended, i.e., not for transplant-intended patients. Thus, to reflect Danish clinical practice, the comparator arm in the model consists of 67% R-ICE and 33% R-DHAP followed by high-dose (chemo)therapy (HDT) (e.g., BEAM) and ASCT in responders. The comparator is summarised in Table 31.

The model is flexible and allows the user to adjust the dosing and administration of salvage chemotherapies and HDT to accommodate local treatment practices, but the efficacy of the SoC is assumed to be comparable to that observed in the SoC arm of the ZUMA-7 trial.

Table 31: Comparator

Comparator	Clinical documentation (63)	Used in the model (based on input from Danish clinical expert)	Expected Danish clinical practice (based on input from Danish clinical expert)
Posology	Two or three cycles of protocol-defined, investigator-selected, platinum-based chemoimmunotherapy. Patients who had a complete or partial response proceeded to high-dose chemotherapy with	Based on input from the clinical expert, 67% receive R-ICE in the model, which comprises rituximab, ifosfamide, carboplatin and etoposide. R-ICE is administered over the first three days of the cycle.	R-ICE comprises the four treatments rituximab, ifosfamide, carboplatin and etoposide. R-ICE is administered over the first three days of the cycle.

<table>
<tr><th>Comparator</th><th>Clinical documentation (63)</th><th>Used in the model (based on input from Danish clinical expert)</th><th>Expected Danish clinical practice (based on input from Danish clinical expert)</th></tr>
<tr><td></td><td>autologous stem cell transplantation.
Although crossover between the treatment groups was not planned, patients who did not have a response to standard care could receive cellular immunotherapy outside the protocol (treatment switching).
41.3% completed stem cell harvest, 35.8% received HDT (BEAM) and 34.6% received the stem cell infusion.</td><td>33 % receive R-DHAP in the model, which comprises rituximab, dexamethasone, cytarabine and cisplatin. R-DHAP is administered over the first four days of the cycle.
A cycle comprises 21 days and patients receive 2.73 cycles of both R-ICE and R-DHAP.
Following R-ICE and R-DHAP, patients undergo stem cell harvest before HDT (BEAM) is administered. BEAM comprises carmustine, etoposide, cytarabine and melphalan. Following BEAM, the stem cells are re-infused.
In accordance with ZUMA-7, in the model, 41.3% complete stem cell harvest, 35.8% receive HDT (BEAM) and 34.6% receive the stem cell infusion.</td><td>R-DHAP comprises the treatments rituximab, dexamethasone, cytarabine and cisplatin. R-DHAP is administered over the first four days of the cycle.
For R-ICE and R-DHAP, a cycle comprises 21 days and patients receive 2-3 cycles depending on observed effectiveness.
Following R-ICE and R-DHAP, patients undergo stem cell harvest and HDT (BEAM) is administered. BEAM comprises carmustine, etoposide, cytarabine and melphalan. BEAM is administered approximately one week before stem cell transplant. Following BEAM, the stem cells are given to the patients.
According to the clinical expert, 72.5% complete stem cell harvest, 62.5% receive HDT (BEAM) and 62.5% receive the stem cell infusion due to the lower age of the treated population in Denmark.</td></tr>
<tr><td>The comparator's position in the Danish clinical practice</td><td>2L</td><td>2L</td><td>2L</td></tr>
<tr><td>Subsequent treatment basket</td><td>The following is based on the safety population from ZUMA-7.
<table>
<tr><th></th><th>% of patients</th><th># of cycles</th></tr>
<tr><td>Chemotherapy</td><td>23%</td><td>3</td></tr>
<tr><td>Nivolumab</td><td>3%</td><td>2</td></tr>
<tr><td>Pembrolizumab</td><td>4%</td><td>5</td></tr>
<tr><td>Pola-BR</td><td>15%</td><td>6</td></tr>
<tr><td>R-Lenalidomide</td><td>6%</td><td>4</td></tr>
<tr><td>R-benda</td><td>0%</td><td>-</td></tr>
<tr><td>Prednisone</td><td>0%</td><td>-</td></tr>
</table></td><td>In the model, we applied the subsequent therapies and number of cycles informed by the consulted clinical expert.
<table>
<tr><th></th><th>% of patients</th><th># of cycles</th></tr>
<tr><td>Chemotherapy</td><td>0%</td><td>-</td></tr>
<tr><td>Nivolumab</td><td>3%</td><td>4.5</td></tr>
<tr><td>Pembrolizumab</td><td>3%</td><td>4.5</td></tr>
<tr><td>Pola-BR</td><td>0%</td><td>-</td></tr>
<tr><td>R-Lenalidomide</td><td>10%</td><td>4.5</td></tr>
</table></td><td>The clinical expert was consulted in terms of which subsequent therapies patients who have been treated with SoC would receive. Please see the table below.
<table>
<tr><th></th><th>% of patients</th><th># of cycles</th></tr>
<tr><td>Chemotherapy</td><td>0%</td><td>-</td></tr>
<tr><td>Nivolumab</td><td>3%</td><td>4.5</td></tr>
<tr><td>Pembrolizumab</td><td>3%</td><td>4.5</td></tr>
</table></td></tr>
</table>

Comparator	Clinical documentation (63)			Used in the model (based on input from Danish clinical expert)			Expected Danish clinical practice (based on input from Danish clinical expert)		
	Radiotherapy	28%	-	R-benda	10%	4.5	Pola-BR	0%	-
	Palliative radiation	0%	-	Prednisone	35%	4.5	R-Lenalidomide	10%	4.5
	allogenic SCT	5%	-	Radiotherapy	0%	-	R-benda	10%	4.5
	CAR T-cell therapy	81%	-	Palliative radiation	20%	4.5	Prednisone	35%	4.5
	ASCT	5%	-	allogenic SCT	5%	-	Radiotherapy	0%	-
				CAR T-cell therapy	0%	-	Palliative radiation	20%	4.5
				ASCT	0%	-	allogenic SCT	5%	-
							CAR T-cell therapy	0%	-
							ASCT	0%	-

By only including R-ICE and R-DHAP in the model, the posology of the comparator used in the model differs slightly from the comparator used in the ZUMA-7 trial to better represent Danish practice as informed by the clinical expert. Additionally, the subsequent treatment option of CAR T-cell therapy following SoC used in the ZUMA-7 trial does not reflect Danish clinical practice where CAR T-cell therapy is not recommended as subsequent therapy after ASCT. If axi-cel has a beneficial effect on OS, the standard OS analysis will underestimate the OS benefit of axi-cel compared to SoC in the absence of switching (i.e., when CAR T-cell therapy is not available in subsequent lines). To accommodate for this difference in subsequent treatment options, the model includes a treatment switching-adjusted HR in terms of OS in the SoC arm.

As presented in Table 31, the clinical expert stated that 70-75% of the transplant-intended patients receive a stem cell harvest in Denmark, around 60-65% of patients receive HDT and infusion of stem cells in Denmark. This is higher than the observed numbers in the ZUMA-7 trial, where only 41.3% of patients in the SoC arm received stem cell harvest, 35.8% received HDT and 34.6% received the stem cell infusion. To secure that the efficacy estimates correlated with the percentages who had received ASCT in the SoC arm, the values from ZUMA-7 were applied. It should also be noted that the higher percentages of patients receiving stem cell harvest, HDT and ASCT in Denmark compared to ZUMA-7 can be explained by the fact that the transplant-intended patient population is younger in Denmark than in the trial. According to the clinical expert, only patients below 70 years old are transplant-intended in Denmark.

8.2.2.4 Relative efficacy outcomes

Relative efficacy results on OS, EFS and TTNT were obtained from ZUMA-7 (please see section 7.2). To extrapolate the results beyond the observation period in ZUMA-7 (24 months), the model includes extrapolation of OS, EFS and TTNT. Extrapolations have been discussed with the Danish clinical expert to identify the situation that best corresponds to Danish clinical practice. Relative efficacy outcomes applied in the model are presented in Table 32. OS, EFS and TTNT all serve as endpoints of interest in Danish clinical practice for cancer treatment.

Table 32: Summary of text regarding *value*

Clinical efficacy outcome	Clinical documentation	Used in the model (value)

EFS	Results from the ZUMA-7 trial on EFS is presented in Table 6 and Table 7, and a Kaplan Meier curve is presented in Figure 3. The relative difference in EFS between the axi-cel arm and the SoC arm was HR 0.40.	Axi-cel: Gompertz function SoC: Exponential function
OS	Results from the ZUMA-7 trial on OS is presented in Table 8 and Table 9, and a Kaplan Meier curve is presented in Figure 4. The relative difference in OS between the axi-cel arm and the SoC arm was HR 0.71.	Axi-cel: Gamma function SoC: Treatment switching-adjusted curve (HR: 2.40, the reciprocal of the 0.416 HR, see Table 38)
TTNT	Results from the ZUMA-7 trial on TTNT is presented in Table 16 and Table 17, and a Kaplan Meier curve is presented in Figure 8. The relative difference in EFS between the axi-cel arm and the SoC arm was [redacted]	Axi-cel: Loglogistic function SoC: Gamma function

Table 33: Summary of text regarding *relevance*

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
EFS	Data from the FAS population was used to estimate the EFS. The clinical expert informed that the Gompertz curve best resembled Danish clinical practice for axi-cel. For the SoC curves, all extrapolations were likely according to the expert, which is why the best statistical fit was used.	EFS serves as a key endpoint of interest in Danish clinical practice.	N/A
OS	Data from the FAS population was used to estimate the EFS. The clinical expert informed that the gamma curve best resembled Danish clinical practice for axi-cel. To	OS is a critical outcome for demonstrating efficacy in cancer studies and serves as a key endpoint of interest in Danish clinical practice.	N/A

Clinical efficacy outcome	Clinical documentation (measurement method)	Relevance of outcome for Danish clinical practice	Relevance of measurement method for Danish clinical practice
	account for the absent use of CAR T-cell therapies in subsequent lines in Danish clinical practice, the treatment switching-adjusted curve was used for SoC.		
TTNT	Data from the FAS population was used to estimate the EFS. The loglogistic and gamma curves were best statistical fit of the clinical plausible curves for axi-cel and SoC, respectively.	TTNT serves as a key endpoint of interest in Danish clinical practice.	N/A

8.2.2.5 Adverse reaction outcomes

AEs were included in the model based on the AEs observed in ZUMA-7 (63). The severe (Grade 3+) AEs observed in the ZUMA-7 trial are presented in Table 34. Treatment-requiring severe AEs were included in the model if they had a meaningful impact on costs and there was a difference of 5 percentage points between the axi-cel and the SoC arm.

The Danish clinical expert was consulted on which of the severe AEs from ZUMA-7 presented in Table 34 that require treatment in Denmark and how these AEs are typically managed. According to the clinical expert, the severe AEs that will require treatment and trigger additional costs are CRS, neurologic events and hypoxia. The AEs that do not require additional treatment are thrombocytopenia, B-Cell aplasia, pyrexia, hypotension, febrile neutropaenia, encephalopathy, hyponatraemia, neutropaenia, anaemia, hypophosphataemia and aphasia.

Table 34: Grade ≥3 AEs observed in the ZUMA-7 trial (safety analysis set) and the AEs included in the model. Source: Locke et al. 2021 (63).

	Clinical documentation		Used in the model (numerical value)	
	Axi-cel (N=170)	SoC (N=168)	Axi-cel (N=170)	SoC (N=168)
Pyrexia, n (%)	15 (9)	1 (1)		
Neutropaenia, n (%)†	118 (69)	69 (41)		
Hypotension, n (%)	19 (11)	5 (3)		
Fatigue, n (%)	11 (6)	4 (2)		

	Clinical documentation		Used in the model (numerical value)	
	Axi-cel (N=170)	SoC (N=168)	Axi-cel (N=170)	SoC (N=168)
Anaemia, n (%)	51 (30)	65 (39)		
Diarrhoea, n (%)	4 (2)	7 (4)		
Headache, n (%)	5 (3)	2 (1)		
Nausea, n (%)	3 (2)	9 (5)		
Sinus tachycardia, n (%)	3 (2)	1 (1)		
Leukopaenia, n (%)‡	50 (29)	37 (22)		
Thrombocytopaenia, n (%)§	25 (15)	95 (57)		
Chills, n (%)	1 (1)	0		
Hypokalaemia, n (%)	10 (6)	11 (7)		
Hypophosphatemia, n (%)	31 (18)	21 (12)		
Cough, n (%)	1 (1)	0		
Decreased appetite, n (%)	7 (4)	6 (4)		
Hypoxia, n (%)	16 (9)	7 (4)	9%	4%
Dizziness, n (%)	2 (1)	1 (1)		
Constipation, n (%)	0	0		
Vomiting, n (%)	0	1 (1)		
Febrile neutropaenia, n (%)	4 (2)	46 (27)		
Cytokine release syndrome, n (%)	11 (6)	0	6%	0
Neurologic event, n (%)	36 (21)	1 (1)	21%	1%

†Neutropaenia refers to the combined preferred terms of neutropaenia and neutrophil count decreased.

‡Leukopaenia refers to the combined preferred terms of leukopaenia and white cell count decreased.

§Thrombocytopenia refers to the combined preferred terms of thrombocytopaenia and platelet count decreased.

Other preferred terms that were reported in one or two patients in the SoC group included somnolence, agitation, hypoesthesia, lethargy, depressed level of consciousness, cognitive disorder, memory impairment, bradyphrenia, taste disorder, hallucination, visual hallucination, nystagmus, head discomfort, and neuralgia.

8.3 Extrapolation of relative efficacy

In the following section, we describe the extrapolations applied in the model. For additional information on extrapolations, please see Appendix G.

8.3.1 Time-to-event data – summarised

The clinical trial data from the ZUMA-7 trial was used to populate the survival inputs in the model. Long-term survival estimates have been derived from extrapolations of the EFS and OS time-to-event data from ZUMA-7 to populate the health states in the model. Both standard parametric models and mixture cure models (MCMs) were fitted to the individual patient-level time-to-event data from ZUMA-7. Spline models based on the algorithm by Royston and Parmar (84), where one-, two-, and three-knot restricted cubic splines models using hazard, odds and normal scales were explored. The process and methods for conducting survival extrapolations and selecting preferred fits followed the guidance of the NICE DSU TSD 14 for survival analysis (85), including the NICE Flexible Methods for Survival Analysis TSD 21 (86).

In the base case, MCMs were considered to account for the long-term remission observed in some patients with DLBCL. It is assumed in the MCMs that the observed survival in the trial population represents a mix of patients who are "cured" and "not cured", perceived as a plateau in a Kaplan Meier curve, which allows for a change in the hazards of death over time (87). The "cured" population has a slightly higher mortality than the general population (SMR: 1.09), and non-cured patients are subjected to an additional risk of excess mortality related to the disease (80). Please see Appendix G for additional information on the mixture cure modelling.

The decision in terms of the preferred extrapolation method considered both the best statistical fit and clinical plausibility. The goodness-of-fit criteria (including the Akaike information criterion (AIC) and the Bayesian information criteria (BIC)) were estimated for each survival function to determine statistical fit, along with a visual inspection compared to trial data (Kaplan Meier plots). This was followed by validation of long-term survival estimates based on feedback from the consulted Danish clinical expert to determine the clinical plausibility. Survival extrapolations for both treatment arms were also modelled using the same functions, as it was assumed that a 'cured' population would be observed at the end of the survival curve (as only cured populations would remain).

Cure-based models were the preferred models for extrapolation of the time-to-event data from the ZUMA-7 trial, as a recent study confirmed that cure-based models most accurately predicted long-term survival outcomes over spline and standard parametric models in the 3L DLBCL population treated with axi-cel using long-term data from ZUMA-1 (88). Table 35 provides an overview of the MCMs used to extrapolate data in the base case. Figure 13 shows the extrapolations used in the base case (adjusted for background mortality).

Table 35: Summary of MCM used to extrapolate data in the model

	Axi-cel	SoC
EFS	Gompertz	Exponential
OS	Gamma	Treatment switching-adjusted curve (HR 2.40, the reciprocal of the 0.416 HR, see Table 38)
TTNT	Loglogistic	Gamma

Abbreviations: Axi-cel: axicabtagene ciloleucel, SoC: Standard of care, EFS: Event-free survival, OS: Overall survival, TTNT: Time to next therapy, MCMs: mixture cure model, HR: Hazard ratio.

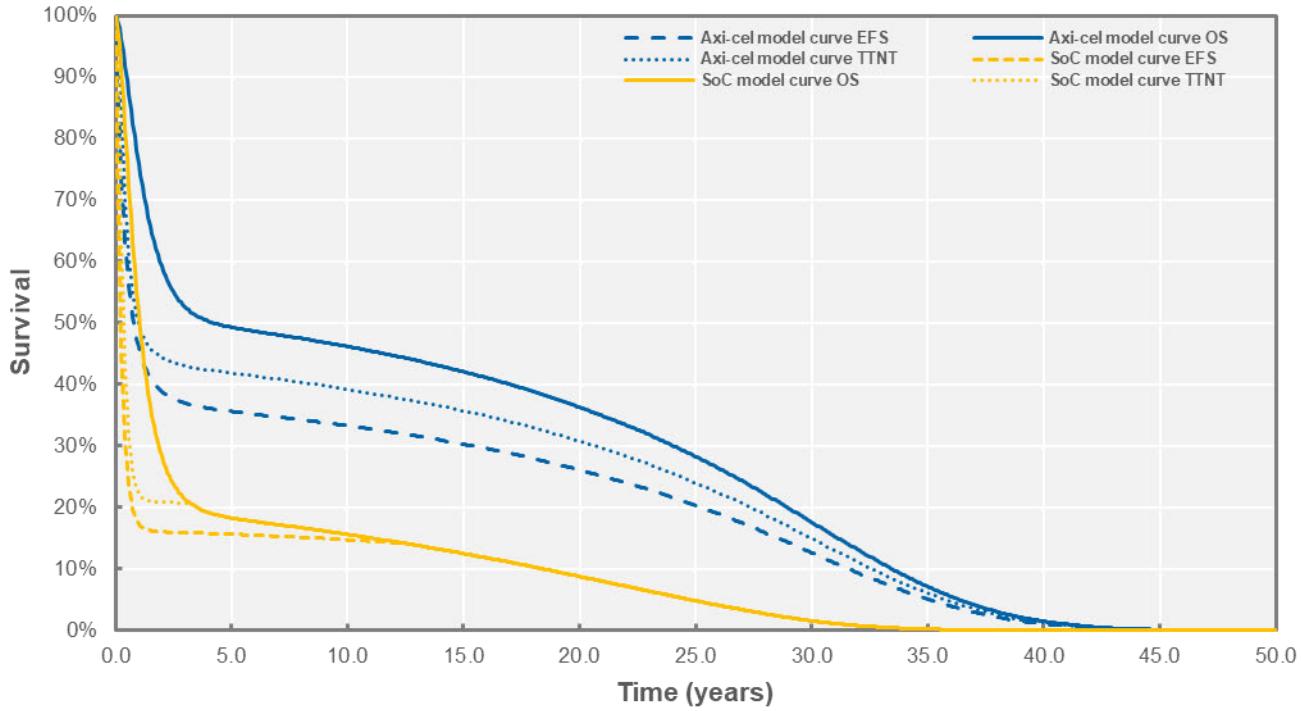

Figure 13: Overview of the extrapolations used in the base case

In the following, we describe the process of selecting the MCM with the best fit for the data. Information on the standard parametric models and spline models can be found in Appendix G.

8.3.2 Extrapolations of EFS

Kaplan Meier plots, Cox regression results and proportion of patients at risk at each time point for EFS from the ZUMA-7 trial are presented in Figure 14.

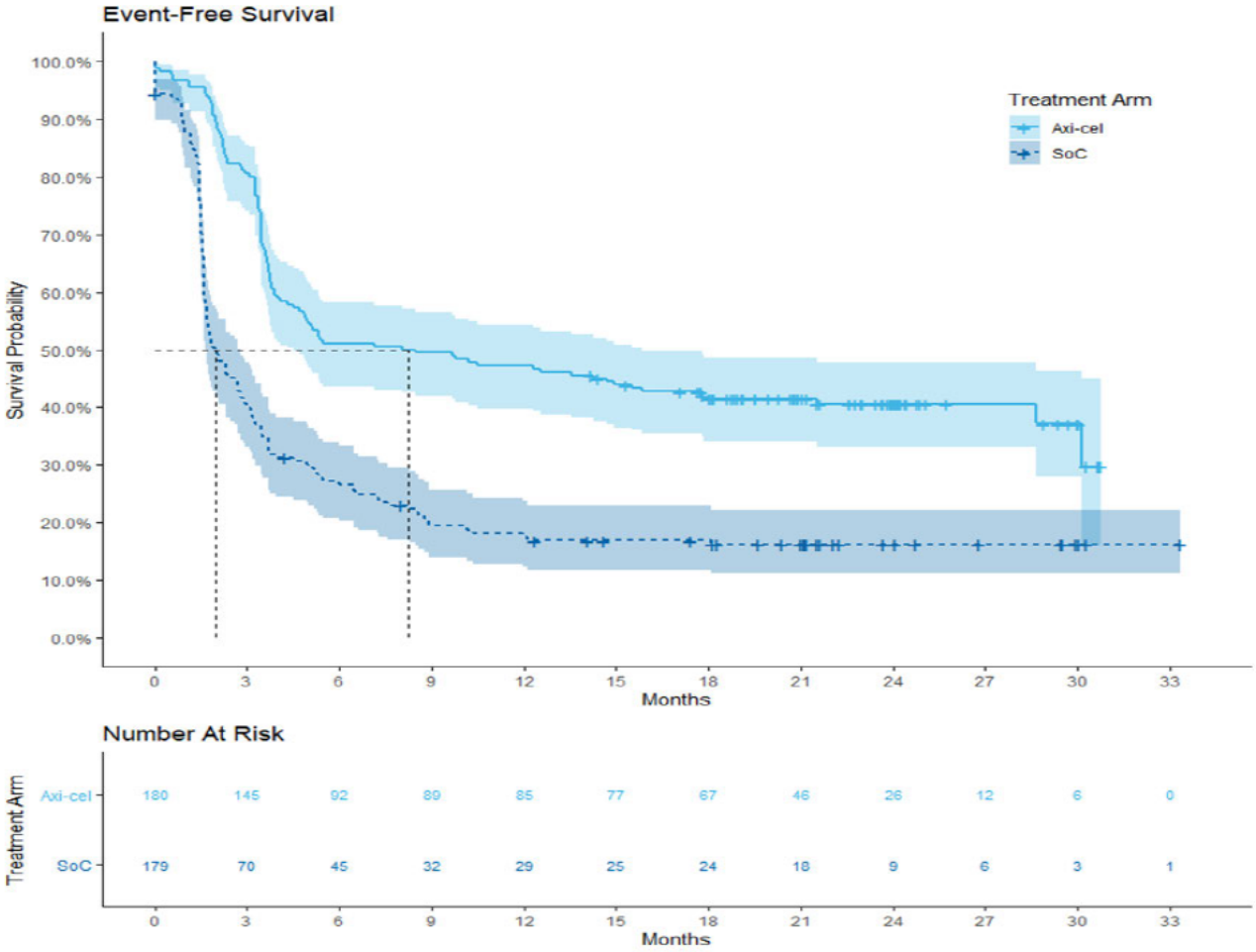

Figure 14: Kaplan Meier plots of EFS and the proportion of patients at risk at different time points

The seven MCMs were fitted to each arm of the ZUMA-7 trial data. The goodness-of-fit criteria for the MCMs are summarised in Table 36. The extrapolations of EFS using MCMs for up to 180 months are presented in Figure 15. The goodness-of-fit criteria and extrapolations with the standard parametric models can be found in Appendix G.

Table 36: Statistical goodness-of-fit for EFS extrapolations

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Mixture cure models				
Exponential	814.0	820.4	743.6	749.9
Weibull	814.7	824.3	744.4	754.0
Gompertz	814.1	823.7	745.6	755.1
Lognormal	816.5	826.1	780.9	790.4
Loglogistic	795.4	805.0	747.8	757.3

Gamma	812.3	821.9	744.3	753.9
Generalised gamma	809.9	822.7	746.3	759.1

Source: Survival_parameters sheet in model. The applied MCMs are highlighted.
Abbreviations: OS: overall survival, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

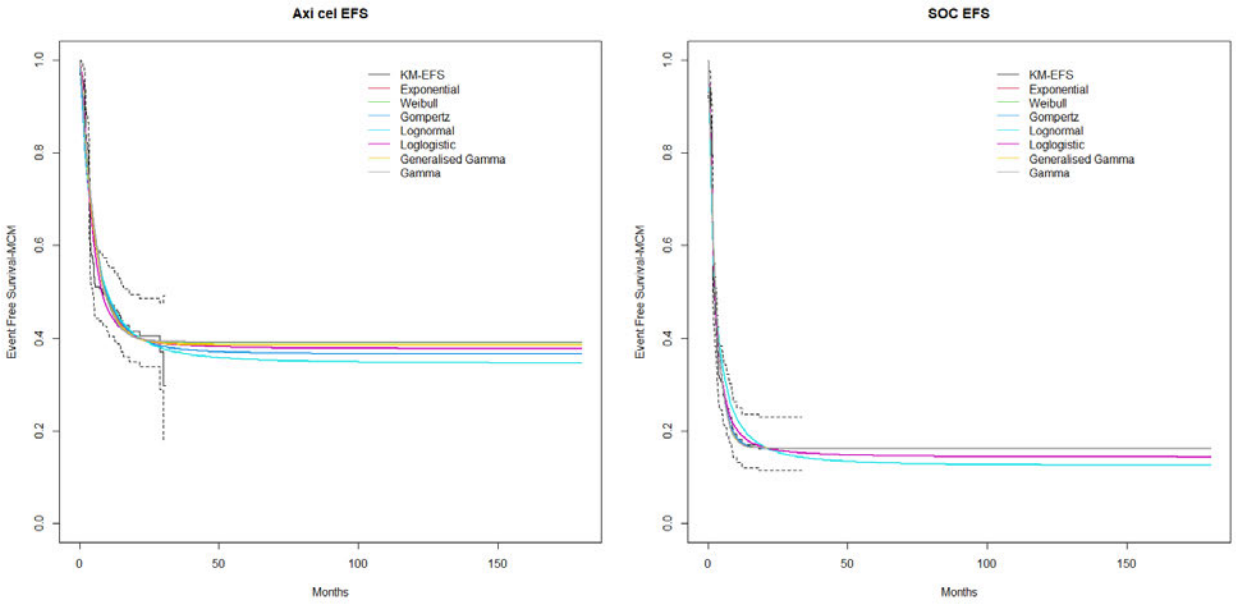

Figure 15: MCMs of partitioned survival: non-proportional hazards models of EFS for axi-cel and SoC

The MCMs were applied in the base case based on the rationale described in section 12.1. The clinical plausibility of the curves in Figure 15 was discussed with the consulted Danish clinical expert, who informed that for axi-cel, the most plausible curve was the Gompertz. For SoC, the clinical expert did not favour any specific curve, and the exponential curve was chosen based on the best statistical fit. Thus, the Gompertz and exponential models were applied to extrapolate EFS for axi-cel and SoC, respectively, in the base case.

8.3.3 Extrapolation of OS

The Kaplan Meier plots and proportion of patients at risk at each time point for OS are provided in Figure 16, with goodness-of-fit criteria for the seven MCMs provided in Table 37. As seen in Table 37, the best statistical fit was largely similar across models; thus, the clinical plausibility was important to select the most appropriate model. The extrapolations of OS using MCMs for up to 180 months are presented in Figure 17. Please note that the SoC data presented in Figure 16 and Table 37 are taken directly from the ZUMA-7 trial and not adjusted for the confounding impact of CAR T-cell therapy in subsequent lines. The goodness-of-fit criteria and extrapolations with the standard parametric models can be found in Appendix G.

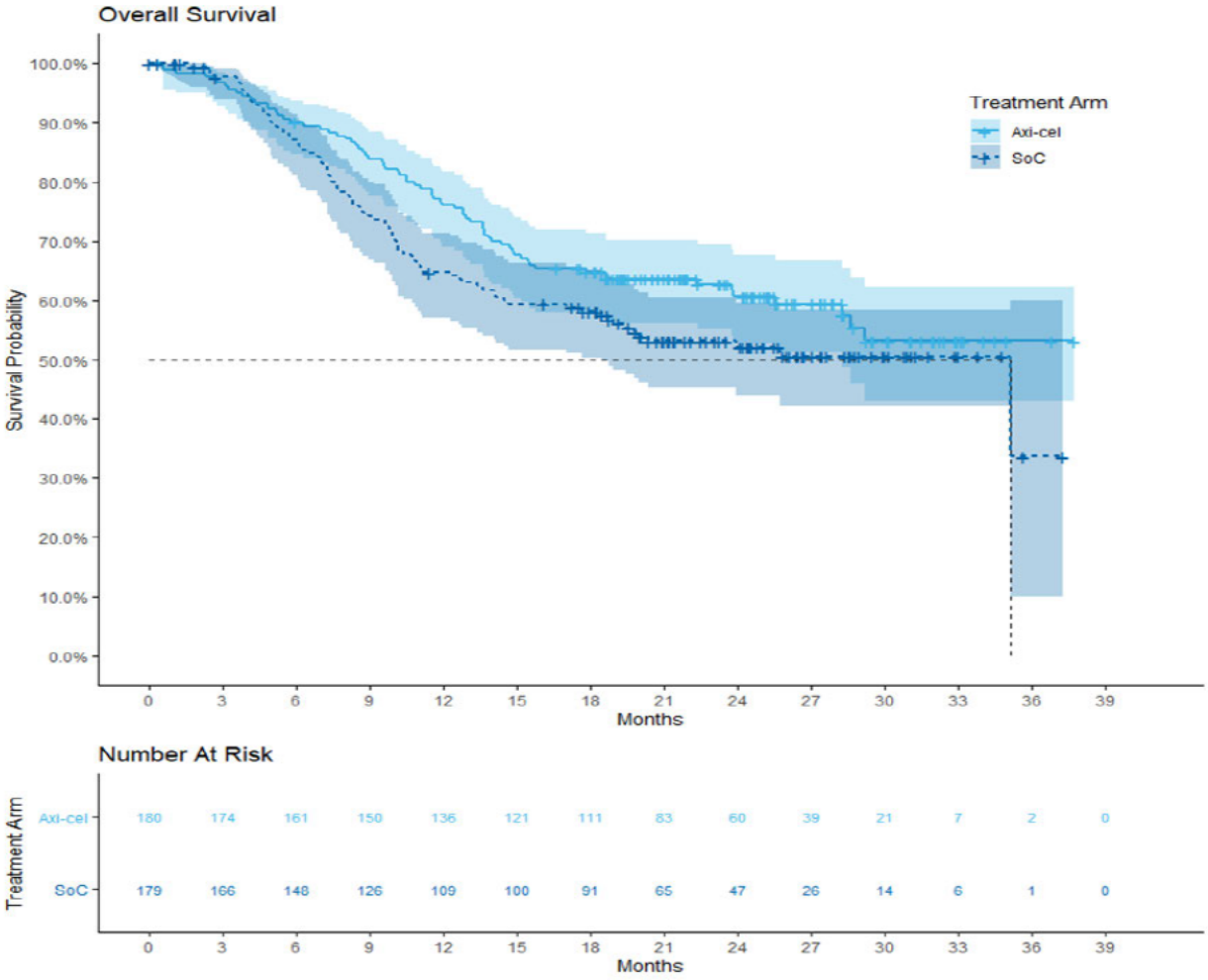

Figure 16: Kaplan Meier plots of OS

Table 37: Statistical goodness-of-fit for OS extrapolations

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Mixture cure models				
Exponential	705.6	712.0	746.6	752.9
Weibull	700.2	709.8	729.3	738.9
Gompertz	704.3	713.9	744.8	754.4
Lognormal	702.7	712.3	717.3	726.9
Loglogistic	700.0	709.6	718.5	728.1
Gamma	700.3	709.9	722.8	732.3

Generalised gamma	702.1	714.9	718.3	731.0

Source: Survival_parameters sheet in model. The applied MCMs are highlighted.
Abbreviations: OS: overall survival, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

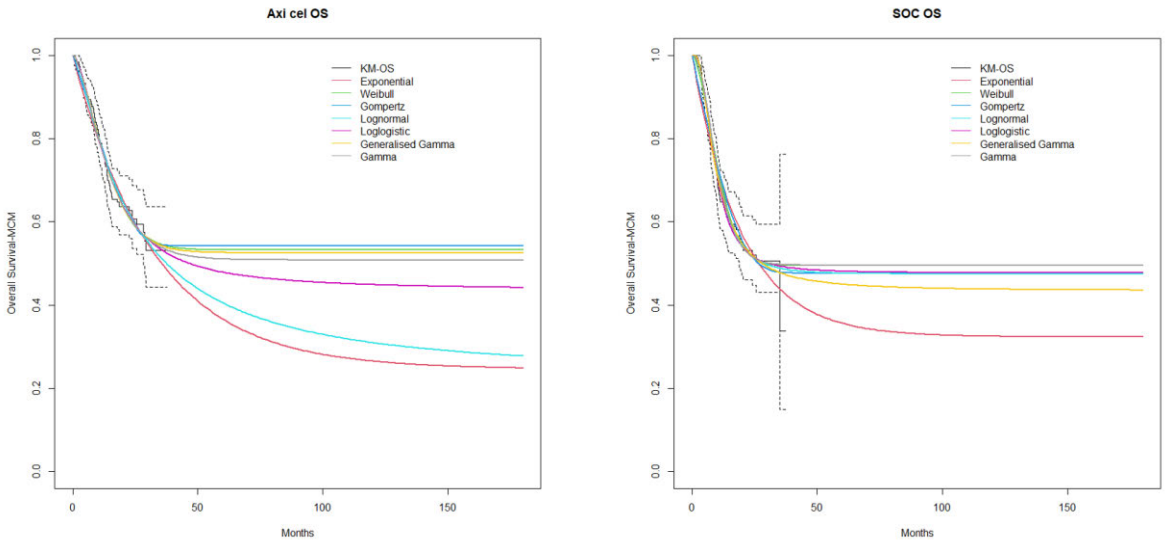

Figure 17: MCMs of partitioned survival: Non-proportional hazards models of OS for axi-cel and SoC

Note: SoC curves not used in the base case, as treatment switching is applied due to the absence of CAR T-cell therapy in subsequent lines.

8.3.3.1 Treatment switching

While axi-cel and other CAR T-cell therapies are indicated for subsequent therapy in patients receiving 2L SoC, the proportion of patients receiving CAR T-cell therapies in subsequent lines of therapy varies across countries, and the ZUMA-7 data does not accurately reflect Danish clinical practice. Of the 120 SoC patients receiving subsequent therapy in ZUMA-7 (safety analysis set), 97 received off-protocol CAR T-cell therapy ("switched") (81%). In Denmark, CAR T is not recommended as subsequent therapy after ASCT. If axi-cel has a beneficial effect on OS, the standard OS analysis will underestimate the OS benefit of axi-cel compared to SoC in the absence of switching, e.g., in countries where CAR T-cell therapy is not available as subsequent therapy or is not used as subsequent therapy to the same extent as in the ZUMA-7 trial. Established statistical methods that can model the OS benefit in the absence of switching are available (69). Methods such as rank-preserving structural failure time (RPSFT) models and inverse probability of censoring weighting (IPCW) models have often been used in oncology to account for this issue and are generally regarded as appropriate methods for handling treatment switching (89). We followed NICE TSD 16 guidance when implementing the methods correcting for treatment switching. This included performing both ICPW and RPSFTM models with full, partial or no recensoring. Ultimately, we found that the RPSFT model with full recensoring gave plausible estimates of the counterfactual survival times, i.e., the survival times that would have been observed in the absence of CAR T-cell therapy in subsequent lines in the SoC arm (69).

For patients in the SoC group who switched to subsequent CAR T-cell therapy during the trial, treatment switching-adjusted HR was estimated using the RPSFT model with full recensoring. The results are provided in Table 38. In the model, the reciprocal HR is applied to the axi-cel curve to estimate the simulated SoC OS curve in the absence of subsequent CAR T-cell therapies.

Source: Data on file.
NR: Not reached, HR: Hazard ratio, SoC: Standard of care, CI: Confidence interval, axi-cel: Axicabtagene ciloleucel, RPSFT: Rank-preserving structural failure time, OS: Overall survival.

In Table 39, the OS HR from the indirect comparison of SCHOLAR-1 vs ZUMA-1 and the ZUMA-7 EFS HR are presented to show the correlation between these hazard ratios and the hazard ratio presented in Table 38. SCHOLAR-1 is an international multicohort retrospective research study that evaluated outcomes in adult patients with DLBCL who were refractory (defined as progressive disease or stable disease as best response at any point during chemotherapy) or relapsed at ≤12 months from ASCT. SCHOLAR-1 pooled patient level data from four cohorts (N = 636), including two observational institutional cohorts and two large phase 3, randomised controlled trials (8). Neelapu et al. (90) compared SCHOLAR-1 with the 2-year outcomes of ZUMA-1. Propensity scores were calculated for each patient by combining the ZUMA-1 and SCHOLAR patients into a single dataset and calculating the probability of being in the ZUMA-1 trial based on demographics and disease characteristics. The primary common support set for response was based on the primary propensity model, which incorporated 7 covariates: age (at determination of refractory status), sex, disease type (diffuse large B-cell lymphoma, transformed follicular lymphoma, or primary mediastinal B-cell lymphoma), relapse within 12 months of ASCT, whether the patient was ever primary refractory (refractory to the initial chemotherapy regardless of refractoriness to subsequent lines of therapy) or refractory to ≥2 consecutive lines of chemotherapy, and the number of prior lines of chemotherapy. Additionally, the presence of post-treatment stem cell transplant (SCT) was added as a time-varying covariate in propensity models used to determine the primary and sensitivity common support sets for survival.

Within the common support data sets, treatment differences in response and survival for axi-cel vs the historical SoC (i.e., non–CAR T-cell therapy) were evaluated. Augmented inverse-probability weighted complete case estimators were used to adjust for the effects of confounding covariates and censoring in the calculation of the survival functions. The difference between these treatment-specific survival functions were calculated: this difference function is the survival-function analog of the average treatment effect. From the treatment-specific survival functions, the treatment-specific median OS times and their differences were calculated, along with treatment-specific OS rates at 3, 6, and 12 months. Among patients in the primary common support set for survival, stratification with regression-adjustment HR estimator was used to estimate the HR between treatments.
Bootstrap 95% CIs were calculated for all quantities. An additional standardised analysis was performed to minimise the loss of patients due to missing covariate data. To address potential imbalances in refractory status that could affect outcomes, the standardisation analyses equally weighted proportions of patients by refractory categorisation (i.e., primary refractory, refractory to ≥2 lines of therapy, or relapse within 1 year after SCT), as well as the presence of ASCT or allogenic SCT after establishing refractoriness to chemotherapy (post refractory SCT) in each study. The survival rates or median OS estimates from these strata within SCHOLAR-1 were weighted by the proportion of patients in those strata within ZUMA-1 to calculate an overall estimate that reflected the distribution across those strata within ZUMA-1. Strata were limited to these 2 factors (i.e., refractory categorisation and presence of post-refractory SCT), because an increased number of prognostic factors would lead to a scarcity of patients across

additional strata. The 2-year survival rate was 54% in ZUMA-1 and 20% in SCHOLAR-1, and a 73% reduction in the risk of death was observed in ZUMA-1 vs SCHOLAR-1 (HR = 0.27).(90).

Table 39: OS HR from ZUMA-1 vs SCHOLAR-1 and ZUMA-7 EFS HR

	HR	Source
ZUMA-1 vs SCHOLAR-1	[redacted]	Neelapu et al. 2021 (90)
ZUMA-7 EFS	[redacted]	Data on file

8.3.3.2 Base case

The MCMs were applied in the base case based on the rationale described in section 12.1. The curve adjusted for treatment switching was applied to SoC to account for the fact that CAR T-cell therapies are not used in subsequent lines in Denmark, while it was frequently used in ZUMA-7. The clinical plausibility of the axi-cel curves in Figure 32 was discussed with the consulted Danish clinical expert together with the treatment switching-adjusted curves for SoC, who informed that for axi-cel, the best fit was the gamma curve, and for SoC, the best fit was the treatment switching-adjusted loglogistic curve (HR: 2.40 (the reciprocal of the 0.416 HR)). Thus, the gamma model was applied for axi-cel in the base case. As the HR for treatment switching is applied to the axi-cel OS curve in the model, which means that a specific extrapolation cannot be chosen for SoC OS, the curve applied as base case for SoC OS is the treatment switching-adjusted gamma curve. As the clinical expert preferred the loglogistic treatment switching-adjusted curve for SoC, a scenario analysis is carried out setting the axi-cel OS curve to loglogistic (i.e., the SoC OS treatment switching-adjusted curve is then loglogistic).

8.3.4 Extrapolation of TTNT

The goodness-of-fit criteria for the MCMs for TTNT are provided in Table 40. The extrapolations of TNTT using MCMs for up to 180 months are presented in Figure 18. The goodness-of-fit criteria and extrapolations with the standard parametric models can be found in Appendix G.

Table 40: Statistical goodness-of-fit for TTNT extrapolations

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Mixture cure models				
Exponential	798.2	804.6	844.1	850.5
Weibull	790.9	800.4	822.3	831.9
Gompertz	799.5	809.1	839.7	849.3
Lognormal	791.9	801.4	819.6	829.1
Loglogistic	778.6	788.2	805.0	814.6

Gamma	787.2	796.8	815.1	824.6
Generalised gamma	787.8	800.6	814.3	827.0

Source: Survival_parameters sheet in model. The applied MCMs are highlighted.
Abbreviations: TTNT: Time to next therapy, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

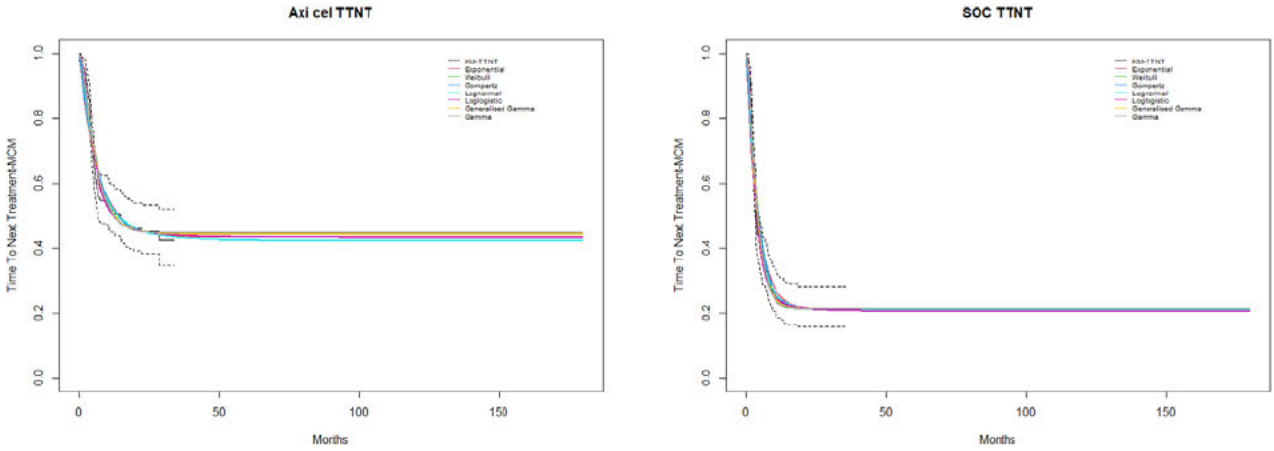

Figure 18: MCMs of partitioned survival: Non-proportional hazards models of TTNT for axi-cel and SoC

The MCMs were applied in the base case based on the rationale described in section 12.1. The clinical plausibility of the curves in Figure 18 was discussed with the consulted Danish clinical expert, who informed that for axi-cel, all curves were clinically plausible. However, for SoC the clinical expert informed that the loglogistic curve could be excluded. The other curves were almost identical and were clinically plausible. Thus, the loglogistic model was used for axi-cel and gamma was used for SoC in the base case.

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

In this section, we describe the HSUV relevant for the assessment of axi-cel compared to SoC. As EQ-5D-5L data was collected in the ZUMA-7 trial, HSUV has been derived from the trial.

Of the 359 patients enrolled in ZUMA-7, 296 patients (165 in the axi-cel arm and 131 in the SoC arm) had baseline HRQoL responses and ≥1 follow-up measure through Day 150 and were included for analysis in the ZUMA-7 QoL analysis set from ZUMA-7. Because median EFS was shorter in the SoC arm than in the axi-cel arm, and most patients stopped completing PRO questionnaires after an EFS event, the QoL analysis contained more axi-cel patients than SoC patients. Overall, in the ZUMA-7 QoL analysis set, 70% of patients had primary refractory disease, 42% had high 2L age-adjusted IPI (2–3), and 30% were ≥65 years old. Of the 296 subjects in the QoL analysis set, 70% were <65 years old, and 66% were male. Overall, 63% had histologically proven DLBCL, and 48% had germinal center B-cell-like cell of origin. The axi-cel cohort had differences >5% compared to SoC as follows: fewer subjects from Europe, more female subjects, more subjects with ECOG status reported as 1, more subjects with disease type as HGBL with or without MYC and BCL2 and/or BCL6 rearrangement, more subjects with germinal center B-cell-like cell of origin and fewer not tested, and more subjects with status as HGBL double-hit with fewer subjects not tested. No formal statistical testing

for differences across treatment arms was undertaken. Data at later time points were less well populated, particularly in the SoC arm, given its greater EFS rate, and should be interpreted with caution.

In ZUMA-7, HRQoL data was collected using the EQ-5D, collected on the five-level response item scale (EQ-5D-5L). In the axi-cel arm, data were collected at the day of screening, the first day of conditioning chemotherapy, the day of axi-cel administration, and months 2, 3, 5, 9, 12, 15, 18, 21 and 24 after randomisation. In the SoC arm, the data were collected at the day of screening, approximately five days after randomisation (during the first cycle of salvage chemotherapy), at the time of disease assessment (assumed to be approximately day 50/month 2), the day of transplant for those receiving ASCT, and then days 100 and 150 post-randomisation (months 3 and 5) as well as months 9, 12, 15, 18, 21 and 24. Study visits were classified as five different time periods, including 1) pre-treatment (all visits with a date before treatment start), 2) axi-cel on-treatment, event-free (visits after the axi-cel start date and prior to the axi-cel treatment end date or date of event (whichever is sooner)), 3) SoC on-treatment, event-free (visits after the SoC treatment start date and prior to the SoC treatment end date or date of event (whichever is sooner)), 4) off-treatment, event-free (all visits that were after the treatment end date and prior to the date of event) 5) post-event (visits after the date of event).

In the QoL analysis set, the mean EQ-5D-5L VAS scores in the axi-cel and SoC arm were comparable at screening. The results of MMRM models showed a statistically significant and clinically meaningful difference in mean change of scores for the EQ-5D-5L VAS from screening in favour of axi-cel at Study Day 100 (estimated difference 13.7 [95% CI: 8.5, 18.8]; adjusted p <0.0001) and Study Day 150 (estimated difference 11.3 [95% CI: 5.4, 17.1]; adjusted p = 0.0004). Figure 19 illustrates the mean EQ-5D-5L VAS score and CI 95% over time by treatment arm, including the number of patients at each time point. To calculate the utilities associated with each health state based on the ZUMA-7 QoL analysis set, observations were collapsed if there were more than one observation within a time period by taking the mean index score for that patient across the multiple observations within the time periods. This was done to avoid patients with more than one visit in a time period driving the results. The utility values associated with each of the time periods were estimated using the MMRM. Each of the calculated EQ-5D-5L indices was the dependent variable in five separate MMRM model series. Covariates included in the MMRM were model-based time period and grade 3 or 4 TEAE (if applicable), each treated as discrete variables. A CS covariance matrix was used for the analyses. Missing data for the EQ-5D-5L, was not imputed or replaced for individual items or the VAS. Missing data was handled under the missing-at-random (MAR) assumption. A likelihood-based approach can adequately address MAR data without the need for multiple imputation and the MMRM model serves as a likelihood-based approach. Thus, the MMRM is sufficient for handling missing data under the MAR assumption.

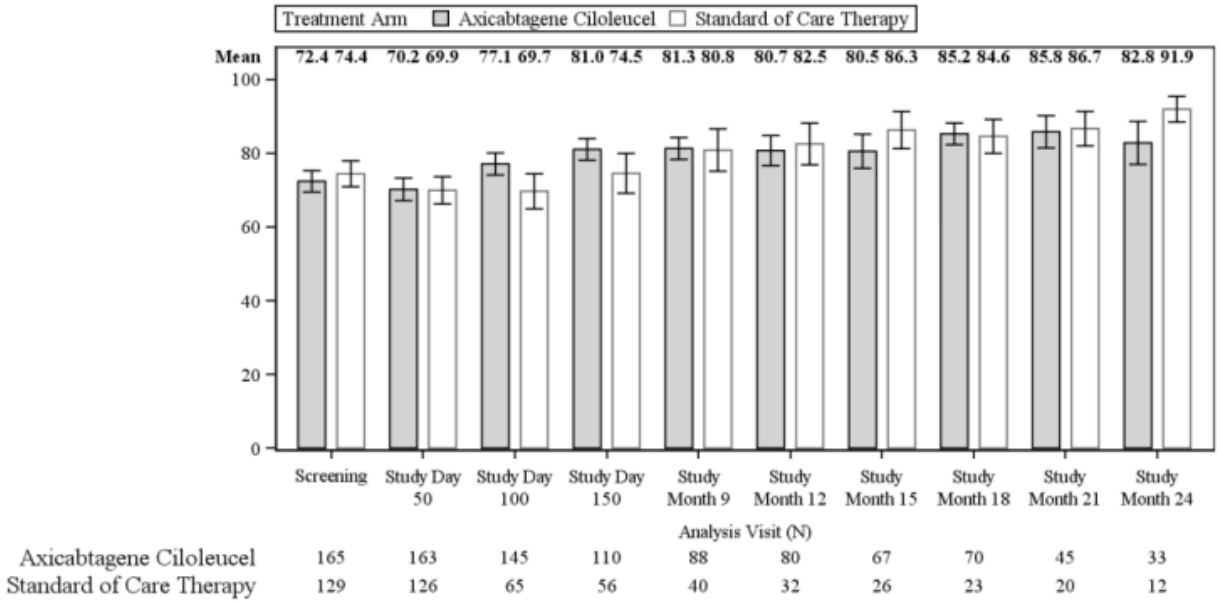

Figure 19: Mean (95% CI) EQ-5D-5L VAS scores over time, by treatment arm (QoL analysis set)

Note: Data cut-off date = 18MAR2021.

Abbreviations: CI: Confidence interval; VAS: Visual analogue scale.

8.4.1 Overview of health state utility values in the model

As valid HRQoL data were collected in clinical trials, these data have been used to inform the health states in the model. The EQ-5D-5L data from ZUMA-7 have been indexed with Danish preference weights from Jensen et al. 2021 (91). Of the patient enrolled in ZUMA-7, 296 patients (165 in the axi-cel arm and 131 in the SoC arm) had baseline HRQoL responses. The health state axi-cel on treatment included responses from 158 patients, the health state SoC on treatment included responses from 116 patients and the health state off treatment included responses from 243 patients. The post-event health state was based on data from the safety management cohort from ZUMA-1 which consisted of 87 EQ-5D-5L observations from 34 patients.

Aligned with the model health states shown in Figure 11, utility data were stratified by clinical outcome measures for the event-free health state. In addition, assessments prior to an event in the axi-cel arm were disaggregated by the period before or after axi-cel infusion. The rationale behind this was that prior to the infusion, patients can be considered in a relapsed state following 1L therapy and given the time taken to manufacture axi-cel after leukapheresis, patients can remain in this state for several weeks. This approach has been taken in previous models for other CAR T-cell therapies in the subsequent therapy setting (92,93). In the model, this utility is applied to the EFS state for axi-cel for the first month, corresponding to the median time from leukapheresis to infusion observed in ZUMA-7, and for the first three months for SoC (94).

The utility values for the event-free health states in the model were based on the mean EQ-5D-5L from ZUMA-7. A utility of 0.848 was applied for the axi-cel “on-treatment, event-free” health state, and a utility value of 0.841 was applied for the SoC “on-treatment, event-free” health state. The utility value applied for “off-treatment” in the event-free health state was 0.858. In ZUMA-7, only few observations were made on the EQ-5D-5L post-event health state,

introducing both statistical and clinical uncertainty. Furthermore, the collection of post-event utilities was not mandated in ZUMA-7, and data collection after switching to subsequent therapy did not usually include PRO reports (95). Although some sites continued to collect PROs after EFS events, these comprised a minority of observations (less than 11% of total PRO observations), further introducing bias. Finally, due to the limited follow-up, this utility estimate does not include decrements due to end of life (72). Therefore, the ZUMA-7 utility values were not applied in the post-event health state in the model. Consequently, the applied utility value in the post-event health state is estimated based on the utility value from the ZUMA-1 trial (83), i.e., the pre-progression utility from ZUMA-1 (3L treatment) was assumed to reflect the post-event state in ZUMA-7 (2L treatment). In ZUMA-1 EQ-5D-5L were collected in the safety management cohort (87 EQ-%D-5L observations from 34 patients).The EQ-5D-5L data from ZUMA-1 was indexed with the Danish preference weights from Jensen et al. 2021 (91) as well. The post-event HSUV was tested in a scenario analysis using a conservative approach and decreasing the HSUV by 20%. Table 41 presents the HSUV applied in the model in the base case.

Table 41: Overview of the HSUV measured during clinical trials and used in the health economic model

	Results [95% CI]	Instrument	Tariff (value set) used	Comments
Event-free health state				
Axi-cel on-treatment	0.848 (0.823, 0.874)	EQ-5D-5L	DK	From ZUMA-7 QoL analysis set
SoC on-treatment	0.841 (0.812, 0.869)	EQ-5D-5L	DK	From ZUMA-7 QoL analysis set
Off-treatment	0.858 (0.835, 0.880)	EQ-5D-5L	DK	From ZUMA-7 QoL analysis set
Post-event health state				
Post-event	0.794 (0.737, 0.851)	EQ-5D-5L	DK	From ZUMA-1

Age adjustments

The HSUV has been adjusted for age according to the guideline from the DMC to account for the increased morbidity and mortality associated with increased age **(96)**. Table 42 presents the population utilities as listed by the DMC **(96)** which have been applied as basis for the age adjustments. The median age in the ZUMA-7 trial was 59 years, and the corresponding age-specific general population utility was 0.818. Based on this, we calculated the age adjustment index (see Table 42) and the HSUVs for each of the four health states (see Table 43).

Table 42: Population HSUVs and age adjustment index

Age group	HSUV	Adjustment index
50-69	0.818	1

Age group	HSUV	Adjustment index
70-79	0.813	0.994
80+	0.721	0.881

Table 43: Age-adjusted HSUVs

Age group	Axi-cel on-treatment, event-free	SoC, on-treatment, evet-free	Off-treatment, event-free	Post-event
50-69	0.848	0.841	0.858	0.794
70-79	0.843	0.836	0.853	0.789
80+	0.747	0.741	0.756	0.700

The age adjustment of the HSUVs was based on the guideline from the DMC in which the age adjustment was based on the EQ-5D-3L questionnaire. When applying the EQ-5D-3L questionnaire to age adjust our HSUVs, the general population utilities become lower relative to the age-adjusted HSUVs applied in the model for patients with r/r DLBCL within 12 months of completing 1L therapy. The HSUVs in the model were estimated based on patient-level data from the two clinical trials ZUMA-7 and ZUMA-1, where the EQ-5D-5L questionnaire had been used to estimate the HSUVs. A recent publication by Jensen et al. 2021 (97) has estimated Danish population utilities based on the EQ-5D-5L questionnaire. In the study, utilities of 0.88 and 0.89 are reported for the general population of 50-59 years and 60-69 years, respectively. If comparing the EQ-5D-5L general population utilities with the HSUVs, the HSUVs are lower than the general population utilities. However, to be compliant with DMC methods, we applied the EQ-5D-3L-based age adjustments in the model but would like to emphasise that the results presented in Jensen et al. 2021 validate the HSUVs estimated in the model.

Long-term remission

In the model, it is possible to revert patients surviving for at least five years without an event to utility values equal to those of the age- and gender-matched general Danish population (see Table 42). This is based on feedback received from clinical experts during the development of the model, who stated that patients who survive for five years without an event can be considered to have effectively achieved long-term response. A prior study has shown that HRQoL exceeds that of the general population after approximately four years in long-term cancer survivors, based on an analysis of the Health and Retirement Study in the US, although this was not specific to large B-cell lymphoma (LBCL) patients (98). The model allows for adjustment of the long-term remission time to a user-identified input (time point at which the utility reverts to a population norm).

However, as the general population utilities applied in the model (from DMC guidelines) are lower than the pre-event off-treatment health state, reverting the patients to general population utilities results in a decrease in health, which contradicts the assumption of long-term remission. The assumption is therefore not applied in the base case. Instead, patients still in the pre-event state after five years continue with the pre-event off-treatment utility of 0.858 as long as they are in the pre-event health state.
To test the impact of the discrepancies between HSUVs and general population utilities (based on EQ-5D-3L from DMC guidelines), two scenario analyses were carried out: 1) the HSUVs were decreased to match the general population

utilities included in the model (based on DMC guidelines) and 2) the general population utilities were changed to those from Jensen et al. 2021 (97), i.e., the HSUVs are lower than the general population utilities. Please see section 8.7.1 for more information on the scenario analyses.

8.5 Resource use and costs

To estimate the resource use and costs associated with treating r/r DLBCL patients with axi-cel and SoC, data from ZUMA-7, the available summary of product characteristics (SPC) of all included drugs, input from the Danish clinical expert, assumptions, and guidelines from Danish hospitals were applied. In the following, a description of each cost element and how the element was valued in the health economic analysis are presented.

8.5.1 Treatment costs of axi-cel and SoC

The costs related to the treatment with axi-cel and SoC were included in the model. All drug costs were based on pharmacy purchasing prices (PPP) obtained at the end of May and beginning of June 2022, and costs incurred at the hospital were based on 2022 DRG tariffs.

Axi-cel treatment-related costs

In the axi-cel arm, the costs related to axi-cel treatment were divided into four distinct phases:

- leukapheresis;
- bridging chemotherapy;
- conditioning chemotherapy; and
- axi-cel administration.

Leukapheresis

During leukapheresis, leucocytes are harvested from the patients' blood. The cost of leukapheresis at the Danish hospitals was based on the 2022 DRG tariff '16PR03' of DKK 9,580 (99). The proportion of patients in the axi-cel arm who received leukapheresis was obtained from ZUMA-7 (99% was applied in the model). The 99% was applied in the model whether the patients received an infusion of axi-cel or not: in ZUMA-7, 94% of patients received an infusion of axi-cel (63), which was applied in the model. It was assumed that leukapheresis is performed at an outpatient visit. The patients who did not receive an axi-cel infusion, either due to AEs or a manufacturing failure, but who did not die prior to infusion, were assumed to have received an alternative therapy in the trial and would therefore be considered to have an EFS event, and so, their treatment would be captured under subsequent therapies. Patients initiated leukapheresis within approximately 5 days of randomisation. The median time from leukapheresis to axi-cel delivery to the trial site was 18 days and was dependent on when the investigator requested delivery. The median time (Q1, Q3) from randomisation to axi-cel infusion was 29 days (27, 34) and depended on patient scheduling and confirmation of eligibility for axi-cel infusion (63).

Bridging therapy

In ZUMA-7, patients in the axi-cel arm could only receive glucocorticoid bridging therapy whilst waiting for manufacturing and infusion. Since CAR T-cell therapy is currently not recommended in Denmark for DLBCL in any treatment lines, a standard practice for bridging therapy has not been established in Denmark. Therefore, the applied bridging therapy in the model was based on bridging therapy in the ZUMA-7 trial, and glucocorticoid was applied. Dexamethasone was applied at a dose of 30 mg daily for two days, and the applied PPP was obtained from www.medicinpriser.dk. Bridging therapy of corticosteroids was allowed prior to lymphodepleting chemotherapy for

subjects with high disease burden, at the discretion of the investigator. In ZUMA-7, 36% of patients in the axi-cel arm received bridging therapy, which was applied in the model (63). Since dexamethasone is administered orally, it was assumed that patients received bridging therapy at home.

Conditioning chemotherapy

According to the SPC on axi-cel, patients should receive lymphodepleting treatment with conditioning chemotherapy with fludarabine (30 mg/m^2 per day IV) and cyclophosphamide (500 mg/ m^2 per day IV) prior to receiving axi-cel (1). The conditioning therapy should be administered on the fifth, the fourth and the third day before the infusion of axi-cel (three days) (1). According to a guideline from Rigshospitalet (100), patients should be hospitalised around one week before the infusion of axi-cel. Therefore, it was assumed that the conditioning therapy was provided during hospitalisation and a unit cost of DKK 10,106 was applied based on the DRG tariff '27MP24'. In the model, it was assumed that 96% of patients would receive conditioning therapy based on ZUMA-7 data. The PPPs of the drugs are presented in Table 44.

Axi-cel administration

The PPP of one infusion of axi-cel is DKK 2,440,000, and to account for the administration of the CAR T-treated cells, the DRG tariff '16PR01' of DKK 5,831 was applied. After the axi-cel infusion, patients should be monitored daily for the first 10 days after the infusion to monitor for AEs (1). If patients are not hospitalised for these ten days, they should stay within two hours of the hospital. In the base case, it was assumed that patients stayed at the hospital for the first ten days after the axi-cel infusion. The DRG tariff '17MA01' of DKK 42,568 was applied as the total cost of the inpatient days after axi-cel infusion. The total axi-cel administration cost was DKK 48,399.

The drug costs included in the model in the axi-cel arm are presented in Table 44, and Table 45 presents the cycle costs related to the drugs included in the axi-cel arm. In subsequent lines, i.e., after SoC in 2L, the treatment-related costs for those receiving CAR T-cell infusion were also included (i.e., leukapheresis, bridging and conditioning therapy, infusion and hospitalisation after CAR T-cell infusion).

Table 44: Applied PPPs in the axi-cel arm

Product name	Active ingredient	Pack size	Strength	PPP (DKK)	Source/Note
Yescarta®	Axi-cel	1 bag	-	2,440,000	Medicinpriser.dk (August 2022)
Dexametason "Abcur"	Dexamethasone	100 tablets	1 mg per tablet	519	Medicinpriser.dk (May 2022). Cost per tablet included in the model
Dexametason "Abcur"	Dexamethasone	100 tablets	4 mg per tablet	216	Medicinpriser.dk (May 2022). Cost per tablet included in the model
Fludarabinphosphat "Actavis"	Fludarabine	1 vial	25 mg/ml with 2 ml per vial	1,310	Medicinpriser.dk (June 2022).

Product name	Active ingredient	Pack size	Strength	PPP (DKK)	Source/Note
Fludarabinphosphat "Ebewe"	Fludarabine	2 vials	25 mg/ml with 5 ml per vial	6,551	Medicinpriser.dk (June 2022). Cost per vial included in the model
Cyclophosphamid "2care4"	Cyclophosphamide	1 vial	200 mg	61	Medicinpriser.dk (May 2022).
Sendoxan	Cyclophosphamide	1 vial	500 mg	154	Medicinpriser.dk (May 2022).
Sendoxan	Cyclophosphamide	1 vial	1000 mg	308	Medicinpriser.dk (May 2022).

Table 45: Doses and cycle costs related to the drugs included in the axi-cel arm

	Dose	Days per cycle	Cost per dose (DKK)	Drug cost per cycle (DKK)	Administration cost per cycle (DKK)
Dexamethasone	30 mg PO	2	16.18	11.68	0.00
Fludarabine	30 mg/m^2 IV	3	1,550.48	5,349.79	10,106.00
Cyclophosphamide	500 mg/m^2 IV	3	301.00		

Abbreviations: DKK: Danish Krone, PO: Per oral, IV: Intravenous.

SoC treatment-related costs

In the SoC arm, costs related to treatment with SoC consisted of:

- drug and administration costs of the salvage chemotherapy regimens;
- stem cell harvesting for ASCT;
- HDT with BEAM; and
- re-infusion of the stem cells (ASCT).

Salvage chemotherapy

In the model, SoC consisted of R-DHAP and R-ICE, based on input from the Danish clinical expert. R-ICE comprises the four drugs rituximab, ifosfamide, carboplatin and etoposide. R-DHAP comprises rituximab, dexamethasone, cytarabine and cisplatin. The applied doses and costs per cycle are presented in Table 47. Based on input from the Danish expert, 33% of the patients in the SoC arm received R-DHAP for 2.73 cycles and 67% received R-ICE for 2.73 cycles, under the assumption that all patients receive at least two cycles and only patients having stem cell harvest will receive three cycles.

The PPP of each drug was obtained from www.medicinpriser.dk, see Table 46. According to a guideline from Aarhus University hospital, both R-DHAP and R-ICE are provided during an inpatient stay, which was assumed to last four days for R-DHAP and three days for R-ICE based on the number of doses per cycle patients receive of each drug included in the regimens (56,101); therefore, inpatient costs were assigned to the administration of R-DHAP and R-ICE in the

model. A unit cost of DKK 10,106 was applied based on the DRG tariff '27MP24'. The costs of chemotherapy have been applied by model cycle. Average patient weight and BSA at baseline have been obtained from ZUMA-7 patient characteristics to inform chemotherapy dosing.

Stem cell harvesting

Following R-ICE and R-DHAP, patients undergo stem cell harvest before HDT is administered. Stem cell harvesting can be done either during an outpatient or an inpatient stay (102). In the model, it was assumed that patients receive stem cell harvest at an outpatient stay. The proportion of patients who receive stem cell harvest was based on ZUMA-7, and 41.3% were applied (94). The unit cost of stem cell harvesting was based on the DRG tariff '16MP05' of DKK 18,391.

HDT with BEAM

HDT consisted of BEAM in the model and comprises carmustine, etoposide, cytarabine and melphalan. In ZUMA-7, 35.8% of the patients in the SoC arm received HDT, which was applied in the model (94). The PPP of each drug included in the BEAM regimen was obtained from www.medicinpriser.dk, see Table 46. It was assumed that the administration costs associated with BEAM were included in the DRG tariff for ASCT (see below).

ASCT

The proportion of patients who receive ASCT was informed by the ZUMA-7 trial, where 34.6% received ASCT (94). The cost of ASCT was based on the DRG tariff '26MP24' of DKK 111,255. The clinical expert informed that patients are hospitalised for two to three weeks after ASCT, and 17.5 days was assumed in the model. According to a guideline from Rigshospitalet on allogenic SCT, patients should be hospitalised for seven to ten days prior to the transplantation, e.g., to receive chemotherapy (103). Since the DRG tariff for ASCT covers 36 inpatients days, no additional costs were added to the tariff to account for the many inpatient days.

Table 46 presents the PPPs of all drugs included in the SoC arm, and Table 47 presents the doses and cycle costs of the included drugs.

Table 46: PPPs applied in the SoC arm

Product name	Active ingredient	Pack size	Strength	PPP per pack	Source/Note
Mabthera	Rituximab	1 vial	1400 mg	12,378	Medicinpriser.dk (June 2022).
Rixathon	Rituximab	2 vials	100 mg	2,676	Medicinpriser.dk (June 2022). Cost per vial included in the model
Rixathon	Rituximab	1 vial	500 mg	6,687	Medicinpriser.dk (June 2022).
Holoxan	Ifosfamide	1 vial	1000 mg	330	Medicinpriser.dk (June 2022).
Carboplatin "Accord"	Carboplatin	1 vial	10 mg/ml with 15 ml per vial	84	Medicinpriser.dk (May 2022).

Product name	Active ingredient	Pack size	Strength	PPP per pack	Source/Note
Carboplatin "Accord"	Carboplatin	1 vial	10 mg/ml with 45 ml per vial	203	Medicinpriser.dk (May 2022).
Etoposid "Fresenius Kabi"	Etoposide	1 vial	20 mg/ml with 5 ml per vial	71	Medicinpriser.dk (June 2022).
Etoposid "Fresenius Kabi"	Etoposide	1 vial	20 mg/ml with 25 ml per vial	279	Medicinpriser.dk (June 2022).
Dexametason "Abcur"	Dexamethasone	100 tablets	1 mg per tablet	519	Medicinpriser.dk (May 2022). Cost per tablet included in the model
Dexametason "Abcur"	Dexamethasone	100 tablets	4 mg per tablet	216	Medicinpriser.dk (May 2022). Cost per tablet included in the model
Cytarabin "Fresenius Kabi"	Cytarabine	1 vial	100 mg/ml with 10 ml per vial	100	Medicinpriser.dk (May 2022).
Cytarabin "Fresenius Kabi"	Cytarabine	1 vial	100 mg/ml with 20 ml per vial	150	Medicinpriser.dk (May 2022). Cost per vial included in the model
Cisplatin "Accord"	Cisplatin	1 vial	1 mg/ml with 50 ml per vial	100	Medicinpriser.dk (May 2022).
Cisplatin "Accord"	Cisplatin	1 vial	1 mg/ml with 100 ml per vial	200	Medicinpriser.dk (May 2022).
Carmustine Obvius	Carmustine	1 vial	100 mg	3,945	Medicinpriser.dk (May 2022).
Melphalan "Macure"	Melphalan	1 vial	50 mg	4,500	Medicinpriser.dk (June 2022).

Abbreviation: PPP: Pharmacy purchasing price.

Table 47: Cycle costs related to the drugs included in the SoC arm

	Dose	Dose per cycle	Cost per dose (DKK)	Drug cost per cycle (DKK)	Administration cost per cycle (DKK)
R-ICE					
Rituximab	375 mg/m^2 IV	1	6,539.67	10,480.04	10,106.00
Etoposide	100 mg/m^2 IV	3	109.95		
Carboplatin	400 mg/m^2 IV	1	355.92		

	Dose	Dose per cycle	Cost per dose (DKK)	Drug cost per cycle (DKK)	Administration cost per cycle (DKK)
Ifosfamide	5000 mg/m² IV	1	3,254.58		
R-DHAP					
Rituximab	375 mg/m² IV	1	6,539.67	7,316.32	10,106.00
Cisplatin	100 mg/m² IV	1	394.50		
Cytarabine	2000 mg/m² IV	1	295.87		
Dexamethasone	40 mg PO	4	21.57		
BEAM					
Carmustine	300 mg/m² IV	1	23,344.24	49,195.41	0.00
Etoposide	200 mg/m² IV	4	219.91		
Cytarabine	200 mg/m² IV	4	29.59		
Melphalan	140 mg/m² IV	1	24,853.19		

Abbreviations: DKK: Danish Krone, PO: Per oral, IV: Intravenous.

The clinical expert informed that patients have three CT scans during their treatment with axi-cel or ASCT: one pre-treatment, one midway and one post treatment. Based on this, three CT scans were included. A unit cost of DKK 3,753 was applied per CT scan based on the 2022 DRG tariff '30PR05'.

8.5.2 Subsequent therapy costs

Costs related to subsequent therapies were included in the model. Data from ZUMA-7 was not applied to inform the subsequent therapies included in the model, as CAR T-cell therapy was a subsequent therapy in ZUMA-7 and CAR T-cell therapy is not reimbursed in Denmark. Therefore, the Danish clinical expert was consulted in terms of the subsequent therapies that are applied in Denmark.

The clinical expert informed that for patients who have received SoC in 2L, around 35% receive prednisone as subsequent therapy, 20% receive palliative radiotherapy, 15% take part in clinical protocols, 5% receive allogenic SCT and 5% receive other treatment options (e.g., PD-L1). The clinical expert informed that for patients (<70 years), it is possible to try new chemotherapies (e.g., R-BENDA and R-lenalidomide) if the best response after R-DHAP, R-ICE or BEAM is SD. According to the expert, 20% would receive these new R-based chemotherapy options, and 10% R-BENDA and 10% R-lenalidomide were applied in the model. No costs associated with participation in clinical protocols were included in the model.

For patients receiving axi-cel in 2L, most patients would receive R-chemotherapy (in the model, R-chemotherapy consisted of R-IVE, which comprises rituximab, ifosfamide, epirubicin and etoposide) or radiotherapy, while 5% of patients would receive nivolumab or pembrolizumab (for both nivolumab and pembrolizumab, 2.5% was applied in the model). The clinical expert stated that 5% of patients would receive ASCT, but none would receive allogenic SCT because of a past negative experience. The clinical expert informed that each regimen has a planned number of cycles, but that this is always based on the patient's response to treatment. If a patient progresses, there is no need to

administer more cycles of the same treatment. The expert estimated that once they start subsequent therapy, all patients receive at least three cycles, and around 50% will expectedly receive six cycles (4.5 cycles were assumed).

Table 48 presents an overview of the subsequent therapies included in the model and the number of cycles patients receive each therapy. In Table 50, the cycle costs of the drugs included as subsequent therapy options are presented, while Table 51 presents the costs of the procedures included as subsequent therapy options in the model. The costs of rituximab, etoposide, ifosfamide and the cost of HDT with BEAM provided before ASCT are presented in Table 46, and these costs are therefore not repeated in this section.

Table 48: Subsequent therapies included in the model and the number of cycles patients receive each therapy

	Axi-cel		SoC	
	Proportion of patients*	**Number of cycles**	**Proportion of patients***	**Number of cycles**
R-chemotherapy	89%	4.5	-	-
Nivolumab	3%	4.5	3%	4.5
Pembrolizumab	3%	4.5	3%	4.5
Radiotherapy	27%	4.5	-	-
ASCT	5%	-	-	-
Allogenic SCT	0%	-	5%	-
Prednisone	-	-	35%	4.5
R-lenalidomide	-	-	10%	4.5
R-BENDA			10%	4.5
Palliative radiotherapy	-	-	20%	4.5
Clinical trial protocols	-	-	15%	-

*Please note that the subsequent therapies in the table are not mutually exclusive and can therefore sum to more than 100%.

Table 49: PPPs of the drugs applied as subsequent therapy options

Product name	Active ingredient	Pack size	Strength	PPP per pack	Source/Note
Bendamustine "Fresenius Kabi"	Bendamustine	5 vials	2.5 mg/ml with 25 mg per vial	367	Medicinpriser.dk (May 2022). Cost per vial included in the model

Product name	Active ingredient	Pack size	Strength	PPP per pack	Source/Note
Bendamustine "Fresenius Kabi"	Bendamustine	5 vials	2.5 mg/ml with 100 mg per vial	1,174	Medicinpriser.dk (May 2022). Cost per vial included in the model
Epirubicin "Teva"	Epirubicin	1 vial	2 mg/ml with 25 ml per vial	111	Medicinpriser.dk (June 2022).
Epirubicin "Teva"	Epirubicin	1 vial	2 mg/ml with 100 ml per vial	443	Medicinpriser.dk (June 2022).
Opdivo®	Nivolumab	1 vial	40 mg	3,691	Medicinpriser.dk (June 2022).
Opdivo®	Nivolumab	1 vial	100 mg	9,168	Medicinpriser.dk (June 2022).
Opdivo®	Nivolumab	1 vial	240 mg	22,004	Medicinpriser.dk (June 2022).
Keytruda®	Pembrolizumab	1 vial	25 mg/ml with 4 ml per vial	23,205	Medicinpriser.dk (June 2022).
Lenalidomid "Zentiva"	Lenalidomide	21 capsules	10 mg per capsule	27,500	Medicinpriser.dk (June 2022). Cost per capsule included in the model
Lenalidomid "Zentiva"	Lenalidomide	21 capsules	15 mg per capsule	29,200	Medicinpriser.dk (June 2022). Cost per capsule included in the model
Lenalidomid "Zentiva"	Lenalidomide	21 capsules	20 mg per capsule	33,200	Medicinpriser.dk (June 2022). Cost per capsule included in the model
Lenalidomid "Zentiva"	Lenalidomide	21 capsules	25 mg per capsule	32,000	Medicinpriser.dk (June 2022). Cost per capsule included in the model
Prednison "DAK"	Prednisone	100 tablets	5 mg per tablet	56	Medicinpriser.dk (June 2022). Cost per tablet

Product name	Active ingredient	Pack size	Strength	PPP per pack	Source/Note
					included in the model
Prednison "DAK"	Prednisone	100 tablets	25 mg per tablet	208	Medicinpriser.dk (June 2022). Cost per tablet included in the model

Table 50: Cycle costs related to the drugs included as subsequent therapies

	Dose	Dose per cycle	Cost per dose (DKK)	Drug cost per cycle (DKK)	Administration cost per cycle (DKK)
R-chemotherapy					
Rituximab	375 mg/m² IV	1	6,539.67	13,275.80	10,106.00
Ifosfamide	3000 mg/m² IV	3	1,952.75		
Epirubicin	50 mg/m² IV	1	218.16		
Etoposide	200 mg/m² IV	3	219.91		
R-BENDA					
Rituximab	375 mg/m² IV	2	6,539.67	13,912.99	6,450.00
Bendamustine	90 mg/m² IV	2	416.82		
Nivolumab	240 mg IV	2	22,003.74	44,007	6,450.00
Pembrolizumab	200 mg IV	1	46,409.22	46,409.22	3,225.00
Prednisone	7.5 mg PO	5	0.62	3.12	0.00
R-Lenalidomide					
Rituximab	375 mg/m² IV	2	6,539.67	68,079.34	6,450.00
Lenalidomide	20 mg PO	21	2,619.05		

Table 51: Costs of procedures included as subsequent therapies

	Unit costs (DKK)	Units per cycle	Source
Radiotherapy	8,604	3.5	DRG tariff 2022 '27MP06'
ASCT	111,255	1	DRG tariff 2022 '26MP24'
Allogenic SCT	747,851	1	DRG tariff 2022 '26MP22'
Palliative radiotherapy	34,020	5	DRG tariff 2022 '27MP05'

Abbreviations: ASCT: Autologous stem cell transplant, SCT: Stem cell transplant, DKK: Danish Krone.

8.5.3 Resource use and costs related to disease management and monitoring

In the model, resource use was stratified in pre-event resource use and post-event resource use. The resource use in the event-free health state reverts to zero after five years, based on the assumption that patients who are still event-free after five years are effectively considered long-term responders with minimal healthcare resource use. This assumption was made based on recent evidence from Assouline et al. 2020 showing comparable OS for relapsed patients with five-year EFS after ASCT compared with that of the general population (9).

An overview of the resource use per month associated with disease management and monitoring is presented in Table 52. The table shows the average number of visits and tests per patient per month associated with the pre-event and post-event health states in the model. The resource use was informed by the NICE submission for axi-cel in 3L (93) and the Danish expert who was consulted regarding the resource use associated with disease management and monitoring practice in Denmark. In addition, to account for the resource use associated with disease management and monitoring, follow-up resource use per month after ASCT and axi-cel treatment was included in the pre-event resource use in the table below.

The clinical expert informed that the resource use associated with disease management and monitoring in the pre-event health state in the model is covered by the resource use in the follow-up after ASCT and axi-cel treatment: therefore, no resource use in the pre-event state was listed in Table 52. For the post-event resource use, the clinical expert stated that patients have one visit every second week until close to death in post-event health state, i.e., two visits per month.

Table 52: Average number of visits/tests per patient per month in the pre- and post-event health states related to disease management and monitoring

	Pre-event resource use	Post-event resource use
Number of visits		
GP visits	0	0
District nurse	0	0
CT scans	0	0
Outpatient visits (months 1 to 6)	0	2
Outpatient visits (months 7 to 12)	0	2
Outpatient visits (years 2 to 3)	0	2
Outpatient visits (years 4 to 5)	0	2
Nurse visits	0	0
Specialist nurse visits	0	0
Inpatient days	0	0

	Pre-event resource use	Post-event resource use
Blood tests	0	0

Resource use and costs related to follow-up after ASCT and axi-cel

The Danish expert was consulted to understand how patients are followed in Denmark after they are discharged from the hospital after having received axi-cel or ASCT.

The clinical expert informed that patients have four to six follow-up visits per year in the first year after ASCT. Hereafter, follow-up visits will occur every six months, with blood work being done at every visit but no planned CT scans. The follow-up visits will continue until year 5. Therefore, 0.42 visits per cycle (i.e., five visits per year) were applied in the first year, and 0.17 visits per cycle (i.e., two visits per year) were applied for year two to five.

The clinical expert informed that patients receiving axi-cel are expected to have 6-12 follow-up visits in the first year and one visit every three months hereafter. Blood work would be done at every visit, but there would be no planned CT scans. The follow-up visits will continue until year five. Therefore, 0.75 visits per cycle (i.e., nine visits per year) were applied in the first year, and 0.33 visits per cycle (i.e., four visits per year) were applied for year two to five.

Table 53: Average number of visits/tests per patient per month during the follow-up period

	Axi-cel		ASCT	
	Part of follow-up?	Frequency per month	Part of follow-up?	Frequency per month
GP visit	☐		☐	
Outpatient visit	☒	0.75 follow-up visits per month in the first year. In year 2-5, there are 0.33 follow-up visits per month. Blood tests are performed at all visits.	☒	In the first year, 0.42 follow-up visits per month. In year 2-5, there are 0.17 follow-up visits per month. Blood tests are performed at all visits.
Blood test	☒		☒	
MR Scan	☐		☐	
CT scan	☐		☐	
Inpatient visits	☐		☐	

Table 54: Applied unit costs (DKK) for each resource

	Unit cost (DKK)	Source
CT scans	3,753	DRG tariff '30PR05'
Outpatient visits (months 1 to 6)	3,225	DRG tariff '17MA98' per visit
Outpatient visits (months 7 to 12)	3,225	DRG tariff '17MA98' per visit

	Unit cost (DKK)	Source
Outpatient visits (years 2 to 3)	3,225	DRG tariff '17MA98' per visit
Outpatient visits (years 4 to 5)	3,225	DRG tariff '17MA98' per visit
Blood test*	230	Rigshospitalet

*Includes serum LDH, liver and renal function, immunoglobulin and calcium phosphate.

8.5.4 Management of adverse events

The model included resource use associated with management of Grade 3+ AEs. The Danish clinical expert was consulted on which of the Grade 3+ AEs observed in ZUMA-7 typically require treatment and how these AEs are managed at Danish hospitals. According to the clinical expert, the majority of AEs can be managed within the inpatient follow-up stay and are therefore not associated with any additional resource use. The Grade 3+ AEs that require additional treatment are CRS, neurologic events and hypoxia, and these have been included in the model.

Management of CRS was assumed according to the EBMT-EHA guidelines and consists of admission to the ICU and administration of tocilizumab (43). In ZUMA-7, the average length of stay for patients transferred to the ICU was five days and thus five ICU days were assumed in the model. The cost of managing CRS was based on a combination of the DRG tariffs 'DC833' and 'BOHJ18B2' including five inpatients days with a total cost of CRS management of DKK 52,166. Hypoxia was assumed to be managed the same way as CRS, as hypoxia can be a symptom of CRS. It should be noted that this assumption most likely overestimates the cost of managing AEs in patients treated with axi-cel.

Management of neurologic events was assumed to correspond to the management of immune effector cell-associated neurotoxicity syndrome (ICANS) as per the EBMT-EHA guidelines (43). We assumed that the cost of neurologic events could be calculated as a mean of the cost of managing Grade 3 and Grade 4 events according to the EBMT-EHA guideline: Grade 3 events are managed with a neurologic consultation and medication, and Grade 4 events are managed with an ICU stay (assumed to be five days), a neurologic consultation and IV administration of methylprednisolone. The cost of managing a Grade 3 neurologic event was DKK 1,905 based on the DRG tariff '23MA98 MDC23'. The cost of managing a Grade 4 neurologic event was DKK 49,071 based on a combination of the DRG tariff 'DC833' and 'BOHJ18B2' including five inpatients days, the DRG tariff '23MA98 MDC23' and the cost of methylprednisolone (unit price DKK 38.88). Thus, in the model, we applied a cost of DKK 26,440 for the management of a neurologic event.

Table 55 presents an overview of the applied unit costs for managing treatment-requiring Grade 3+ AEs and the sources for each unit cost. An overview of the Grade 3+ AEs observed in ZUMA-7 was provided in Table 34 (63).

Table 55: Costs of managing AEs

	Unit cost (DKK)	Source
Management of CRS	52,166	Based on the 2022 DRG tariff 'DC833' combined with 'BOHJ18B2'
Management of neurologic events	26,440	The unit cost is based on the mean cost of treating Grade 3 and Grade 4 neurologic events. Applied tariffs for Grade 3: '"23MA98 MDC23'.

	Unit cost (DKK)	Source
		Applied tariffs for Grade 4: 'DC833 combined with 'BOHJ18B2', '23MA98 MDC23' and the cost of methylprednisolone (unit price DKK 38.88)
Management of hypoxia	52,166	Assumed to be managed the same way, as CRS as hypoxia can be a symptom of CRS

8.5.5 End-of-life costs

Patients who transition to the "Death" health state incur a one-time end-of-life cost. This cost was included due to the seriousness of the disease where a large proportion of patients are assumed to die in both treatment arms. This cost represents the cost of palliative care of DLBCL patients at the hospital. The applied end-of-life cost was DKK 193,320, which was based on the DRG tariff '26HJ03' and 30 days.

8.5.6 Patient and transportation costs

The cost of patient time spent on activities related to axi-cel and SoC treatment, managing AEs and transportation to and from the hospital were included in accordance with DMC guidelines (64). Based on the DMC guidelines, a cost of DKK 181 per patient hour was applied. Costs related to the time spent by caregivers were not included in the model due to missing references with estimates on the time spent by caregivers on treatment-related activities.

Transportation costs were also included. A distance of 20 km to and from the hospital (40 km in total per visit) was assumed, and a unit cost per km of DKK 3.51 was applied in accordance with DMC guidelines (64). Thus, a transportation cost of DKK 140 was applied for each hospital visit. It was assumed that patients spent 30 minutes on transportation to and from the hospital i.e., 60 minutes per visit.

8.5.6.1 Patient time in the axi-cel arm

In the axi-cel arm, patients spend time on the following activities related to axi-cel treatment:

- leukapheresis;
- conditioning chemotherapy; and
- CAR T-cell infusion.

The patient time spent on leukapheresis was estimated based on a guideline on stem cell harvest from Rigshospitalet (102). According to the guideline, harvesting of cells from the blood can be performed either at an outpatient visit or an inpatient visit, and more than one harvest can be performed if insufficient levels of cells are harvested the first time. In the model, the harvest was assumed to be performed outpatient and last three hours, and only one harvest per patient was assumed. According to the guideline, it takes around three hours to harvest cells; therefore, three hours of patient time was assumed for leukapheresis. Since bridging therapy in the model consisted of dexamethasone, which is administered orally, no patient time associated with bridging therapy was included in the model.

According to a guideline on CAR T-cell therapy from Rigshospitalet (100), patients are hospitalised one week prior to the CAR T-cell infusion to receive the conditioning chemotherapy. With 16 hours of patient time per inpatient day, 112 hours of patient time were estimated for conditioning chemotherapy (16 hours x 7 days). When the conditioning

chemotherapy is finalised, the CAR T-cell infusion is performed. According to the SPC on axi-cel, patients should be monitored daily for the first ten days after the infusion to monitor for AEs. Based on this, ten inpatient days following axi-cel infusion were assumed, i.e., 160 hours of patient time.

One hour of patient time spent on transportation for leukapheresis was added, and one hour of patient time spent on transportation was added to the axi-cel inpatient stay. Table 56 presents an overview of the total patient time associated with axi-cel treatment.

As mentioned, the clinical expert informed that patients have three scans when they receive axi-cel treatment (one pre-treatment scan, one midway scan and one post-treatment scan). It was assumed that these scans were performed when the patient would already be at the hospital, i.e., no transportation time for CT scans was included in the model.

Table 56: Patient time associated with axi-cel treatment

	Leukapheresis	Conditioning chemotherapy	Axi-cel infusion and post-infusion monitoring	CT scans (per scan)
Patient time	3 hours	112 hours	160 hours	1 hour
Transportation time	1 hour	0 hours	1 hours	0 hours
Total patient time	**4 hours**	**112 hours**	**161 hours**	**1 hour**

8.5.6.2 Patient time in the SoC arm

In the SoC arm, patients spend time on the following activities related to SoC treatment:

- administration of the salvage chemotherapy regimens;
- stem cell harvest for ASCT;
- HDT with BEAM; and
- re-infusion of the stem cells (ASCT).

According to guidelines from Aarhus University hospital (56,101), R-DHAP and R-ICE are administered during an inpatient stay for four and three days, respectively, per series. Thus, 64 hours of patient time were applied for R-DHAP, and 48 hours were applied for R-ICE treatment. One hour of patient time was added for transportation to and from the hospital for both regimens.

To estimate the patient time spent on stem cell harvesting for ASCT, a guideline from Rigshospitalet was applied (102). According to the guideline, stem cell harvesting can be performed either at an outpatient visit or as an inpatient stay and can be performed more than once. In the model, a three-hour outpatient visit was applied, and only one harvest was assumed. The patient time related to stem cell harvest was estimated to be four hours (incl. transportation time).

According to a guideline from Rigshospitalet, patients should be hospitalised seven to ten days prior to ASCT to receive chemotherapy (HDT). Thus, seven inpatient days were applied prior to ASCT for HDT with BEAM, i.e., 112 hours of patient time (16 hours x 7 days). According to the clinical expert, patients are typically hospitalised for 2.5 weeks after ASCT: thus, 17.5 inpatient days were applied, i.e., 280 hours of patient time (16 hours x 17.5 days). One

hour of transportation time was added and the total patient time spent on ASCT was estimated to 393 hours. Table 57 presents an overview of the patient time spent in the SoC arm.

As for axi-cel, the clinical expert informed that patients have three scans when they receive SoC and later ASCT (one pre-scan, one midway scan and one post-scan). The same assumption was made in terms of when patients would have these scans, and no separate visits for CT scans were included in the model.

Table 57: Patient time associated with SoC treatment

	R-ICE	R-DHAP	Stem cell harvest	ASCT (including HDT)	CT scans (per scan)
Patient time	48 hours	64 hours	3 hours	392 hours	1 hour
Transportation time	1 hour	1 hour	1 hours	1 hours	0 hours
Total patient time	**49 hours**	**65 hours**	**4 hours**	**393 hours**	**1 hour**

8.5.6.3 Patient time related to subsequent therapies

The patient time associated with the subsequent therapies included in the model is described in the following.
The patient time associated with the R-based chemotherapy regimens that were included as subsequent therapies was assumed to be the same as for R-DHAP and R-ICE in 2L, i.e., 64 hours (65 hours with transportation) per series.
The patient time spent per series of R-BENDA was based on guidelines from Rigshospitalet (104,105), where patients have two visits to the hospital, with the duration of the first visit being approximately six hours and the second visit taking approximately one hour. Based on this, seven hours of treatment time and two hours of transportation time were applied per series (nine hours in total). For R-lenalidomide, one rituximab infusion per cycle was applied, lasting 4.5 hours per infusion. Since lenalidomide is administered per oral, no patient time for lenalidomide was included. One hour of transportation was included, resulting in 5.5 hours per series of R-lenalidomide.

For ASCT and allogenic ASCT, the same patient time as for ASCT in 2L was assumed in subsequent lines.
For the single-agent regimens (nivolumab and pembrolizumab), the patient time was based on the SPCs, and 30 minutes were applied with one hour of transportation per administration. Prednisone is administered orally and can be administered by patients at home; thus, no patient time was included for prednisone.
According to a guideline from Rigshospitalet (106), radiotherapy takes around 15-20 minutes, and based on this, 30 minutes were assumed per treatment to also account for preparation time. One hour of transportation time per treatment was added. The DRG tariffs used for radiotherapy and palliative radiotherapy included 3-4 fractions and at least 5 fractions, respectively. Therefore, one series in the model consisted of 3.5 fractions for radiotherapy and 5 fractions for palliative radiotherapy.

A summary of the patient time associated with each subsequent therapy regimen is provided in Table 58.

Table 58: Patient time associated with the subsequent therapies per treatment

	Patient time	Transportation time	Total patient time
R-chemotherapy	64 hours	1 hours	**65 hours**

	Patient time	Transportation time	Total patient time
Nivolumab	0.5 hours	1 hours	**1.5 hours**
Pembrolizumab	0.5 hours	1 hours	**1.5 hours**
Radiotherapy (per fraction)	0.5 hours	1 hours	**1.5 hours**
ASCT	392 hours	1 hours	**393 hours**
Allogenic SCT	392 hours	1 hours	**393 hours**
Prednisone	0 hours	0 hours	**0 hours**
R-lenalidomide	4.5 hours	1 hours	**5.5 hours**
R-BENDA	7 hours	2 hours	**9 hours**
Palliative radiotherapy (per fraction)	0.5 hours	1 hours	**1.5 hours**

8.5.6.4 Patient time spend on managing AEs

The model included the Grade 3+ treatment-requiring AEs: CRS, neurologic events and hypoxia. Management of the included AEs were based on the EBMT-EHA guidelines (43). Based on ZUMA-7, it was assumed that patients would be admitted to the ICU for five days if they experienced a CRS event. Further, it was assumed that hypoxia would be managed the same way as CRS. Since patients would already be hospitalised for follow-up, no transportation time or costs was assumed for management of CRS. Thus, in the model, 80 hours of patient time was applied for management of CRS and hypoxia (5 days x 16 hours). Patients could suffer from either Grade 3 or Grade 4 neurologic events; therefore, patient time associated with management of neurologic events was assumed to be a mean of the patient time required for management of Grade 3 and Grade 4. Management of Grade 3 neurologic events did not trigger any additional patient time, while management of Grade 4 neurologic events was associated with five days at the ICU. Since patients would already be hospitalised for follow-up, no transportation time was assumed for management of neurologic events. Thus, in the model, 40 hours of patient time was applied for management of neurologic events (5 days x 16 hours/2).

8.5.6.5 Patient time related to other activities

It was assumed that the duration of all outpatient visits was 30 minutes with one hour of transportation time per visit.

8.6 Results

This section includes an overview of the base case analysis presented as a table in Table 59 and the result of the base case analysis.

8.6.1 Base case overview

Table 59: Base case overview

Patient population	Adult patients with DLBCL and HGBCL who have refractory disease or have relapsed within 12 months from completion of 1L chemoimmunotherapy and who are intended for ASCT
Intervention	Axicabtagene ciloleucel
Comparator	SoC
Type of model	Three-state partitioned survival model
Time horizon	50 years
Treatment line	2L DLBCL
Measurement and valuation of health effects	HRQoL measured with EQ-5D-5L in ZUMA-7. Danish population weights were used to estimate health-state utility values
Included costs	Pharmaceutical costs Treatment-related costs Costs of subsequent therapies Disease management and monitoring costs Follow-up costs after axi-cel and ASCT Managing AE costs End-of-life costs Patient costs Transportation costs
Dosage of pharmaceutical	A single dose of axi-cel contains 2 x 10^6 CAR-positive viable T-cells per kg of body weight (or a maximum of 2 x 10^8 CAR-positive viable T-cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag (1)
MCM for EFS	Axi-cel: Gompertz SoC: Exponential
MCM for OS	Axi-cel: Gamma SoC: Treatment switching adjusted curve (HR 2.40)
MCM TTNT	Axi-cel: Loglogistic

	SoC: Gamma
HSUV on-treatment axi-cel	0.848
HSUV on-treatment SoC	0.841
HSUV off-treatment pre-event	0.858
HSUV post-event	0.794

8.6.2 Base case results

This section presents the base case results of the CU analysis for axi-cel compared to SoC. The overall purpose of the model was to estimate the cost per QALY for axi-cel relative to the current SoC. Results are presented over a time horizon of 50 years.

In the base case, an incremental QALY gain of 4.51 and an incremental cost of DKK 2,263,747 were calculated for axi-cel compared to SoC, resulting in an ICER of DKK 501,397 per QALY, over a time horizon of 50 years. Table 60 presents a thorough overview of the results in terms of life years gained, QALYs and costs.

Table 60: Base case results (discounted)

Per patient	Axi-cel	SoC	Difference
Life years gained			
Total life years gained	8.82	3.32	5.50
Life years gained (event-free health state)	6.25	2.49	3.76
Life years gained (post-event health state)	2.57	0.83	1.74
QALYs			
Total QALYs	7.29	2.77	4.51
QALYs (event-free health state)	5.28	2.12	3.16
QALYs (post-event health state)	2.01	0.66	1.35
QALYs (adverse events)	0.00	0.00	0.00
Costs, DKK			
Total costs	2,780,219	516,473	2,263,747

Per patient	Axi-cel	SoC	Difference
Drug costs (incl. subsequent lines)	2,305,363	80,814	2,224,549
Hospital costs	354,427	361,711	-7,284
Adverse event costs	13,796	2,258	11,538
Patient time and transportation costs	106,633	71,698	34,944

Incremental results	Axi-cel vs SoC
ICER (DKK per QALY)	501,397

8.7 Sensitivity analyses

Uncertainty in the input parameters in the health economic model has been explored through extensive sensitivity analyses. Functionality is included in the model to enable input parameters to be varied systematically to evaluate their influence on the ICER.

8.7.1 Deterministic sensitivity analyses

A DSA was performed in the present application, and the specific parameters included in the DSA can be found in the Excel model on the sheet "Parameters". The input parameters in the DSA were adjusted by using standard error (SE). In cases where no SE was available, the point estimate was varied by +/- 20% of the point estimate. Table 62 presents the DSA results on the 10 parameters with the largest impact on the base case ICER. A tornado diagram is illustrated in Figure 20.

Aside from the one-way sensitivity analyses, various scenario analyses were also conducted. We conducted scenario analyses with shorter time horizons (5, 10 and 25 years) in accordance with DMC guidelines. A scenario analysis applying information from the clinical expert on proportion of patients in the SoC group receiving stem cell harvest, HDT and ASCT was also conducted, since ZUMA-7 values were applied in the base case. According to the clinical expert, 70-75% of the transplant-intended patients receive a stem cell harvest in Denmark and 73% was applied in the scenario analysis. The 73% in Denmark is higher than the observed number in the ZUMA-7 trial (41.3%), and the clinical expert informed that the reason for this is that the ASCT-eligible patient population is younger in Denmark compared to the ZUMA-7 population, because only patients below 70 years are transplant-eligible in Denmark. The clinical expert stated that around 60-65% of patients receive HDT, and 63% was applied in the scenario analysis. According to the expert, approximately 50% of the primary refractory patients and 75% of the relapsed patients receive ASCT after the harvest, and 63% was applied in the scenario analysis. Moreover, the clinical expert preferred the loglogistic treatment switching-adjusted curve for SoC OS. Therefore, using the loglogistic curve to inform OS was applied in a scenario analysis (i.e., as the model applies the treatment switching HR to the axi-cel OS curve, the axi-cel curve was set to loglogistic to estimate the loglogistic treatment switching curve for SoC OS).

As described in section 8.4.1, when age adjusting the HSUVs based on the EQ-5D-3L questionnaire from the DMC guideline for age adjusting HRQoL (96), the HSUVs for patients with r/r DLBCL within 12 months of completing 1L

therapy become higher relative to the values for the general Danish population. In a scenario analysis, the HSUVs were decreased to match the general population utilities (EQ-5D-3L values). The Danish general population utility of 0.818 was applied in the pre-event health state, and the post-event utility was decreased by applying the relative difference between the ZUMA-7 pre-event off-treatment utility (0.858) and the ZUMA-1 post-event utility (0.794) to the general population utility (0.818), i.e., 0.818*(0.794/0.858), which gives a HSUV of 0.757 in the post-event health state.

Additionally, the impact of changing the general population utilities to those from Jensen et al. 2021 (97) was explored, i.e., in this case, the HSUVs are lower than the general population utilities. In this case, it was assumed that patients without an event for 5 years reverted to the general population utility, i.e., the health of a patient in long-term remission increases after 5 years without an event.

Table 61 presents an overview of the HSUV, general population utilities and assumptions applied in the two scenario analyses.

Table 61: Overview of the HSUV, general population utilities and assumptions applied in scenario analyses

	Base case	Decreased HSUVs to match the level of the general population (EQ-5D-3L)	General population utilities changed to EQ-5D-5L
Event-free health state			
Axi-cel on-treatment	0.848	0.818	0.848
SoC on-treatment	0.841	0.818	0.841
Off-treatment	0.858	0.818	0.858
Post-event health state			
Post-event	0.794	0.757	0.794
General population utility	EQ-5D-3L (96)	EQ-5D-3L (96)	EQ-5D-5L (97)
Patients who are event-free after 5 years revert to general population utilities	No	No	Yes

The results from the scenario analyses are presented in Table 63.

Table 62: One-way sensitivity analyses results

Parameter	Low value (-20%)	High value (+20%)	Inc. cost low value	Inc. cost high value	Inc. QALY low value	Inc. QALY high value	ICER low value	ICER high value	Diff.
Axi-cel: acquisition cost	1,952,000	2,928,000	1,807,952	2,719,541	4.51	4.51	400,443	602,351	201,908
Hazard ratio SoC OS to axi-	1.92	2.88	2,238,408	2,277,807	3.57	5.18	627,002	439,414	187,588

cel OS (ZUMA-7)									
Axi-cel: % receiving axi-cel	0.91	0.97	2,175,077	2,352,416	4.51	4.51	481,758	521,036	39,279
Population norm male: 70-79	0.65	0.98	2,263,747	2,263,747	4.34	4.69	521,340	482,923	38,417
Utility: post-event	0.74	0.85	2,263,747	2,263,747	4.42	4.61	512,422	490,836	21,587
Mean age (years)	56	58	2,262,910	2,264,866	4.63	4.40	488,707	515,189	26,481
Population norm female: 70-79	0.65	0.98	2,263,747	2,263,747	4.43	4.60	511,476	491,707	19,769
Population norm male: 80+	0.58	0.87	2,263,747	2,263,747	4.43	4.60	511,303	491,867	19,436
Population norm male: 50-59	0.65	0.98	2,263,747	2,263,747	4.44	4.59	509,376	493,664	15,712
Utility: off-treatment pre-event	0.84	0.88	2,263,747	2,263,747	4.43	4.60	510,522	492,592	17,930

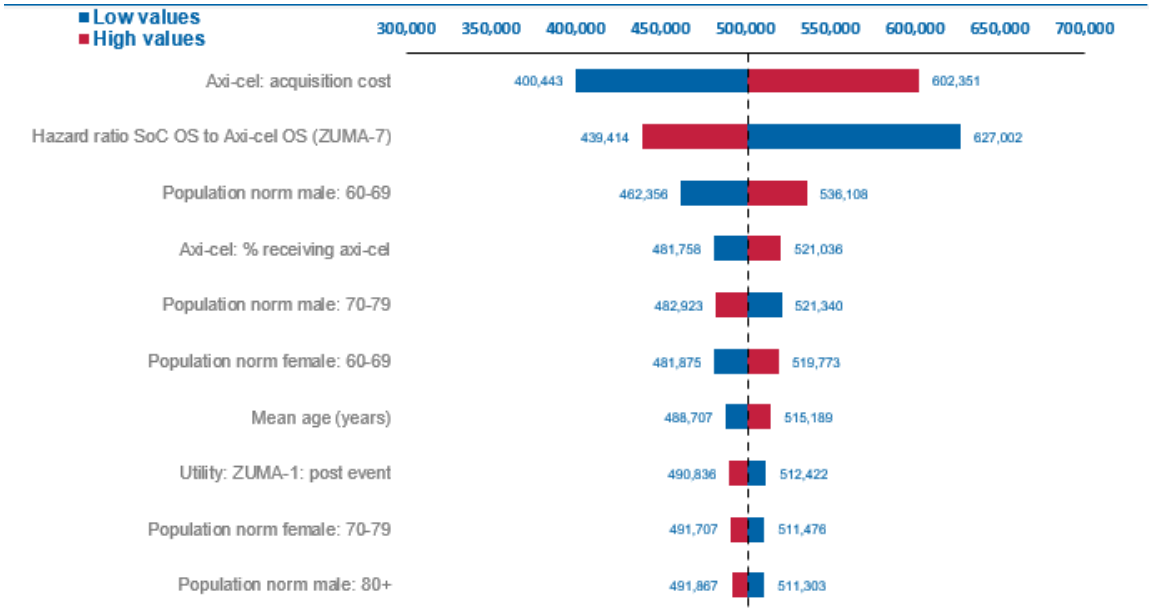

Figure 20: Tornado diagram

Table 63: Scenario analyses

Parameter	Incremental QALY	Incremental cost (DKK)	ICER	Diff. from base case
Time horizon: 5 years	1.06	2,240,762	501,397	1,620,350
Time horizon: 10 years	2.07	2,241,649	501,397	584,052
Time horizon: 25 years	4.03	2,248,775	501,397	56,108
Clinical expert inputs applied in the SoC arm	4.51	2,188,610	501,397	-16,642
Loglogistic curve applied for axi-cel OS	4.31	2,263,743	501,397	23,228
Decreasing HSUVs to reflect the level of the Danish general population	4.30	2,263,747	501,397	24,729
Change general population utilities to EQ-5D-5L values	4.72	2,263,747	479,710	-21,687

The tornado diagram in Figure 20 shows that the base case ICER is highly affected by changes in the PPP of axi-cel and the HR for SoC OS to axi-cel OS. The other parameters included in the DSA had a minor impact on the base case ICER. The scenario analyses with shorter time horizons showed that reducing the time horizon from 50 years to five years had a large impact on the ICER, which could be due to the fact that treatment costs related to ASCT and axi-cel fall in the first year. Reducing the time horizon by 50% (25 years), applying the inputs provided by the clinical expert in the SoC arm, applying the loglogistic curve for axi-cel OS, decreasing the HSUVs to the level of the general Danish population utilities (EQ-5D-3L), or changing the general population utilities to EQ-5D-5L data had less impact on the ICER of the base case.

8.7.2 Probabilistic sensitivity analysis

To assess the uncertainty surrounding the variables included in the model, a PSA was performed using 1,000 iterations. Several parameters in the model are not necessarily fixed values but possess a certain variability. This variability was approximated through the PSA. The PSA evaluated the economic results when several parameters of the models were varied simultaneously. The specific parameters included in the PSA can be found in the Excel model on the sheet “Parameters”. An overview of the PSA data is provided in Appendix J.

Figure 21 presents the cost-effectiveness plane, and Figure 22 illustrates the cost-effectiveness probability at different willingness-to-pay (WTP) thresholds. As seen in Figure 21, all alternative ICERs in the cost-effectiveness place are located in the Northeast quadrant of the graph, where axi-cel is more effective and more costly.

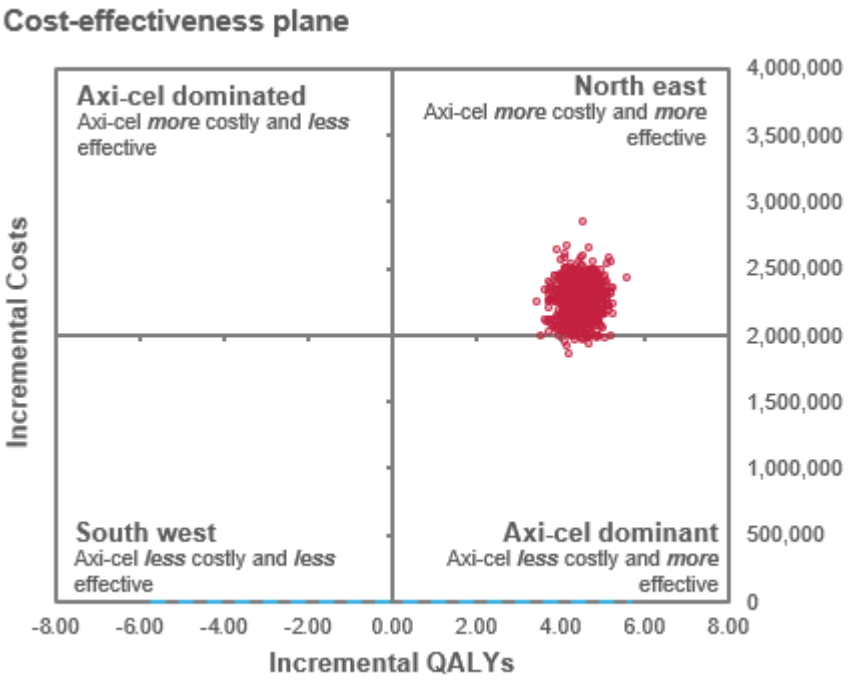

Figure 21: Cost-effectiveness plane from PSA

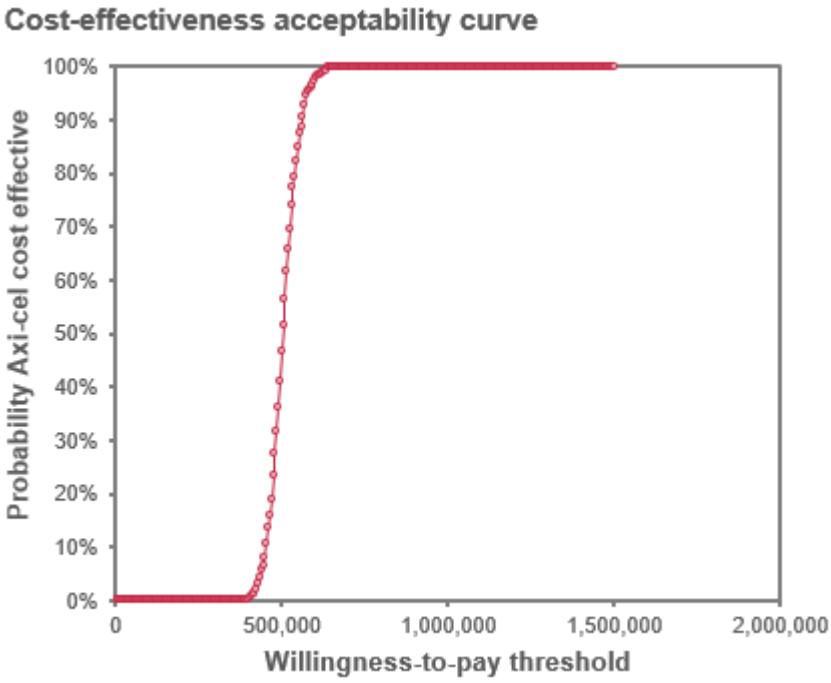

Figure 22: Cost-effectiveness acceptability curve (CEAC) from PSA

9. Budget impact analysis

The purpose of the budget impact analysis is to estimate the budgetary impact of recommending axi-cel as standard 2L treatment of r/r DLBCL patients. The budget impact is estimated per year in the first five years after the recommendation of axi-cel. The budget impact analysis compares the expenditures in the scenario where axi-cel is recommended as a possible standard treatment and the scenario where axi-cel is not recommended as a possible standard treatment. The total budget impact per year is the difference between the two scenarios. The expenditure per patient is equivalent to the cost per patient without patient and transportation costs.

9.1 Number of patients and expected market share

The number of patients with r/r DLBCL ≤12 months after completing 1L therapy who are candidates to axi-cel treatment was estimated based on the following inputs:

- the Danish adult population at risk;
- the incidence of DLBCL in Denmark;
- the proportion with r/r ≤12 months;
- the proportion of patients with r/r ≤12 months who initiate 2L treatment; and
- the proportion of patients who are eligible for ASCT.

Table 64 presents the parameters used to estimate the number of patients who are eligible for axi-cel treatment.

Table 64: Estimation of the number of patients who are eligible for axi-cel treatment

Parameter	Value	Share	Source
Adult population at risk	4,721,691	-	Statistics Denmark
Incidence of DLBCL in Denmark	450	0.01%	DLG
Patients with r/r ≤12 months	35	8%	LYFO register. Validated by the clinical expert
Patients starting 2L treatment	26	74%	LYFO register. Validated by the clinical expert
Patients eligible for ASCT, i.e., candidates to axi-cel	10	38%	LYFO register. Validated by the clinical expert

Table 65 presents the number of patients expected to be treated with axi-cel and SoC over the first five years if axi-cel is introduced. The numbers were estimated based on the number of candidates to axi-cel and the expected patient uptake. Gilead expects that most axi-cel candidates will receive axi-cel if it is recommended and a total of ten patients were included in the budget impact analysis. It is also expected that the uptake will be gradual over the first five years after recommendation. In the budget impact analysis, most eligible patients are assumed to receive axi-cel in year 3 and onwards, if recommended. Table 66 presents the number of patients expected to be treated with axi-cel and SoC over the next five years if axi-cel is not introduced.

Table 65: Number of patients expected to be treated over a five-year period– if axi-cel is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Axi-cel	4	7	9	9	9

	Year 1	Year 2	Year 3	Year 4	Year 5
SoC	6	3	1	1	1
Total number of patients	**10**	**10**	**10**	**10**	**10**

Table 66: Number of patients expected to be treated over a five-year period – if axi-cel is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Axi-cel	0	0	0	0	0
SoC	10	10	10	10	10
Total number of patients	**10**	**10**	**10**	**10**	**10**

9.1.1 Expenditure per patient

In Table 67, we present the cost per patient for the first five years for a patient receiving axi-cel in year 1 and a patient receiving SoC in year 1. The per patient costs are in the budget impact analysis multiplied with the number of patients to estimate the total budget impact if axi-cel is recommended and if axi-cel is not recommended.

Table 67: Cost per patient per year since treatment*

	Year 1	Year 2	Year 3	Year 4	Year 5
Axi-cel	2,495,289	67,485	34,995	23,311	19,464
SoC	325,690	67,749	21,847	10,252	5,849

*Axi-cel and ASCT occur in year 1.

9.2 Budget impact results

An overview of the results of the budget impact analysis is presented in Table 68. The table shows the total costs of treatment per year in the case where axi-cel is recommend and in the case where axi-cel is not recommend as standard treatment. The budget impact of recommending axi-cel for use at the Danish hospitals is DKK 19.8 million in year 5. Over all five years, the budget impact is DKK 82.9 million. It is important to note that the drug costs presented in Table 68 are based on PPPs. A graphic presentation of the results is presented in Figure 23.

Table 68: Expected budget impact of recommending axi-cel for 2L r/r DLBCL ≤12 months (DKK)

	Year 1	Year 2	Year 3	Year 4	Year 5
Axi-cel is recommended	11,935,298	19,120,527	23,729,993	23,923,665	24,102,085

	Year 1	Year 2	Year 3	Year 4	Year 5
Of which: Drug costs	9,683,008	16,367,118	20,820,681	20,830,105	20,832,945
Of which: Hospital costs	2,252,290	2,753,410	2,909,312	3,093,560	3,269,139
Minus: Axi-cel is NOT recommended	3,256,900	3,934,388	4,152,856	4,255,380	4,313,866
Of which: Drug costs	789,412	797,644	798,394	805,464	809,769
Of which: Hospital costs	2,467,487	3,136,744	3,354,462	3,449,916	3,504,097
Budget impact of the recommendation	8,678,398	15,186,139	19,577,138	19,668,285	19,788,219

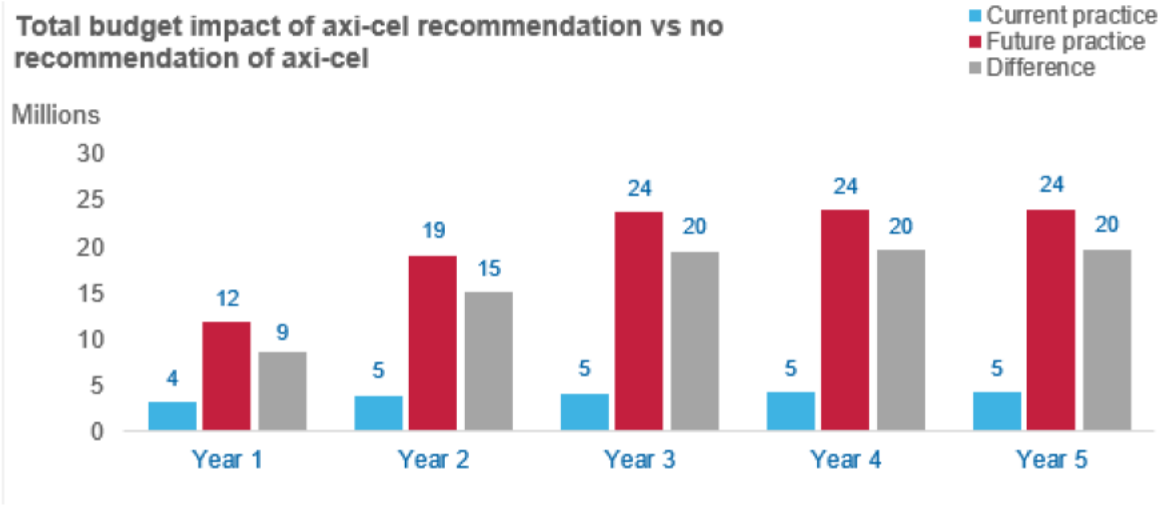

Figure 23: Budget impact each year in the analysis if axi-cel is recommended vs if axi-cel is not recommended, rounded to millions DKK

9.3 Budget impact sensitivity

Sensitivity analyses were performed for the budget impact analysis to assess the uncertainty in the estimated budgetary impact on the Danish regions' budget. The performed sensitivity analyses are presented in Table 69.

Table 69: Sensitivity analyses performed in the budget impact analysis (DKK)

	Year 1		Year 2		Year 3		Year 4		Year 5	
	-20%	+20%	-20%	+20%	-20%	+20%	-20%	+20%	-20%	+20%
Proportion with r/r ≤12 months	6,942,718	10,414,077	12,148,911	18,223,367	15,661,710	23,492,565	15,734,628	23,601,943	15,830,575	23,745,862
Proportion of patients with r/r ≤12 months who initiate 2L treatment	6,942,718	10,414,077	12,148,911	18,223,367	15,661,710	23,492,565	15,734,628	23,601,943	15,830,575	23,745,862
Proportion being eligible for ASCT	6,942,718	10,414,077	12,148,911	18,223,367	15,661,710	23,492,565	15,734,628	23,601,943	15,830,575	23,745,862

10. Discussion on the submitted documentation

Clinical evidence

Axi-cel provides a new innovative, potentially curative treatment option in 2L DLBCL. The clinical documentation for the efficacy and safety of axi-cel was based on the ZUMA-7 trial, the first phase III, randomised, open-label, multicentre study that evaluates the efficacy of axi-cel compared with SoC as 2L therapy in adults with DLBCL who were refractory or relapsed within a year of 1L chemoimmunotherapy.

The primary objective of ZUMA-7 was to determine whether axi-cel is superior to SoC, as measured by central assessment of EFS. The selection of EFS as primary endpoint provides several advantages compared to alternative endpoints such as OS and PFS.

Firstly, OS as the primary endpoint for evaluating efficacy of cancer treatments can be challenging, e.g., due to the molecular, immunophenotypic, and biologic heterogeneity of haematological malignancies (HMs), which present a major challenge for enrolling a sufficient number of patients to adequately power the analysis of OS due to fragmentation of the eligible population (75). With multiple lines of therapy available in most HMs, survival benefit attributable to the new treatment could be confounded by post-progression treatments. As such, surrogate endpoints based on tumour assessment which consider earlier events such as treatment failure, relapse or progression in addition to death may be more meaningful indicators of efficacy in HMs (75).

Secondly, EFS may offer better assessment of the efficacy of a particular drug compared to survival because it is unaffected by subsequent uncontrolled, potentially biased interventions after failure to attain, or relapse from, remission (107–109). In addition, EFS has the advantage of reaching an endpoint sooner than OS: at the 24-month follow-up of the ZUMA-7 trial, 72 (40%) subjects in the axi-cel group and 81 patients (45%) in the SoC group had died (21). Given the earlier occurrence of disease progression/commencement of a new lymphoma therapy (both components of EFS), EFS was quicker to evaluate than survival (21).

Finally, compared to OS and PFS, EFS has the added value of capturing the burden of disease because treatment failure, PR or relapse signify a reduced QoL and substantial morbidity or mortality associated with disease progression, use of toxic salvage therapies or both (75). For patients achieving a durable CR, EFS captures the clinical relevance of delaying or preventing relapse, which is known to increase the likelihood of long-term survival or cure. EFS therefore enables a holistic evaluation of disease-related outcomes of a treatment that may fail to achieve statistical significance on OS. As part of the EMA evaluation, the CHMP stated regarding the ZUMA-7 protocol that ‘the choice of EFS as primary endpoint is endorsed, and it is agreed that it is an appropriate endpoint for demonstrating clinical benefit in 2L DLBCL, as it allows a comprehensive analysis of all the potential clinically relevant positive and negative outcomes’ (110).

In terms of the clinical value of axi-cel as a 2L treatment in DLBCL patients who have relapsed or are refractory within 12 months of 1L chemoimmunotherapy, the ZUMA-7 trial demonstrated the efficacy of axi-cel versus SoC in terms of a 4-fold increase in EFS (8.3 months vs 2.0 months; $p<0.0001$). Furthermore, the safety profile of axi-cel in ZUMA-7 was largely comparable to the one observed in ZUMA-1 and real-world use to date; compared to ZUMA-1, there was a reduced occurrence of CRS, NE, and overall grade ≥3 AEs. In addition, more patients successfully completed treatment with axi-cel vs SoC.

Economic evidence

In the health economic analysis, an incremental QALY gain associated with axi-cel of 4.51 was estimated, and an incremental cost associated with axi-cel of DKK 2,263,747 was estimated. Thus, in the base case, the ICER for axi-cel compared to SoC was DKK 501,397 per QALY. Several sensitivity analyses were undertaken to investigate the robustness of the base case result. The DSA found that the parameters with the largest impact on the base case ICER were the PPP of axi-cel and the HR for SoC OS to axi-cel OS. The PSA included all parameters relevant for the analysis conducted in the present application and showed that axi-cel is a more effective and more costly alternative compared to the current Danish SoC in 100% of the simulations. The robustness of the result was supported by the study by Perales et al. 2022 (111), which evaluated the cost-effectiveness of axi-cel compared to SoC for 2L DLBCL in a US setting. The study reported very similar results to those reported in the present application. Perales et al. 2022 reported an ICER of USD 66,381 per QALY gained (DKK 499,432) compared to the DKK 501,397 per QALY reported in the present application.

To account for the differences in patient characteristics in the ZUMA-7 trial, base case model and Danish clinical practice, the characteristics of the modelled patients were aligned to match the Danish population based on expert clinician feedback and validation.

The CU analysis utilised robust head-to-head data from ZUMA-7 and explored various approaches to extrapolating survival outcomes beyond the ZUMA-7 trial data. These suggest that the existing OS trend observed in the ZUMA-7 trial may grow to substantial long-term benefits for patients with DLBCL. Furthermore, the prolonged EFS as observed for treatment with axi-cel is a key driver in the improvement in HRQoL. These results are supported by the recently published primary PRO analysis of ZUMA-7, which shows a quicker return to normal HRQoL in the axi-cel arm compared to SoC (82).

Many of the inputs applied in the model were either informed or validated by a Danish clinical expert with vast experience in DLBCL or informed by guidelines from Danish hospitals: thus, we are confident that the inputs used in the model reflect Danish clinical practice for treating DLBCL. In addition, the efficacy outcomes applied in the model came from ZUMA-7, which is the largest head-to-head trial of any CAR T vs SoC providing strong evidence for the efficacy of axi-cel relative to current SoC. The model has undergone internal quality checks as well as an external quality assurance process. The model has been “pressure-tested” in advisory board meetings with health economic experts and cost-effectiveness market payers, including review of the ZUMA-7 development plan in 2L DLBCL, review of the CEA methods, model inputs, extrapolation methodology, base case model findings and scenario analysis results.

11. List of experts

Peter Brown, Consultant at the Department of Haematology – Rigshospitalet

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

No literature search was performed in the assessment of axi-cel due to the availability of the head-to-head trial ZUMA-7 where the efficacy and safety of axi-cel compared to SoC was assessed.

Appendix B Main characteristics of the ZUMA-7 trial

Table 70: Main characteristics of the ZUMA-7 trial

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	**NCT number: NCT03391466**
Objective	The primary objective of the ZUMA-7 trial was to determine if Yescarta® is superior to SoC in the treatment of r/r DLBCL as measured by EFS determined by blinded central review. The key secondary objectives were to evaluate the efficacy of Yescarta® compared to SoC for ORR, OS, EFS based on investigator disease assessments, mEFS, PFS, DOR and duration of CR among responding patients, safety, patient-reported outcomes (PROs) and HRQoL.

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	NCT number: NCT03391466

Publications – title, author, journal, year	**Publications listed for the ZUMA-7 trial on clinicaltrials.gov** Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, Lister TA; Alliance, Australasian Leukaemia and Lymphoma Group; Eastern Cooperative Oncology Group; European Mantle Cell Lymphoma Consortium; Italian Lymphoma Foundation; European Organisation for Research; Treatment of Cancer/Dutch Hemato-Oncology Group; Grupo Español de Médula Ósea; German High-Grade Lymphoma Study Group; Germa' Hodgkin's Study Group; Japanese Lymphoma Study Group; Lymphoma Study Association; NCIC Clinical Trials Group; Nordic Lymphoma Study Group; Southwest Oncology Group; United Kingdom National Cancer Research Institute. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014 Sep 20;32(27):3059-68 (65). Swerdlow SH, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. Blood. 2016 May 19;127(20):2375-90. doi: 10.1182/blood-2016-01-643569. Epub 2016 Mar 15. Review (19). The Lancet Haematology. The role of conferences in tackling inequalities. Lancet Haematol. 2022 Feb;9(2):e81. doi: 10.1016/S2352-3026(22)00008-4 (112). Del Pozo Martín Y. 2021 ASH annual meeting. Lancet Haematol. 2022 Feb;9(2):E92-e93. doi: 10.1016/S2352-3026(21)00384-7. Epub 2021 Dec 16 (113). Locke FL, Miklos DB, Jacobson CA, Perales MA, Kersten MJ, Oluwole OO, Ghobadi A, Rapoport AP, McGuirk J, Pagel JM, Muñoz J, Farooq U, van Meerten T, Reagan PM, Sureda A, Flinn IW, Vandenberghe P, Song KW, Dickinson M, Minnema MC, Riedell PA, Leslie LA, Chaganti S, Yang Y, Filosto S, Shah J, Schupp M, To C, Cheng P, Gordon LI, Westin JR; All ZUMA-7 Investigators and Contributing Kite Members. Axicabtagene Ciloleucel as Second-Line Therapy for Large B-Cell Lymphoma. N Engl J Med. 2022 Feb 17;386(7):640-654. doi: 10.1056/NEJMoa2116133. Epub 2021 Dec 11 (63). Ernst M, Oeser A, Besiroglu B, Caro-Valenzuela J, Abd El Aziz M, Monsef I, Borchmann P, Estcourt LJ, Skoetz N, Goldkuhle M. Chimeric antigen receptor (CAR) T-cell therapy for people with relapsed or refractory diffuse large B-cell lymphoma. Cochrane Database Syst Rev. 2021 Sep 13;9:Cd013365. doi: 10.1002/14651858.CD013365.pub2. Review (114). Kambhampati S, Hunter B, Varnavski A, Fakhri B, Kaplan L, Ai WZ, Pampaloni M, Huang CY, M[ar]tin T 3rd, Damon L, Andreadis CB. Ofatumumab, Etoposide, and Cytarabine Intensive Mobilization Regimen in Patients with High-risk Relapsed/Refractory Diffuse Large B-Cell Lymphoma Undergoing Autologous Stem Cell Transplantation. Clin Lymphoma Myeloma Leuk. 2021 Apr;21(4):246-256.e2. doi: 10.1016/j.clml.2020.11.005. Epub 2020 Nov 11 (115).
Study type and design	The ZUMA-7 trial was an international, randomised, open-label, multicentre phase 3 study. After screening, patients underwent randomisation in a 1:1 ratio to receive axi-cel or investigator-selected 2L SoC chemo-immunotherapy. Randomisation was stratified according to response to 1L therapy (refractory vs relapsed disease) and the 2L age-adjusted IPI (IPI 0 or 1 risk factor indicating low or intermediate risk vs 2 or 3 risk factors indicating high risk) (63).

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	NCT number: NCT03391466

Sample size (n)

437 patients were screened for participation in the ZUMA-7 trial and 359 underwent randomisation. A total of 180 patients were assigned to the axi-cel group and 179 to the standard-care group (63).

	Axi-cel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Full analysis set, n (%)	180 (100)	179 (100)	359 (100)
Safety analysis set, n (%)	170 (94)	168 (94)	338 (94)
Safety anal–sis set - ASCT, n (%)	NA	62 (35)	62 (17)
QoL analysis set, n (%)	165 (92)	131 (73)	296 (82)
Retreatment analysis set, n (%)	9 (5)	NA	9 (3)

Note: The full analysis set consists of all randomised subjects and subjects are analysed based on randomised treatment arm. The safety analysis set is defined as the subset of all randomised subjects who receive at least 1 dose of axi-cel as protocol therapy or standard of care salvage chemotherapy as protocol therapy, and subjects are analysed by the protocol therapy they received. The safety analysis set – ASCT is defined as the subset of subjects who are randomised to the standard of care therapy arm and undergo ASCT as part of protocol therapy. The QoL analysis set is defined as the subset of subjects in the full analysis set who have a baseline and any post baseline assessment up to Day 150 post-randomisation QoL assessment. The safety retreatment analysis set consists of subjects in the axi-cel arm who undergo retreatment with axi-cel (63).

Main inclusion and exclusion criteria	**Key inclusion criteria** • Histologically proven large B-cell lymphoma, including the following types defined by WHO 2016: DLBCL not otherwise specified (GCB or activated B-cell type [ABC]) High-grade B-cell lymphoma (HGBL) with or without MYC and BCL2 and/or BCL6 rearrangement DLBCL arising from FL T-cell/histiocyte rich large B-cell lymphoma DLBCL associated with chronic inflammation Primary cutaneous DLBCL, leg type Epstein-Barr virus (EBV) + DLBCL • Relapsed or refractory disease after 1L chemoimmunotherapy o Refractory disease defined as no complete remission to 1L therapy; individuals who are intolerant to 1L therapy are excluded. • PD as best response to 1L therapy • SD as best response after at least 4 cycles of 1L therapy (e.g., four cycles of R-CHOP) • PR as best response after at least 6 cycles and biopsy-proven residual disease or disease progression ≤12 months of therapy • Relapsed disease defined as complete remission to 1L therapy followed by biopsy-proven relapse ≤12 months of 1L therapy • Individuals must have received adequate 1L therapy, including at a minimum: o anti-CD20 monoclonal antibody unless investigator determines that tumour is CD20-negative; and o an anthracycline-containing chemotherapy regimen. • No known history or suspicion of CNS involvement by lymphoma • Eastern cooperative oncology group (ECOG) performance status of 0 or 1 • Adequate bone marrow function, as evidenced by: o absolute neutrophil count (ANC) ≥ 1000/uL; o platelet ≥75,000/uL; and o absolute lymphocyte count ≥ 100/uL. • Adequate renal, hepatic, cardiac, and pulmonary function as evidenced by: o creatinine clearance (Cockcroft Gault) ≥ 60 mL/min; o serum alanine aminotransferase/aspartate aminotransferase (ALT/AST) ≤ 2.5 Upper limit of normal (ULN); o total bilirubin ≤ 1.5 mg/dl;

- cardiac ejection fraction ≥50%, no evidence of pericardial effusion as determined by an echocardiogram (ECHO), and no clinically significant electrocardiogram (ECG) findings;
- no clinically significant pleural effusion; and
- baseline oxygen saturation >92% on room air.

Key exclusion criteria

- History of malignancy other than nonmelanoma skin cancer or carcinoma in situ (e.g., cervix, bladder, breast) unless disease-free for at least 3 years
- Received more than one line of therapy for DLBCL
- History of autologous or allogeneic SCT
- Presence of fungal, bacterial, viral, or other infection that is uncontrolled or requiring intravenous antimicrobials for management
- Known history of infection with human immunodeficiency virus (HIV) or hepatitis B (HBsAg positive) or hepatitis C virus (anti-HCV positive). If there is a positive history of treated hepatitis B or hepatitis C, the viral load must be undetectable per quantitative polymerase chain reaction (PCR) and/or nucleic acid testing.
- Individuals with detectable cerebrospinal fluid malignant cells or known brain metastases, or with a history of cerebrospinal fluid malignant cells or brain metastases
- History or presence of non-malignant CNS disorder such as seizure disorder, cerebrovascular ischemia/haemorrhage, dementia, cerebellar disease, or any autoimmune disease with CNS involvement
- Presence of any indwelling line or drain. Dedicated central venous access catheter such as a Port-a-Cath or Hickman catheter are permitted.
- History of myocardial infarction, cardiac angioplasty or stenting, unstable angina, New York Heart Association Class II or greater congestive heart failure, or other clinically significant cardiac diseases within 12 months of enrolment
- History of symptomatic deep vein thrombosis or pulmonary embolism within 6 months of enrolment
- History of autoimmune disease, requiring systemic immunosuppression and/or systemic disease-modifying agents within the last 2 years
- History of anti-CD19 or CAR-T therapy or history of prior randomisation in ZUMA-7

Note: Other protocol-defined Inclusion/Exclusion criteria may apply.

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	NCT number: NCT03391466
Intervention	A total of 180 patients were randomly assigned to receive axicabtagene ciloleucel. Patients randomised to the axi-cel arm of the study underwent leukapheresis (for collection of T-cells to manufacture the patient's dose of axicabtagene ciloleucel), optional bridging therapy (to temporise high disease burden), lymphodepleting chemotherapy (to deplete the subject's endogenous lymphocytes and to promote a favourable cytokine and chemokine environment for optimal CAR T-cell expansion and function), followed by infusion of axi-cel as a single infusion with a target dose of 2×10^6 CAR T-cells per kg of body weight (63).
Comparator(s)	A total of 179 patients were randomised to receive SoC, which comprised investigator-selected SoC chemoimmunotherapy (63). Two or three cycles of platinum-based chemo-immunotherapy were given (R-ICE, R-ESHAP, R-GDP, R-DHAP or R-DHAX). Patients who had a complete or partial response proceeded to HDT + ASCT (63). Patients who did not respond could receive additional treatment off the protocol. 16 patients (10%) received 1 cycle, 91 patients (54%) received 2 cycles, and 61 patients (36%) received 3 cycles of SoC chemotherapy.
Follow-up time	Disease assessments occurred on days 50, 100, and 150 after randomisation, followed by every three months until two years of follow-up, and then every six months until five years of follow-up (five years follow-up are expectedly reached in 2023. Analyses to be used for this assessment have a median follow-up of 24.9 months (63).
Is the study used in the health economic model?	Yes

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	NCT number: NCT03391466

Primary, secondary and exploratory endpoints	**Primary endpoints** EFS: defined as the time from randomisation to the earliest date of disease progression according to the Lugano classification (65), the commencement of new therapy for lymphoma, death from any cause, or a best response of SD up to and including the response on the day 150 assessment after randomisation, according to blinded central review **Key secondary endpoints** ORR OS **Other secondary endpoints** • Modified EFS (defined the same way as EFS, except that failure to attain CR or PR by day 150 assessment is not considered an event) by blinded central review and investigator assessment PFS (defined per Lungano classification or death) DOR by blinded central assessments Percentage of adverse events and clinically significant changes in safety lab values, including antibodies to axicabtagene ciloleucel, changes from screening in the global health status QoL scale and the physical functioning domain of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 (EORTC QLQ-C30) Changes from screening in the Euro-QoL, 5 dimensions, 5 levels (EQ-5D-5L) index and visual analogue scale (VAS) scores **Exploratory endpoints** For axi-cel treatment arm only: Levels of cytokines in the serum Levels of anti-CD19 CAR T cells in blood For both treatment arms: Tumour molecular and histological characteristics by level of CD19, programmed death ligand 1, and molecular and cytogenetic subclassifications Changes in the Work Productivity and Activity Impairment Questionnaire (WPAI) from screening to post-baseline TTNT

Trial name: A Phase 3, Randomized, Open-Label, multicentre study Evaluating the Efficacy of Axicabtagene Ciloleucel versus Standard of Care Therapy in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma (ZUMA-7)	NCT number: NCT03391466
Method of analysis	The protocol-specified primary efficacy analysis was to be conducted when 250 events, as assessed by blinded central review, had occurred. Statistical testing of the primary and key secondary end points was conducted hierarchically. Event-free survival was tested first; conditional on significantly longer event-free survival being observed in the axi-cel group than in the standard-care group, response was tested at the 2.5% level at the time of the primary analysis of event-free survival. Conditional on significantly longer event-free survival and a significantly higher percentage of patients with a response being observed in the axi-cel group than in the standard of care group, OS was to be tested up to three times, according to the rho-family spending function, at an overall alpha level of 2.5%. The primary analysis of OS occurred after 210 OS events were observed or no later than five years after the first subject was randomised. The study was originally planned for three looks (K=3), including two for interim analyses and a final analysis. Efficacy analyses were conducted according to the intention-to-treat principle and included all the patients who underwent randomisation. Kaplan–Meier estimates were provided for time-to-event endpoints. Estimated hazard ratios with two-sided 95% CIs were calculated from a Cox proportional-hazards model with stratification according to the randomisation stratification factors. Stratified log-rank P values (two-sided) were calculated for time-to-event endpoints. A stratified Cochran– Mantel–Haenszel test was performed for analysis of response.
Subgroup analyses	In the assessment of axi-cel, we will not include data on any subpopulation from the ZUMA-7 trial. However, in the ZUMA-7 trial, EFS has been analysed in subgroups based on the following covariates (63): • Age at randomisation (≥65, <65) • Response to 1L therapy (primary refractory, relapse ≤6 months of initiation of 1L therapy vs relapse >6 and ≤12 months of initiation or completion of first-line therapy) • Age-adjusted IPI (0-1 vs 2-3) at time of screening • Molecular subgroup (GBC, ABC) • Double hit (C-MYC alterations and either BCL-2 or BCL-6 alterations) status by FISH Triple hit (BCL-2, BCL-6, and C-MYC alterations) status by FISH.
Other relevant information	None

Appendix C Baseline characteristics of patients ZUMA-7 used for the comparative analysis of efficacy and safety

Table 71 presents the baseline characteristics of the patient population from the ZUMA-7 trial.

Table 71: Baseline characteristics of patients in included in the ZUMA-7 trial. Source: Locke et al. (63).

Characteristic	Axi-cel	Standard Care	Total
	(N = 180)	(N = 179)	(N = 359)
Age			
Median (range) – years	58 (21-80)	60 (26-81)	59 (21-81)
≥65 year – no. (%)	51 (28)	58 (32)	109 (30)
Male sex – no. (%)	110 (61)	127 (71)	237 (66)
Race or ethnic group – no. (%)†			
American Indian or Alaska Native	0	1 (1)	1 (<1)
Asian	12 (7)	10 (6)	22 (6)
Black	11 (6)	7 (4)	18 (5)
Native Hawaiian or other Pacific Islander	2 (1)	1 (1)	3 (1)
White	145 (81)	152 (85)	297 (83)
Other	10 (6)	8 (4)	18 (5)
Hispanic or Latino ethnic group – no. (%)†			
Yes	10 (6)	8 (4)	18 (5)
No	167 (93)	169 (94)	336 (94)
Not reported	3 (2)	2 (1)	5 (1)
ECOG performance-status score of 1 – no. (%)‡	85 (47)	79 (44)	164 (46)
Disease stage – no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	146 (82)	285 (79)
Second-line age-adjusted IPI or 2 or 3 (no. (%)§	82 (46)	79 (44)	161 (45)
Molecular subgroup according to central laboratory – no.(%)¶			

Germinal center B-cell-like	109 (61)	99 (55)	208 (58)
Activated B-cell-like	16 (9)	9 (5)	25 (7)
Unclassified	17 (9)	14 (8)	31 (9)
Not applicable	10 (6)	16 (9)	26 (7)
Missing data	28 (16)	41 (23)	69 (19)
Response to first-line therapy at randomisation – no. (%)			
Primary refractory disease	133 (74)	131 (73)	264 (74)
Relapse at ≤12 months after the imitation or completion of first line-therapy	47 (26)	48 (27)	95 (26)
Disease type according to central laboratory – no. (%)			
Diffuse large B-cell lymphoma‖	126 (70)	129 (67)	246 (69)
High-grade B-cell lymphoma, not otherwise specified	0	1 (1)	1(<1)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BCL6 or both	31 (17)	25 (14)	56 (16)
Not confirmed or missing data	18 (10)	28 (16)	46 (13)
Other	5 (3)	5 (3)	10 (3)
Disease type according to the investigator – no. (%)			
Large B-cell lymphoma, not otherwise specified	110 (61)	116 (65)	226 (63)
T-cell or histiocyte-rich large B-cell lymphoma	5 (3)	6 (3)	11 (3)
Epstein-Barr virus-positive diffuse large B-cell Lymphoma	2 (1)	0	2 (1)
Large-cell transformation from follicular lymphoma	19 (11)	27 (15)	46 (13)
High-grade B-cell lymphoma, including rearrangement of MYC with BCL2 or BL6 or both	43 (24)	27 (15)	70 (19)
Primary cutaneous diffuse large B-cell lymphoma, leg type	1 (1)	0	1 (<1)
Other	0	3 (2)	3 (1)
Prognostic marker according to central laboratory – no. (%)			
High-grade B-cell lymphoma, double or triple hit	31 (17)	25 (14)	56 (16)

Double-expressor lymphoma	57 (32)	62 (35)	119 (33)
MYC rearrangement	15 (8)	7 (4)	22 (6)
Not applicable	74 (41)	70 (39)	144 (40)
Missing data	3 (2)	15 (8)	18 (5)
CD19+ status on immunohistochemical testing – no. (%)**	144 (80)	134 (75)	278 (77)
Bone marrow involvement – no. (%)††	17 (9)	15 (8)	32 (9)
Elevated lactate dehydrogenase level – no. (%)‡‡	101 (56)	94 (53)	195 (54)
Median tumour burden (Range) mm^2§§	2123 (181-22,538)	2069 (251-20,117)	2118 (181-22,538)

* Patients were randomly assigned to receive axi-cel (axi-cel) or standard care. Percentages may not total 100 because of rounding.

† Race and ethnic group were determined by the investigator.

‡ Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with a score of 0 indicating no symptoms and higher scores indicating greater disability. A score of 1 indicates that the patient is ambulatory but restricted from strenuous activity.

§ Values are the second-line age-adjusted International Prognostic Index (IPI) at randomisation, which were similar to the second-line age-adjusted IPI according to the investigator as entered into the clinical database. The second-line age-adjusted IPI is used to assess prognostic risk on the basis of various factors after adjustment for patient age and extranodal status at the time of diagnosis of refractory disease; risk categories are assessed as low (0 factors), intermediate (1 factor), or high (2 or 3 factors).

¶ The molecular subgroup as assessed by the investigator was as follows: germinal center B-cell–like in 96 patients (53%) in the axi-cel group, 84 (47%) in the standard-care group, and 180 (50%) overall; non–germinal center B-cell–like in 47 (26%), 54 (30%), and 101 (28%), respectively. The molecular subgroup was not assessed in 37 patients (21%) in the axi-cel group, 41 (23%) in the standard-care group, and 78 (22%) overall.

‖ The definition of diffuse large B-cell lymphoma according to the central laboratory included cases of incomplete evaluation that were due to inadequate sample amount or sample type, for which further classification of the subtype was not possible. Diffuse large B-cell lymphoma, not otherwise specified, according to the World Health Organization 2016 definition,12 is also included.

** CD19 staining was not required for participation in the trial. Testing was conducted by the central laboratory.

†† The data shown were as collected on the diagnosis history case-report form.

‡‡ An elevated lactate dehydrogenase level was defined as a level that was above the upper limit of the normal range according to the local laboratory.

§§ Tumour burden was determined on the basis of the sum of product diameters of the target lesions, according to the Cheson criteria,16 and was assessed by the central laboratory.

Comparability of patients across studies

Not applicable since only one study was included.

Comparability of the study population with Danish patients eligible for treatment

The Danish clinical experts consulted during the preparation of the present application gave a description of the Danish patient population with r/r DLBCL. The Danish clinical experts informed that the median age at relapse in Denmark is 69 years compared to a median age of the total ZUMA-7 population of 59 years. Around 67% of those who

relapse are ≥65 years in Denmark, which was 30% of the total population in the ZUMA-7 trial. According to the experts, most relapsed patients are men, and they indicated that 40% of patients who have been treated with 1L therapies have refractory disease after 1L therapies, i.e., have SD as best response to 1L therapies. In the ZUMA-7 trial, 66% of the total population were men, and 74% of the total population had primary refractory disease after 1L therapy. They also informed that 97% of the Danish patient population have DLBCL as disease type compared to 69% of the total population from the ZUMA-7. The rest of the characteristics in Table 71 were similar between the Danish population and the trial population.

GILEAD

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table 72: Definition, validity and clinical relevance of included outcomes from the ZUMA-7 trial

Outcome measure	Definition	Validity	Clinical relevance
EFS	In ZUMA-7, EFS was defined as the time from randomisation to the earliest date of disease progression per the Lugano Classification (65), commencement of new lymphoma therapy, death from any cause, or a best response of SD up to and including the response on the day 150 assessment after randomisation, according to blinded central review.	There is comprehensive evidence for the validity of EFS as a trial-level and a patient-level surrogate for OS in 1L DLBCL from a large-scale meta-analysis of RCTs and patient-level data from retrospective cohorts (29,80,116,117). Together, these analyses established EFS at 12 months and EFS at 24 months as robust early efficacy endpoints and prognostic surrogates for OS in newly diagnosed DLBCL patients treated with immunochemotherapy. Landmark survival analyses of observational data also identified EFS at 24 months as a strong predictor of long-term survival following 1L treatment of lymphoma indications, with achievement of EFS at 24 months indicative of stabilisation or normalisation of mortality compared to the sex- and age-matched general population (116,118–121). Full validation of surrogacy in these indications will require further correlation studies in the context of RCTs. The patient-level correlation between EFS and OS in r/r DLBCL after ASCT is complicated by the	EFS is increasingly used as a primary endpoint in trials of HM such as lymphomas (75). The selection of EFS as primary endpoint provides several advantages compared to alternative endpoints such as OS and PFS. OS as the primary endpoint for evaluating cancer drugs can be challenging, e.g., due to the molecular, immunophenotypic, and biologic heterogeneity of HMs, which present a major challenge for enrolment of patient numbers sufficient to adequately power analysis of OS due to fragmentation of the eligible population (75). With multiple lines of therapy available in most HMs, survival benefit attributable to the new treatment could be confounded by post-progression treatments. As such, surrogate endpoints based on tumour assessment which consider earlier events such as treatment failure, relapse or progression in addition to death may be more meaningful indicators of efficacy in HMs and could also accelerate drug development (75). In addition, the FDA and EMA consider EFS an appropriate surrogate endpoint for both the traditional and the accelerated approval in HMs (75). EFS may offer better assessment of the efficacy of a particular drug compared to survival because it is unaffected by subsequent uncontrolled, potentially biased interventions after failure to attain, or relapse from, remission (107–109). EFS has the advantage of reaching an endpoint sooner than OS: at the 24-month follow-up of the ZUMA-7 trial, 72 (40%) subjects in the axi-cel group and 81 (45%) of the SoC arm had died (21). Given the earlier occurrence of disease progression/commencement of a new lymphoma therapy (both components of

Outcome measure	Definition	Validity	Clinical relevance
		disease- and treatment-specific considerations. EFS at month 12 and EFS at 24 months were shown not to be strong surrogates for OS following ASCT due to ongoing risk of relapse and rapid progression since the efficacy of ASCT in this population is limited, with 5-year EFS around 40% (total cohort, n=215) and lymphoma relapse being a dominant cause of death (9,122). Once event-free status for at least 5 years post-ASCT has been achieved, a correlation with OS can be drawn.	EFS), EFS was quicker to evaluate than survival (21). Compared to OS and PFS, EFS has the added value of capturing the burden of disease because treatment failure, PR or relapse signify a reduced QoL and substantial morbidity or mortality associated with disease progression, use of toxic salvage therapies or both (75). For patients achieving a durable CR, EFS captures the clinical relevance of delaying or preventing relapse, which is known to increase the likelihood of long-term survival or cure. EFS therefore enables a holistic evaluation of disease-related outcomes of a treatment that may fail to achieve statistical significance on OS. As part of the EMA evaluation, the CHMP stated with regard to the ZUMA-7 protocol that 'the choice of EFS as primary endpoint is endorsed and it is agreed that it is an appropriate endpoint for demonstrating clinical benefit in 2L DLBCL as it allows a comprehensive analysis of all the potential clinically relevant positive and negative outcomes' (110).
OS	In the ZUMA-7 trial, OS was defined as the time from randomisation to death from any cause.	See clinical relevance.	OS is the golden standard for demonstrating efficacy in cancer studies and is a patient-relevant outcome. In the present analysis, OS was analysed as an interim analysis of 24 months. In previous DMC evaluations of CAR T-cell therapy in DLBCL, the expert committee has stated that it was relevant to assess OS after 2 years, and that 10 percentage points was a clinically relevant difference in the proportion of patients being alive after 2 years (36,123,124).
PFS	In the ZUMA-7 trial, PFS was defined as the time from randomisation to disease progression per the Lugano Classification (65), as determined by investigator assessment or death from any cause.	See clinical relevance.	PFS is a frequently used outcome for demonstrating efficacy in cancer studies. In previous DMC evaluations of CAR T-cell therapy in DLBCL, the expert committee has stated that based on their vast experience with the currently available treatments for DLBCL, an improvement of 3 months in median PFS is clinically relevant (36,124).

Outcome measure	Definition	Validity	Clinical relevance
ORR	In the ZUMA-7 trial, ORR was defined as the incidence of either a CR or a PR by the Lugano Classification (65).	See clinical relevance.	Response rates have been suggested as an important outcome by the expert committee in a previous CAR T-cell therapy protocol, where the expert committee was interested in the proportion of patients achieving CR (36). CR was regarded as relevant, as CR increases the patient's possibility of being cured, potentially through STC. The expert committee determined a clinically relevant difference in the proportion of patients achieving CR of 10 percentage points after 1 year.
DOR	In the ZUMA-7 trial, DOR was defined as the time from first response to disease progression per the Lugano Classification (65) or death from any cause.	See clinical relevance.	It is clinically relevant to assess the duration of response because the effect of the drug on this outcome is attributable directly to the drug, not the natural history of the disease (125). In addition, DOR requires a smaller population and can be assessed earlier compared with, e.g., OS (125). For the present analysis, DOR is less favourable for axi-cel compared to other outcomes, mainly because DOR is calculated from the start of CR or PR, so the patient number in the SoC group is quite low for DOR analysis, as most of the patients in the SoC group did not respond to salvage chemotherapy and received 3L treatment (i.e., they are not part of the DOR calculation). It was assumed that >60% of the responders in the SoC group are mostly patients who have undergone SCT, comparison of DOR is mostly axi-cel vs ASCT.
TTNT	In the ZUMA-7 trial, TTNT was defined as the time from the randomisation date to the start of the subsequent new lymphoma therapy (including retreatment or subsequent SCT for subjects	See clinical relevance.	For aggressive cancers with a poor prognosis such as r/r DLBCL, the time to next therapy is a clinically relevant outcome, especially for patients (125). TTNT is a clinically meaningful outcome that reflects duration of disease and symptom control (125). In addition, TTNT offers a better reflection of the patient's treatment experiences than conventional disease-related outcomes by incorporating the time course of treatment tolerability and patient compliance (125).

Outcome measure	Definition	Validity	Clinical relevance
	in the axi-cel group) or death from any cause.		
QoL	QoL was assessed with the EQ-5D-5L VAS questionnaire, which is a generic and preference-weighted measure of health status captured on the day of assessment.	The EQ-5D-5L is a comprehensive and widely used to assess HRQoL in cancer research, including studies with non-Hodgkin's lymphoma. The EQ-5D has been validated in cancer populations and has shown evidence for reliability and validity (126).	The EQ-5D-5L is a widely used PRO survey designed to measure HRQoL in the general population and used in a vast number of clinical trials of new drugs. The minimal clinically relevant difference was defined as a change of 0.06 point in the EQ-5D-5L index and a change of 7 points from screening in EQ-5D-5L VAS score (127).

Results per study

Table 73: Results from the ZUMA-7 trial

NCT number: NCT03391466											
				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**		
EFS	Axi-cel	180	Median EFS at month 24: 8.3 months (95% CI: 4.5, 15.8)	3.0 months	1.9, 4.5	Not reported	HR: 0.40	0.31, 0.51	<0.001	The median EFS was from Kaplan Meier analysis.HR with 95% CI was calculated from a Cox proportional-hazards model with stratification	Locke et al. 2021 (63)

NCT number: NCT03391466												
				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		
	SoC	179	Median EFS at month 24: 2.0 months (95% CI: 1.6, 2.8)							according to the randomisation stratification factors (response to 1L therapy (primary refractory versus relapse ≤6 months of 1L therapy versus relapse >6 and ≤12 months of 1L therapy) and 2L age-adjusted IPI (0 to 1 versus 2 to 3) as collected via interactive voice/web response system (63)). The absolute difference was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68).	
OS	Axi-cel	180	OS rate at month 24: 61% (53%, 68%)							The interim OS analysis presented in Locke et al. 2021 was updated to include data on 14 discontinued patients. The survival rates were from Kaplan Meier analysis. Stratified Cox regression models were used to provide the estimated OS HR and 95% CLs. The absolute difference was calculated based on the HR using the method suggested in Appendix 6 in the DMC guideline (68).	Locke et al. 2021 (63)
	SoC	179	OS rate at month 24: 51.3% (43.4%, 58.7%)	11%	1%, 19%	Not reported	HR: 0.71	0.52, 0.97	0.0159		

NCT number: NCT03391466												
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
PFS	Axi-cel	180	Median PFS at month 24: 14.7 months (5.4, not estimable)	3.9	2.0, 6.3	Not reported	HR: 0.49	0.37, 0.65	<.0001	The analysis of PFS was conducted on the FAS population and analysed with the same methods as the analysis of EFS. Disease outcomes were based on investigator assessment. Stratified Cox regression models were used to provide the estimated HR and 95% CIs for axi-cel relative to SoC. The absolute difference was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68).	Locke et al. 2021 (63)
	SoC	179	Median PFS at month 24: 3.7 months (2.9, 5.3)								
ORR	Axi-cel	180	83% (77.1%, 88.5%)	34.0%	25.4%, 39.7%)	Not reported	RR: 1.7	1.5, 1.8	Not reported	A stratified CMH test was performed, and the OR from the CMH test was used to calculate the RR according to the method suggested in Appendix 2 in the DMC guideline (68). The absolute difference in rates was estimated based on the calculated RR according to the method suggested in Appendix 5 in the DMC guideline (68). The stratification factors in the CMH test were the same as for EFS.	Locke et al. 2021 (63)
	SoC	179	50% (42.7%, 57.8%)								

NCT number: NCT03391466											
				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		
DOR	Axi-cel	180	Median: 26.9 months (13.6, not estimable)	Difference in DOR rates at 24 months: 10%	-0.3%, 22%	Not reported	HR: 0.74	0.49, 1.12	0.0695	The analysis of DOR was performed using the same methods as the analysis of EFS. Stratified Cox regression models were used to provide the estimated HR and 95% CIs for axi-cel relative to SoC. The absolute difference in rates was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68).	Locke et al. 2021 (63)
	SoC	179	Median: 8.9 months (5.7, not estimable)								
TTNT	Axi-cel	180	[redacted]	[redacted]						The analysis of TTNT was performed in the FAS population using the same methods as the analysis of EFS. Stratified Cox regression models were used to provide the estimated HR and 95% CIs for axi-cel relative to SoC. The absolute difference in medians was calculated based on the HR with the method suggested in Appendix 6 in the DMC guideline (68).	Data on file (21)
	SoC	179	[redacted]		[redacted]	Not reported	[redacted]	[redacted]	[redacted]		

NCT number: NCT03391466												
				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		
EQ-5D-5L VAS	Axi-cel	[redacted]	[redacted]	[redacted]	[redacted]	Not reported	NA	NA	NA	All PROs were assessed at screening (within 14 days of randomisation), start of chemotherapy (within 5 days of randomisation in the SoC group and 5 days prior to the administration of axi-cel in the axi-cel group), the date of the axi-cel administration or the date of transplant, day 50 (-7 to +21 days after randomisation), day 100 (± 14 days) and day 150 (± 14 days). In the long-term follow-up period beginning at month 9, PROs were assessed every three months (± 28 days) until month 24.	Data on file (21)
	SoC	[redacted]	[redacted]								
EQ-5D-5L VAS MMRM–Axi-cel - SoC	[redacted]	[redacted]	[redacted]			[redacted]	NA	NA	NA	Estimates from MMRM model. Adjusted p-values were calculated using the False Discovery Rate methodology.	Data on file (21)
			[redacted]			[redacted]	NA	NA	NA		

NCT number: NCT03391466												
				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		
			[redacted]			[redacted]	NA	NA	NA		
			[redacted]			[redacted]	NA	NA	NA		
			[redacted]			[redacted]	NA	NA	NA		

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Appendix E Safety data for axi-cel and SoC

ZUMA-7 (NCT03391466)

				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**		
Proportion of subjects with at least one TEAE	Axi-cel	170	100% (98%, 100%)	0%	-2.0%, 2.0%	Not reported	RR: 1.0	1.0, 1.0	Not reported	Absolute differences in proportions presented and relative differences presented as RR. 95% CI calculated with Clopper-Pearson's exact method.	Locke et al. 2021 (63)
	SoC	168	100% (98%, 100%)								
Proportion of subjects with at least one Grade 3 or higher TEAE	Axi-cel	170	91% (86.9%, 95.4%)	7.8%	0.8%, 14.9%	Not reported	RR: 1.1	1.0, 1.2	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Locke et al. 2021 (63)
	SoC	168	83% (77.7%, 89.0%)								
Proportion of subjects with at least one SAE	Axi-cel	170	50% (42.5%, 57.5%)	4.2%	-6.5%, 14.8%	Not reported	RR: 1.1	0.9, 1.4	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Locke et al. 2021 (63)
	SoC	168	46% (38.3%, 53.4%)								
Proportion of subjects	Axi-cel	170	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	Not reported		Data on file (21)

ZUMA-7 (NCT03391466)											
with at least one Grade 3 or higher SAE	SoC	168	[redacted]							Absolute differences in proportions presented and relative differences presented as RR.	
Proportion with Grade 3+ neutropaenia	Axi-cel	170	69% (62.5%, 76.3%)	28.3%	18.2%, 38.5%	Not reported	RR: 1.7	1.4, 2.1	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Locke et al. 2021 (63)
	SoC	168	41% (33.6%, 48.5%)								
Proportion with CRS	Axi-cel	170	92% (88.4%, 96.3%)	NA	NA	NA	NA	NA	NA	CRS events did not occur in the SoC arm and therefore, no absolute or relative differences in proportions are presented.	Locke et al. 2021 (63)
Proportion with CRS Grade 3+	Axi-cel	170	6% (2.8%, 10.3%)	NA	NA	NA	NA	NA	NA	CRS events did not occur in the SoC arm and therefore, no absolute or relative differences in proportions are presented.	Locke et al. 2021 (63)
Proportion with any TE neurological event	Axi-cel	170	60% (52.6%, 67.4%)	40.4%	30.9%, 49.9%	Not reported	RR: 3.1	2.2, 4.2	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Locke et al. 2021 (63)
	SoC	168	20% (13.6%, 25.7%)								
Proportion with Grade	Axi-cel	170	21% (15.0%, 27.3%)	20.6%	14.4%, 26.8%	Not reported	RR: 35.6	4.9, 256.5	Not reported	Absolute differences in proportions presented and relative	Locke et al. 2021 (63)

ZUMA-7 (NCT03391466)											
3+ TE neurological events	SoC	168	1% (0.0%, 3.3%)							differences presented as RR. 95% CI calculated with Clopper-Pearson's exact method.	
Any serious neurological events	Axi-cel	170	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR. 95% CI calculated with Clopper-Pearson's exact method.	Data on file (21)
	SoC	168	[redacted]								
Any serious Grade 3+ neurological event	Axi-cel	170	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR. Upper limit of confidence interval calculated by dividing 3 with n (3/n) as suggested by the Cochrane handbook (version 5.1.0 (73)). 0.5 was added to the SoC arm to calculate the RR due to zero events.	Data on file (21)
	SoC	168	[redacted]								
Proportion with tremor	Axi-cel	170	26% (19.3%, 32.5%)	25.3%	18.7%, 31.9%	Not reported	RR: 43.5	6.1, 312.0	Not reported	Absolute differences in proportions presented and relative differences presented as RR. 95% CI calculated with Clopper-Pearson's exact method.	Locke et al. 2021 (63)
	SoC	168	1% (0.0%, 3.3%)								
Proportion with	Axi-cel	170	24% (17.2%, 29.9%)	21.1%	14.4%, 27.9%	Not reported	RR: 9.9	3.6, 27.0	Not reported		Locke et al. 2021 (63)

ZUMA-7 (NCT03391466)											
confusional state	SoC	168	2% (0.1%, 4.7%)							Absolute differences in proportions presented and relative differences presented as RR.	
Patient with resolved events among any Grade neurological event	Axi-cel	170	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR. 95% CI calculated with Clopper-Pearson's exact method.	Data on file (21)
	SoC	168	[redacted]								
All-cause discontinuation in the subjects who received axi-cel or SoC	Axi-cel	180	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Data on file (21)
	SoC	179	[redacted]								
All-cause discontinuation in the subjects who did not receive axi-cel or SoC	Axi-cel	180	[redacted]	[redacted]	[redacted]	Not reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR.	Data on file (21)
	SoC	179	[redacted]								

ZUMA-7 (NCT03391466)										
Discontinuation due to AEs	Axi-cel	170	[redacted]	[redacted]	[redacted]	[redacted]	reported	[redacted]	[redacted]	Not reported	Absolute differences in proportions presented and relative differences presented as RR. The upper limit of the confidence interval for axi-cel was calculated by dividing 3 with n (3/n) as suggested by the Cochrane handbook (version 5.1.0 (73)). The confidence intervals in the SoC group were calculated with Clopper-Pearson's exact method. The RR was calculated by adding 0.5 to the axi-cel arm due to zero events.
	SoC	168	[redacted]								

Appendix F Comparative analysis of efficacy and safety

The comparative analysis presented in the current application is a direct comparative analysis and results are presented in Appendix E.

Appendix G Extrapolation

In the following we present first the method of mixture cure modelling and then a presentation of the methodology and results for extrapolating EFS, OS and TTNT data from the ZUMA-7 trial.

12.1 Mixture cure modelling

It is well established that standard parametric survival models are limited in their use for modelling hazard functions that follow more complex patterns (128). Given a realistic probability of long-term cure for some patients with DLBCL, observed survival in a cohort of patients is composed of two groups of patients: those with short-term mortality who fail to achieve a cure in one group, and those with mortality related to non-DLBCL causes with potential long-term survival in the other group, termed the 'cure fraction'. This leads to a change in the hazards of death over time, or a plateau in the survival, as those who are cured are eventually revealed, which can be observed as a plateau in the Kaplan Meier curve.

MCMs work on the assumption that observed survival in the trial population represents a mix of patients who are "cured" and "not cured" (87). The survival of the cured population is similar to that of the general population associated with all-cause mortality obtained from age- and gender-matched Danish lifetables as per background mortality. Moreover, the non-cured patients are burdened by the additional risk of excess mortality related to the disease. 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_u will be derived from the latest published lifetables from Denmark to reflect current all-cause mortality. Similarly, for EFS, an MCM has been used to extrapolate long-term estimates. In the model, the parametric survival curves for the two groups can be found on the 'survival' tab.

The rationale for choosing MCMs is described below. 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 and exogenous mortality data. However, good practice dictates that it should only be used when a "cure" is clinically feasible. Empirical evidence has suggested that relapsed patients with DLBCL who remain event-free for at least five years after ASCT have long-term survival comparable to non-cancer patients (9). This was supported by feedback from interviews with clinical experts during the development of the model. ASCT reflects an opportunity for a sustained remission in DLBCL, and previous studies have shown this effect for CAR T-cell therapies in the 3L setting (129). Furthermore, a recent study looking at the accuracy of different extrapolation techniques in the ZUMA-1 trial (a phase II single-arm study of patients given axi-cel in 3L DLBCL) found that MCMs were the most accurate models for predicting OS in the long term (88). This study fitted spline, mixture cure, non-mixture cure and single-distribution models to the 12-month ZUMA-1 data cut. Extrapolations were then evaluated against the 24-, 36- and 48-month follow-up data using a range of metrics, including AIC and BIC. Single parametric models

poorly predicted long-term survival in axi-cel-treated patients: therefore; the use of MCMs can be justified in this case.

It should be noted that for EFS, the probability of being cured in terms of long-term survival is not being explicitly estimated, as the definition of EFS includes not only survival, but also disease progression or use of next lymphoma therapy, as per the ZUMA-7 protocol. Accordingly, the "cure" fraction estimated in the EFS model evaluates a group that has not experienced an event, which is expected to be highly correlated to the cure fraction for OS. For this reason, it is better described as the event-free fraction. Whilst a "cured" patient would not be expected to progress, this depends on the timing of the cure (either pre- or post-event). Given the fact that some patients could theoretically be cured as a result of their subsequent therapy, particularly in the SoC arm, where they are eligible for subsequent CAR T-cell therapy, a post-event cure is clinically feasible. It is assumed in the MCMs that patients who are cured are cured from time 0 (randomisation) for the purposes of the statistical fit to the data. As a result, the cure fraction for OS would be expected to be higher than for EFS to account for both pre- and post-event cures (i.e., at 2L and beyond), whereas EFS only captures the event-free cure (i.e., cure at 2L). For both OS and EFS, the survival function for the non-cured patients has been evaluated with the following functional forms:

- exponential;
- Weibull;
- Gompertz;
- lognormal;
- loglogistic;
- gamma; and
- generalised gamma.

The cure fraction is simultaneously estimated using logistic regression with maximum likelihood estimation. In Table 74, we list the cure fraction as estimated by the MCMs and ZUMA-7. Please note that the cure fractions should be interpreted with caution, since cure fractions represent the proportion of patients that experiences adjusted general population mortality, as determined by the logistic model, which only uses data on the pattern of death observed in the trial.

To determine whether joint extrapolation models could be fitted for both the axi-cel and SoC arms, the proportional hazards assumption was evaluated. The proportional hazards assumption requires the hazard in one treatment arm to be a constant proportion to the hazard in the other treatment arm, with the proportion equating to the HR. Although the hazard may vary with time, the ratio of the hazard rates is constant. To assess the proportional hazards assumption, a three-step process was followed. First, Cox regression models and Kaplan Meier curves were reviewed to assess the presence of an overall treatment effect of axi-cel over SoC, with the graph and the confidence intervals of the HR providing an indication as to whether this treatment effect is observed across a sufficient amount of the trial follow-up time. Secondly, the proportional hazards assumption of the Cox models was statistically and graphically evaluated using a Schoenfeld residuals plot and the proportional hazards test as outlined by Grambsch and Therneau (130). Finally, a diagnostic plot of the log cumulative hazards over the log of the follow-up time for ZUMA-7 (log-log plots) was assessed. The three-stage process represents a robust statistical method for assessing proportional hazards, with failure at each step providing sufficient grounds to dismiss the proportional hazards assumption. The proportional hazards assumption was upheld if 1) a treatment effect was observed, 2) the fit to the Schoenfeld

residual plot was approximately horizontal, 3) the proportional hazards test was not statistically significant and 4) the curves on the log-log plots did not cross.

Table 74: Cure fraction from the MCMs and ZUMA-7

	Axi-cel		SoC	
Distribution	**EFS**	**OS**	**EFS**	**OS**
Exponential	39%	25%	16%	32%
Weibull	39%	53%	16%	49%
Gompertz	36%	54%	16%	48%
Lognormal	35%	24%	13%	48%
Loglogistic	38%	44%	14%	48%
Gamma	39%	51%	16%	50%
Generalised gamma	39%	53%	16%	42%

Source: ZUMA-7 (82).
Abbreviations: MCM: Mixture cure model, Axi-cel: Axicabtagene ciloleucel, SoC: Standard of care, EFS: Event-free survival, OS: Overall survival.

12.2 Extrapolation of event-free survival

Kaplan Meier plots and Cox regression results for EFS from the ZUMA-7 trial are presented in Figure 24. A treatment effect for axi-cel was observed, and the proportional hazards assumption seemed to be valid; however, the parallelism between curves was lost towards the end of the log-log plot for EFS (see Figure 25). Therefore, the proportional hazards assumption was assumed not to hold for EFS across the entire time horizon, and independent survival models have been fitted for EFS for axi-cel and SoC in accordance with the NICE DSU guidance (85).

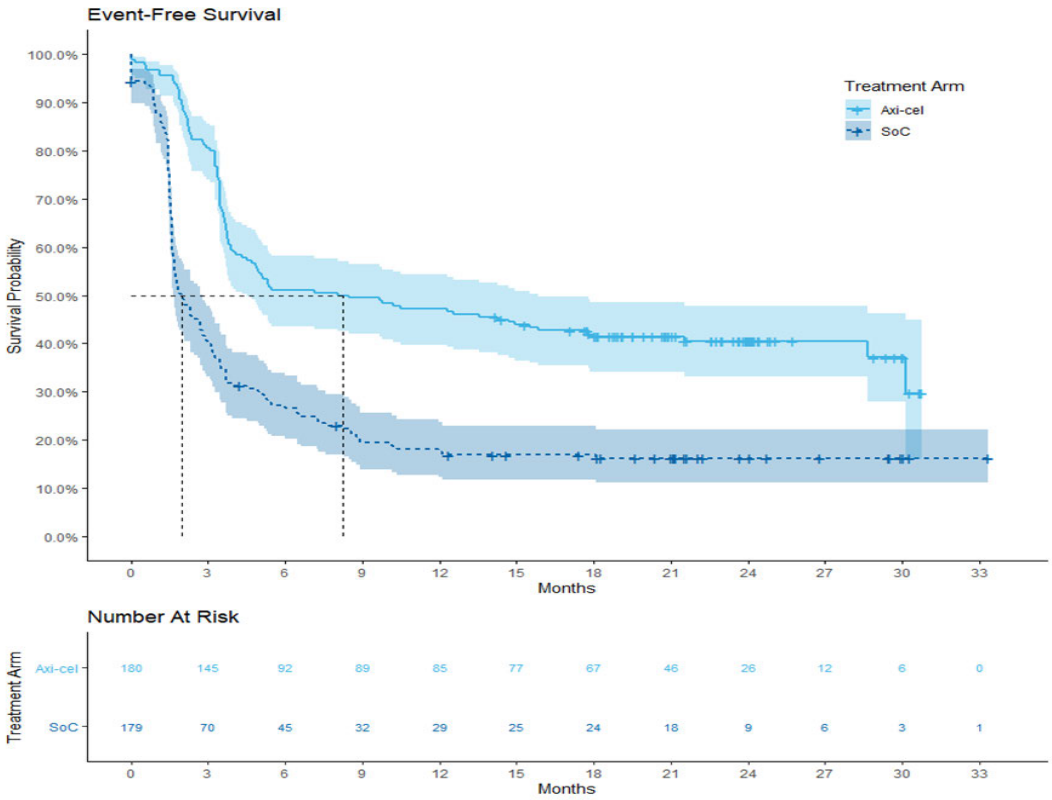


Figure 24: Kaplan Meier plot for EFS

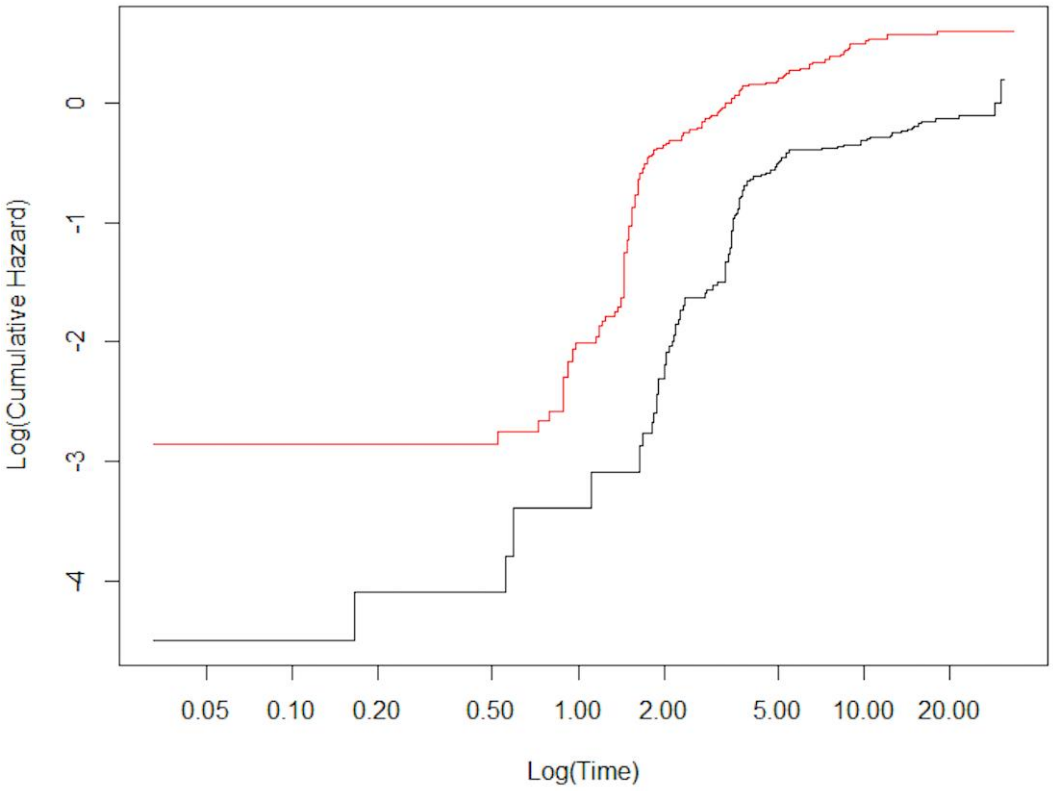


Figure 25: Log-log plot for EFS model

The seven standard parametric models, the seven MCMs and the spline models were fitted to each arm of the ZUMA-7 trial data. The goodness-of-fit criteria for the standard parametric

models and MCMs are summarised in Table 75, and the extrapolations of EFS using standard parametric models and MCMs for up to 180 months are presented in Figure 26 and Figure 27, respectively.

Table 75: Statistical goodness-of-fit for EFS extrapolations

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Standard parametric curves				
Exponential	866.9	870.1	855.7	858.9
Weibull	846.8	853.2	809.0	815.4
Gompertz	813.9	820.3	749.7	756.1
Lognormal	828.5	834.9	789.2	795.6
Loglogistic	830.5	836.9	771.7	778.0
Gamma	852.9	859.3	824.5	830.9
Generalised gamma	829.4	838.9	790.7	800.2
Mixture cure models				
Exponential	814.0	820.4	743.6	749.9
Weibull	814.7	824.3	744.4	754.0
Gompertz	814.1	823.7	745.6	755.1
Lognormal	816.5	826.1	780.9	790.4
Loglogistic	795.4	805.0	747.8	757.3
Gamma	812.3	821.9	744.3	753.9
Generalised gamma	809.9	822.7	746.3	759.1
Spline models				
One knot odds	806.2	815.7	773.3	782.9
Two knots odds	781.8	794.6	714.2	726.9
Three knots odds	773.2	789.1	704.0	719.9
One knot hazard	804.0	813.6	778.1	787.7
Two knots hazard	788.1	800.8	719.6	732.3
Three knots hazard	770.7	786.7	698.6	714.6
One knot normal	827.2	836.8	788.3	797.8

Two knots normal	780.2885	793.0603	719.0	731.7
Three knots normal	790.1753	806.1401	717.7	733.7

Source: Survival_parameters sheet and spline parameters sheet in model.
Abbreviations: EFS: event free survival, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

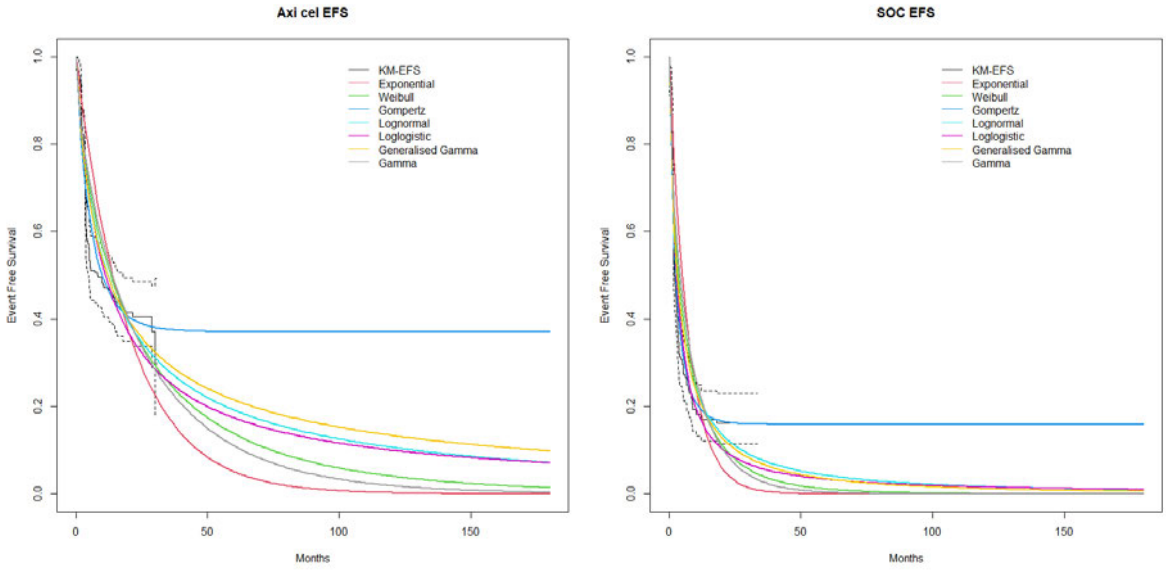


Figure 26: Standard parametric models of partitioned survival: non-proportional hazards models of EFS for axi-cel and SoC

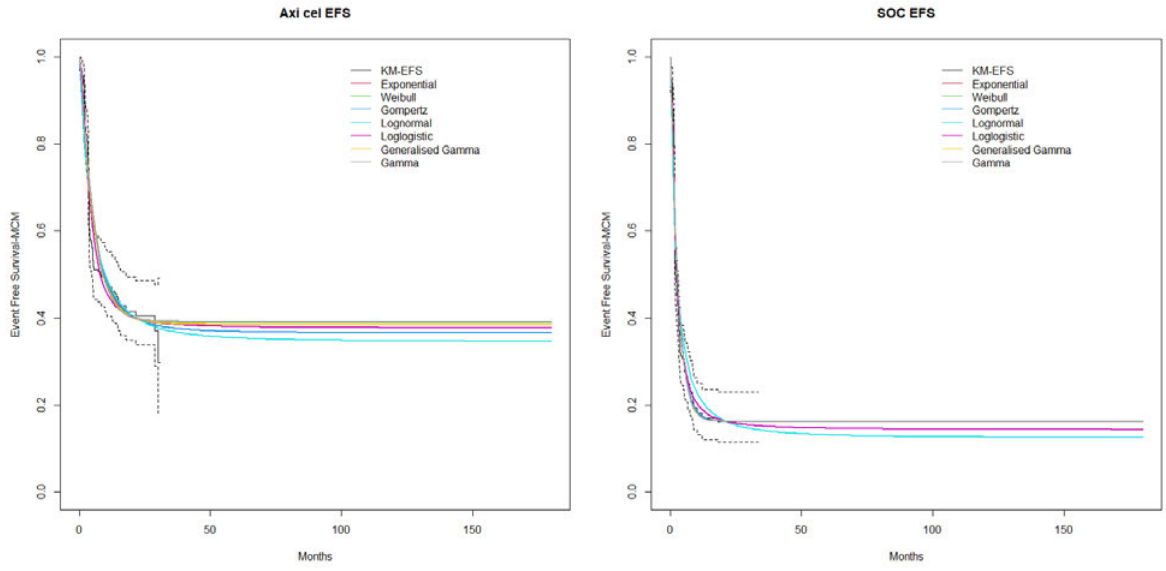


Figure 27: MCMs of partitioned survival: non-proportional hazards models of EFS for axi-cel and SoC

Of the standard parametric models, the Gompertz model provided the best statistical fit for both axi-cel and SoC. In contrast to the standard parametric models, the MCMs using a loglogistic model for the uncured fraction provided the best fit for axi-cel and demonstrated a clear plateau in survival as observed in ZUMA-7 and the exponential model for SoC. The EFS curves for the one-, two- and three-knot spline models using hazard, odds and normal scales are provided in Figure 28.

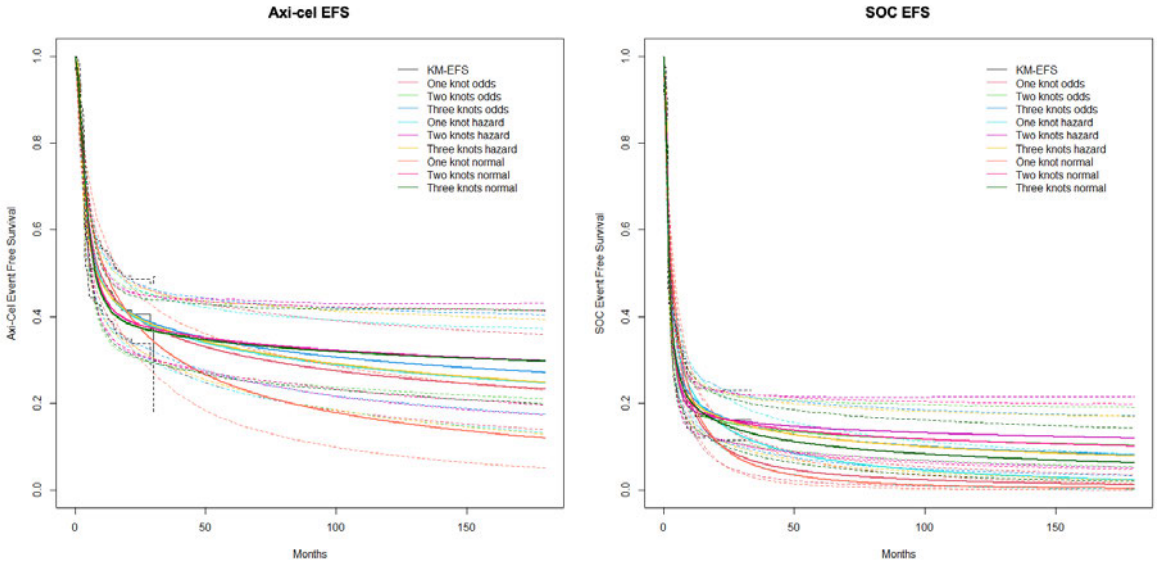


Figure 28: EFS curves from restricted cubic spline models for axi-cel and SoC

The MCMs were applied in the base case based on the rationale described in section 12.1. The clinical plausibility of the curves in Figure 27 was discussed with the consulted Danish clinical expert, who informed that for axi-cel, the most plausible curve was the Gompertz. For SoC the clinical expert did not favour any specific curve, and the exponential curve was chosen because it was the best statistical fit. Thus, the Gompertz and exponential models were applied to extrapolate EFS in the base case.

12.3 Extrapolation of overall survival

The Kaplan Meier plots for OS are provided in Figure 29, log-log plots are provided in Figure 30 and goodness-of-fit criteria for the seven parametric distributions and the seven MCMs are provided in Table 76. As seen in Table 76, the best statistical fit was largely similar across models; thus, the clinical plausibility was important to the selection of the most appropriate model. The presented data is based on the ZUMA-7 trial, in which patients in the SoC arm could receive CAR T-cell therapy in subsequent lines, and is not reflective of Danish clinical practice, where CAR T-cell therapy is not recommended in subsequent lines. The SoC data presented is therefore not the data used in the base case.

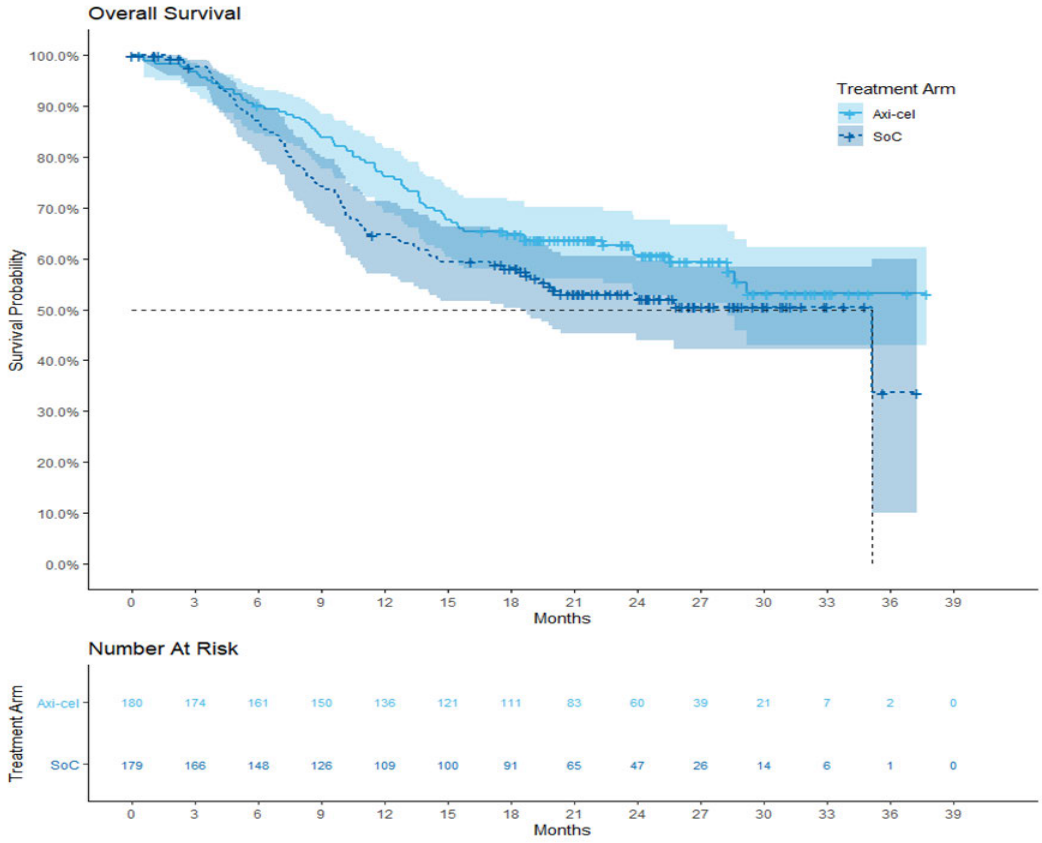


Figure 29: Kaplan-Meier plots of overall survival

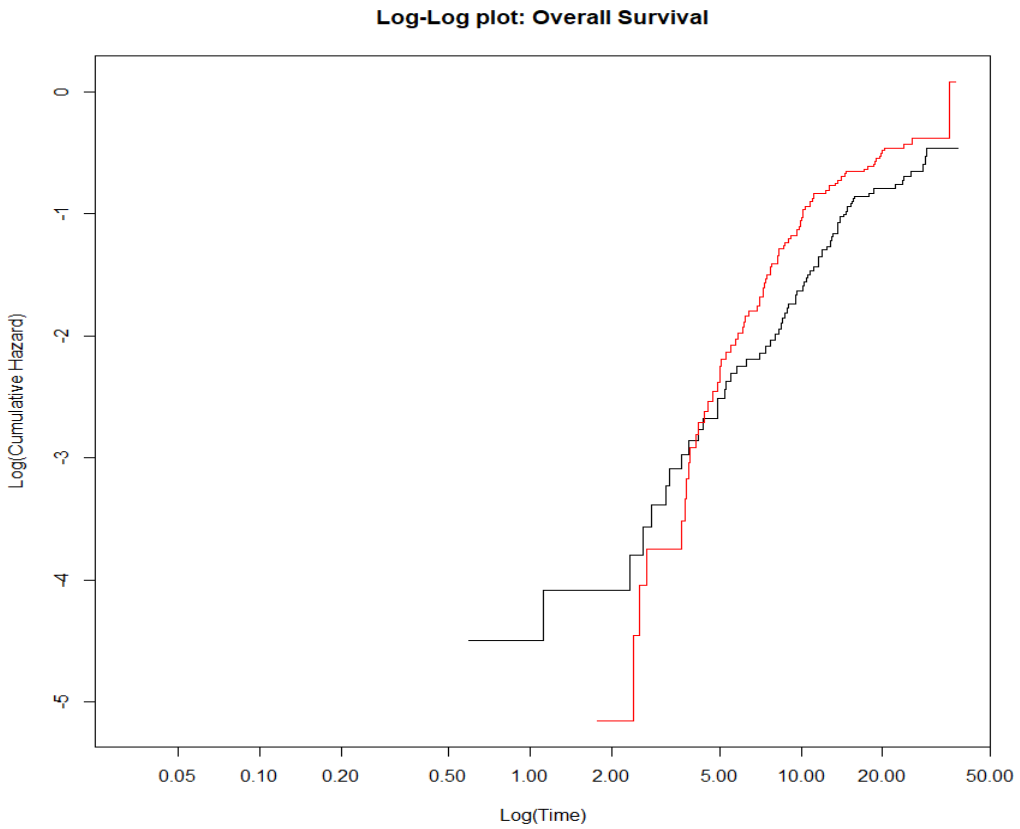


Table 76: Statistical goodness-of-fit for OS extrapolations

	Axi-cel		SoC*	
	AIC	BIC	AIC	BIC
Standard parametric curves				
Exponential	704.1	707.2	747.2	750.3
Weibull	705.3	711.7	748.0	754.3
Gompertz	705.8	712.2	747.4	753.8
Lognormal	701.1	707.5	731.7	738.1
Loglogistic	702.2	708.6	739.2	745.6
Gamma	704.9	711.2	746.4	752.8
Generalised gamma	703.1	712.7	718.6	728.1
Mixture cure models				
Exponential	705.6	712.0	746.6	752.9
Weibull	700.2	709.8	729.3	738.9
Gompertz	704.3	713.9	744.8	754.4
Lognormal	702.7	712.3	717.3	726.9
Loglogistic	700.0	709.6	718.5	728.1
Gamma	700.3	709.9	722.8	732.3
Generalised gamma	702.1	714.9	718.3	731.0
Spline models				
One knot odds	702.1	711.7	744.2	753.8
Two knots odds	698.6	711.4	745.8	758.6
Three knots odds	699.8	715.7	747.4	763.4
One knot hazard	702.3	711.9	744.9	754.4
Two knots hazard	698.4	711.2	746.0	758.8
Three knots hazard	700.0	715.9	747.7	763.6
One knot normal	703.1	712.7	743.3	752.9
Two knots normal	698.7	711.5	745.2	758.0
Three knots normal	699.4	715.4	747.1	763.0

Source: Survival_parameters sheet and spline sheet in model.
Note: *SoC curves not used in the base case, as treatment switching is applied due to the absence of CAR T-cell therapy in subsequent lines.
Abbreviations: OS: overall survival, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

The extrapolations of OS with the standard parametric models and MCMs up to 180 months are presented in Figure 31 and Figure 32, respectively. Please note that these have not been corrected for background mortality or fitted to a relative survival framework.

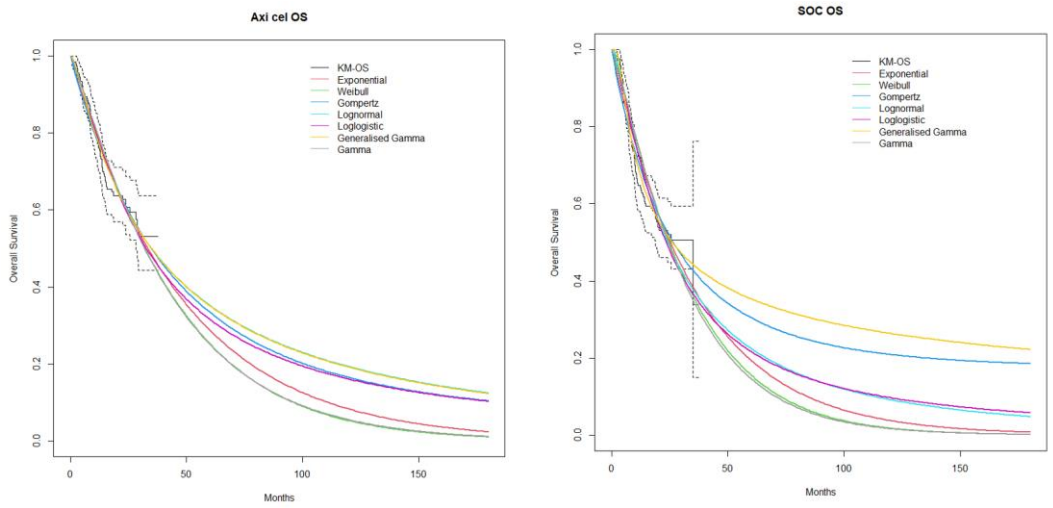


Figure 31: Parametric distribution models of partitioned survival: Non-proportional hazards models of OS for axi-cel and SoC

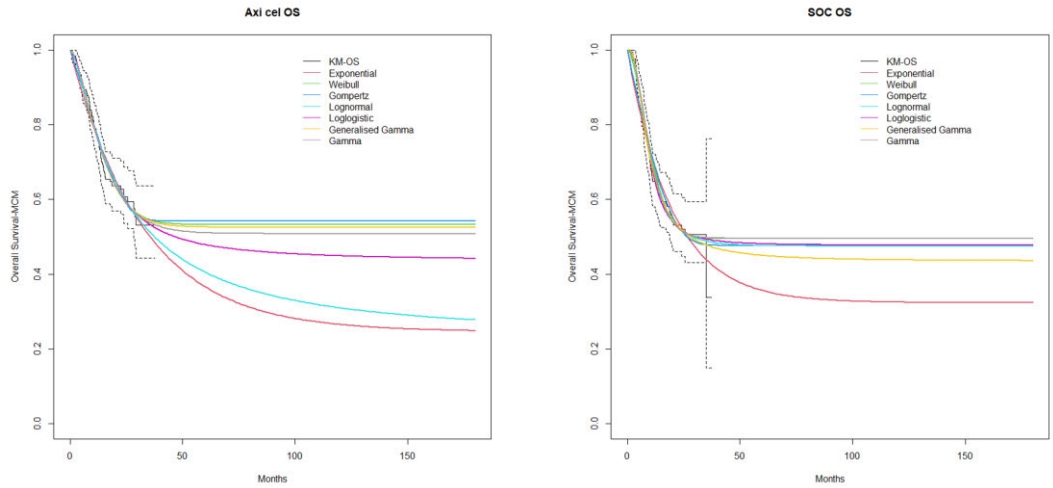


Figure 32: MCMs of partitioned survival: Non-proportional hazards models of OS for axi-cel and SoC

Note: SoC curves not used in the base case, as treatment switching is applied due to the absence of CAR T-cell therapy in subsequent lines.

Of the standard parametric models, the lognormal model provided the best statistical fit. Of the MCMs that were clinically plausible, the loglogistic model provided the best statistical fit. The OS curves for the one-, two-, and three-knot spline models using hazard, odds and normal scales are provided in Figure 33.

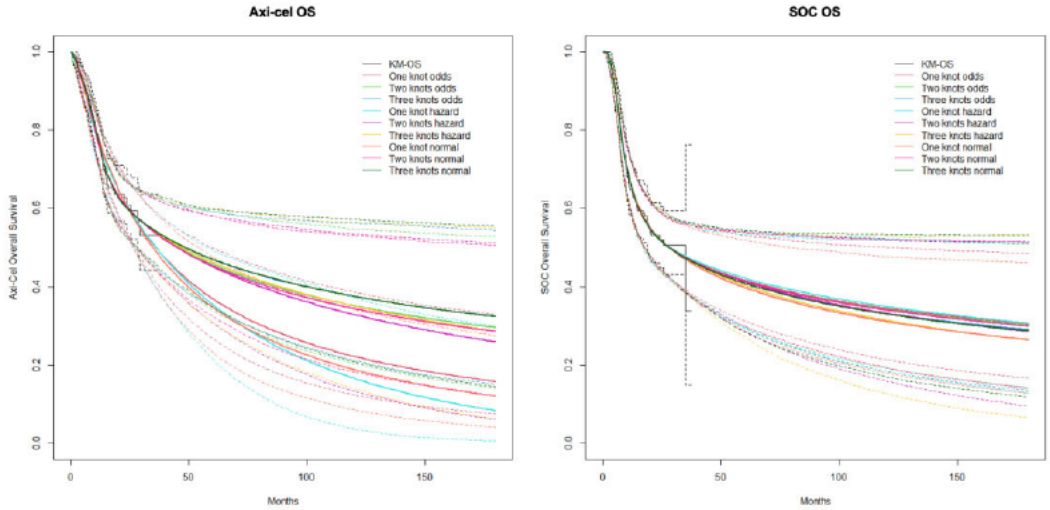


Figure 33: OS curves from restricted cubic spline models for axi-cel and SoC

To assess the clinical validity of the different models, we generated conditional survival estimates based on whether patients survived up to certain landmark survival times. The conditional survival function $CS(t|s)$ is defined as the probability of surviving an additional t years, given that a patient has already survived s years (131).

$$CS(t|s) = P(T > t + s|T > s) = \frac{S(s+t)}{S(s)}$$

Table 77 shows estimates of the conditional survival at 5 and 10 years for patients who survive up to 24 months.

Table 77: Conditional survival at 5 and 10 years, if patient is alive at 24 months

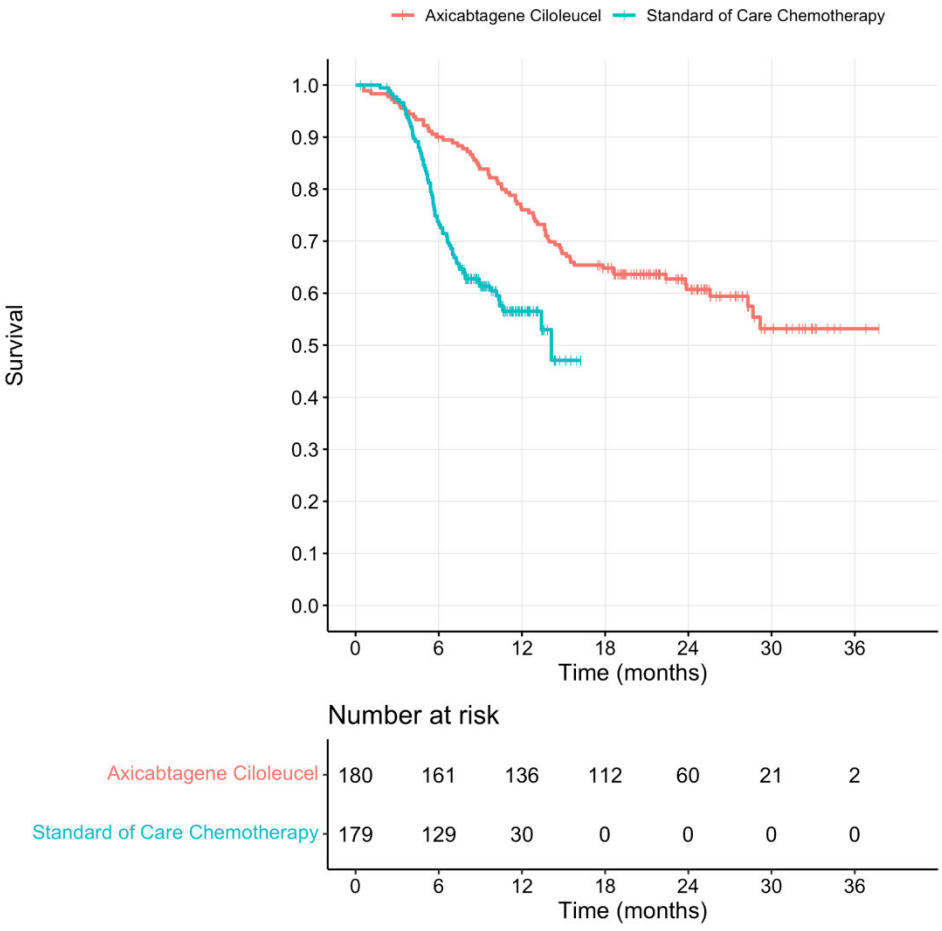
	Probability of survival to 5 or 10 years			
	Axi-cel		SoC*	
	5 years	10 years	5 years	10 years
Standard parametric curves				
Exponential	47.4%	13.6%	36.3%	6.7%
Weibull	41.8%	8.7%	31.4%	4.0%
Gompertz	54.9%	27.1%	62.0%	47.9%
Lognormal	52.9%	26.9%	45.3%	18.9%
Loglogistic	58.2%	31.9%	44.8%	20.5%
Gamma	41.7%	9.1%	29.5%	3.5%
Generalised gamma	58.1%	31.7%	69.4%	52.6%
Mixture cure models				
Exponential	58.9%	40.1%	70.3%	62.4%

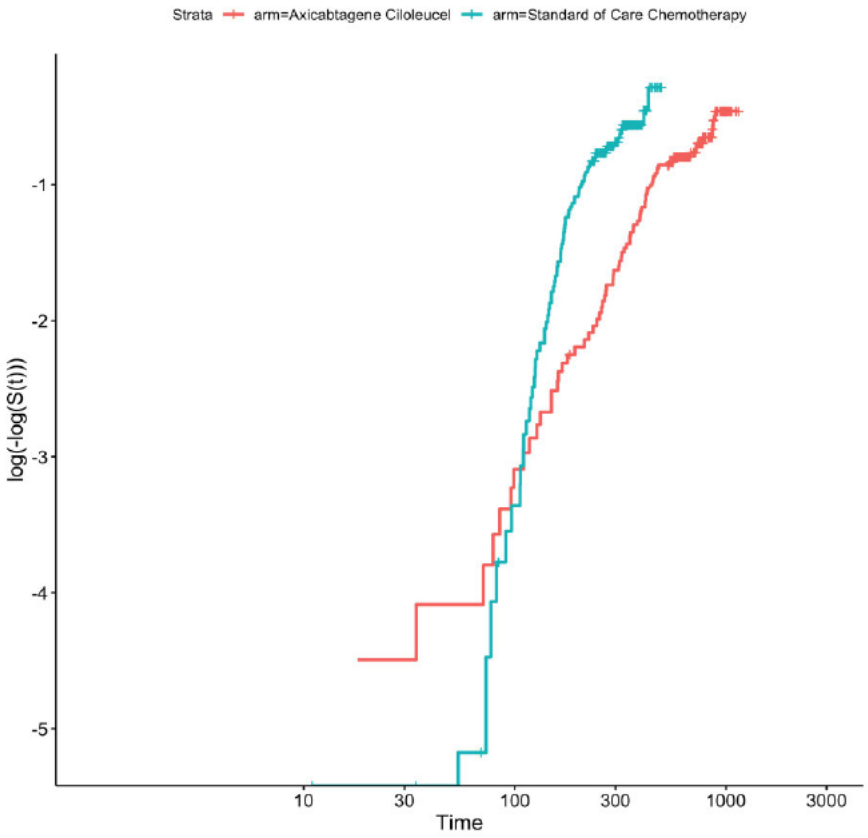
Weibull	87.2%	82.0%	94.1%	88.6%
Gompertz	88.8%	83.6%	90.6%	85.3%
Lognormal	65.4%	47.0%	90.7%	85.1%
Loglogistic	77.9%	68.8%	91.1%	85.1%
Gamma	83.3%	78.0%	94.2%	88.7%
Generalised gamma	85.9%	80.8%	84.0%	76.2%

Source: Calculated from Excel model (Undiscounted OS).
Note: *not treatment switching adjusted.
Abbreviations: Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

12.3.1 Treatment switching adjusted SoC OS

As described in section 8.3.3.1 treatment switching adjusted HR estimated using the RPSFT model with full recensoring was used to inform the SoC OS curve. The Kaplan Meier plots for treatment switching adjusted OS are provided in 34 and log-log plots are provided in 35.





12.3.2 Clinical validation of the OS curves

The best statistical fit was largely similar across model functions, and therefore, clinical plausibility was an important determinant of which models were the most appropriate. The clinical plausibility of the axi-cel curves in Figure 32 was discussed with the consulted Danish clinical expert. The clinical expert identified the treatment switching-adjusted loglogistic curve for SoC and the gamma curve for axi-cel as the best fit. Furthermore, the clinical expert informed that the exponential, lognormal and loglogistic curves were not clinically plausible for axi-cel OS. As the HR for treatment switching is applied to the axi-cel OS curve in the model, which means that a specific extrapolation cannot be chosen for SoC OS, the curve applied in the model for SoC OS is gamma. As the clinical expert preferred the loglogistic treatment switching-adjusted curve for SoC, a scenario analysis is carried out setting the axi-cel OS curve to loglogistic.

Validation of survival outcomes

Validation of the modelled survival outcomes based on data from ZUMA-7 (with CAR T-cell therapy in subsequent treatment lines) were explored against the EFS and OS findings from the full analysis set. Modelled EFS outcomes alongside those from the ZUMA-7 full analysis set are provided in Table 78. Modelled OS outcomes alongside those from the ZUMA-7 trial are provided in Table 79.

Table 78: Modelled median EFS versus median EFS from the axi-cel and SoC arms from ZUMA-7 (central assessment, investigator-assessed)

	Axi-cel	SoC

Modelled EFS, median, months	7.0	2.0
ZUMA-7 EFS, centrally assessed, median (95% CI), months	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
ZUMA-7 EFS, investigator-assessed, median (95% CI), months	10.8 (5.0, 28.6)	2.3 (1.7, 3.1)

Source: Locke et al. 2021 (63).
Abbreviations: EFS: Event-free survival, OS: Overall survival, CI: Confidence interval, axi-cel: Axicabtagene ciloleucel, SoC: Standard of care.

Table 79: Modelled median OS versus median OS from the axi-cel and SoC arms from ZUMA-7

	Axi-cel	SoC
Modelled OS, median, months	72.0	25.0
ZUMA-7 OS, full analysis set, median (95% CI), months	Not reached (28.3, NE)	25.7 (17.68.5, NE)

Source: Locke et al. 2021 (63) and Clinical trial report OS addendum (132).
Abbreviations: NE: not estimable, OS: overall survival, CI: Confidence interval, Axi-cel: Axicabtagene ciloleucel, SoC: Standard of care.

The population in ZUMA-7 is closely aligned with that in ORCHARRD and CORAL in terms of eligibility criteria and baseline characteristics. With regard to diagnosis the three studies have similar criteria with only minor differences. While the CORAL study only included subjects with a diagnosis of DLBCL both ORCHARRD and ZUMA-7 had a bit broader eligibility criteria. However, most participants enrolled in ZUMA-7 63% had a diagnosis of DLBCL and the majority (93%) of participants in the ORCHARRD study also had a diagnosis of DLBCL. Similar to the population in ZUMA-7, patients in CORAL and ORCHARRD required patients to be refractory/relapsed after first line therapy. Additionally, the baseline characteristics were comparable between the three studies with the exception of the proportion of participants that were/r at 12 months, which was higher in ZUMA-7, and the share of participants identified as being disease stage III/IV which was also higher in ZUMA-7.

In the ORCHARRD trial, the comparison of ofatumumab (n=74) versus rituximab in combination with DHAP (n=83) (O-DHAP versus R-DHAP), no statistically significant difference was found between study arms for PFS or secondary survival endpoints of EFS and OS (133). Median OS was 13.2 months and 13.9 months with R-DHAP and O-DHAP, respectively.

Additionally, EFS findings from the CORAL trial comparing R-ICE versus R-DHAP may also provide relevant context, as both CORAL and ZUMA-7 included patients with prior rituximab treatment and high proportions of patients with relapse beyond one year (11). No statistically significant difference was observed between the CORAL study arms for EFS or the secondary survival endpoints of PFS and OS, further supporting the SoC survival outcomes modelled here.
In Table 80, EFS and OF estimates from ZUMA-7, CORAL and ORCHARRD are compared.

Table 80: Comparison of axi-cel with SoC per ZUMA-7 and published studies

	ZUMA-7		CORAL		ORCHARRD	
	Axi-cel	SoC	R-ICE	R-DHAP	R-DHAP	O-DHAP
EFS	2-y: 40.5%	2-y: 16.3%	3-y: 26%	3-y: 35%	2-y: 18%	2-y: 16%
OS	2-y: 60.7%	2-y: 52.1%	2-y ~56% 3-y: 47%	2-y: ~57% 3-y: 51%	2-y: 38%	2-y: 41%

Source: Locke et al. 2021 (63).
Abbreviations: EFS: Event-free survival, OS: overall survival, Axi-cel: Axicabtagene ciloleucel, SoC: Standard of care.

Figure 36 has been included to further validate the OS extrapolation and the figure shows the modelled SoC curve (cross-over adjusted) and illustrates that the modelled SoC curve fits between the long-term Kaplan Meier data from the ORCHARRD and SCHOLAR-1 studies further validating the choice of treatment switching model.

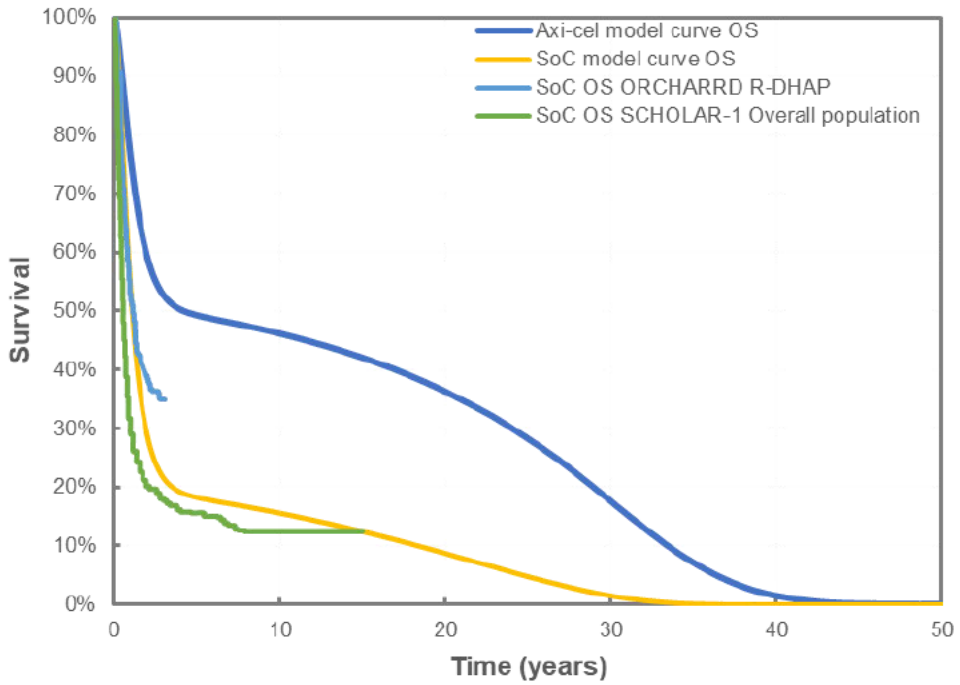
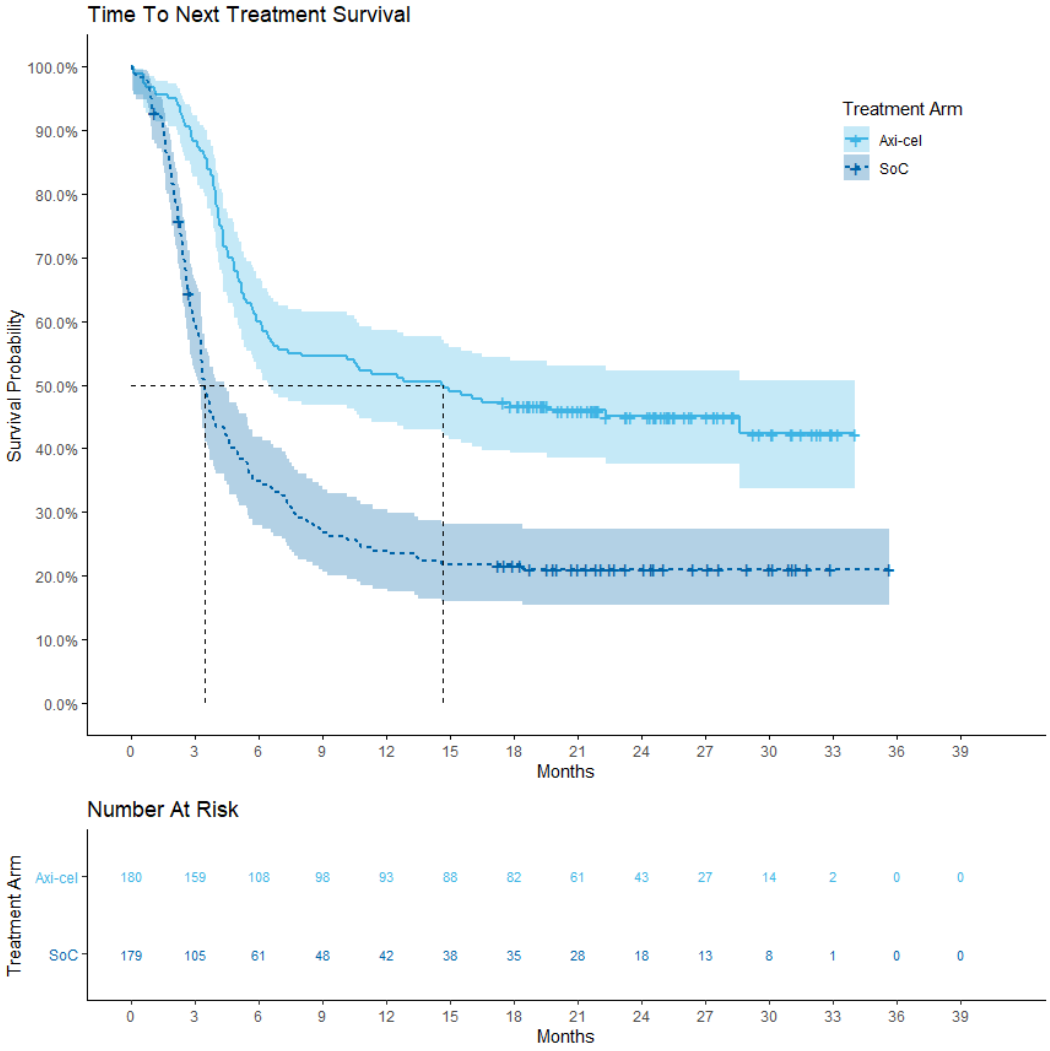


Figure 36: Modelled OS curves and Kaplan Meier curves from ORCHARRD and SCHOLAR-1

12.4 Extrapolation of time to next therapy

The Kaplan Meier plots for TTNT are provided in Figure 37 and log-log plots are provided in Figure 38.

The goodness-of-fit criteria for the seven parametric models and the seven MCMs for TTNT are provided in Table 81. The extrapolations of TTNT with each standard parametric model up to 180 months are provided in Figure 39, and the MCMs are provided in Figure 40.



Kaplan-Meier plots for TTNT

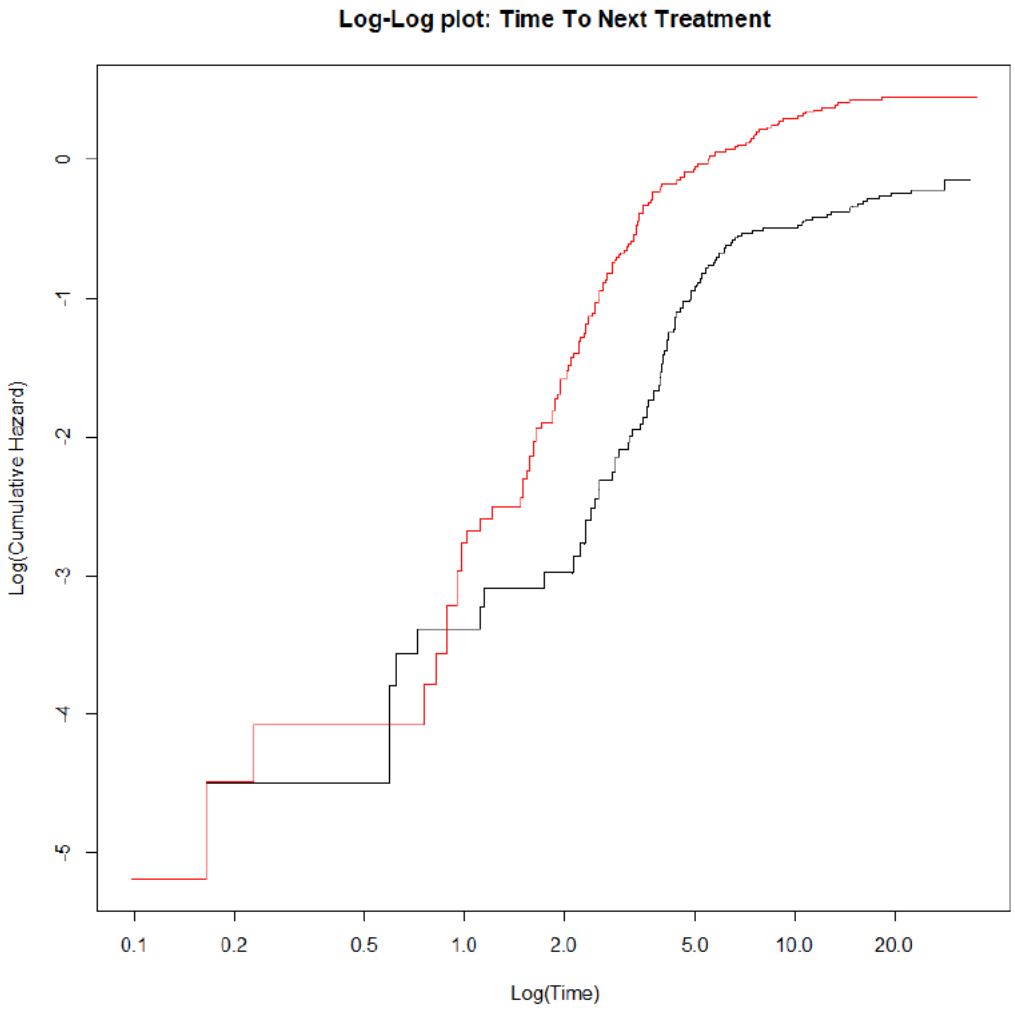


Table 81: Statistical goodness-of-fit for TTNT extrapolations

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Standard parametric curves				
Exponential	845.7	848.9	933.9	937.1
Weibull	834.2	840.5	917.8	924.1
Gompertz	801.5	807.9	857.0	863.4
Lognormal	814.0	820.4	872.1	878.5
Loglogistic	819.7	826.1	868.3	874.7
Gamma	838.7	845.1	928.1	934.5
Generalised gamma	809.4	818.9	860.7	870.3

Mixture cure models				
Exponential	798.2	804.6	844.1	850.5
Weibull	790.9	800.4	822.3	831.9
Gompertz	799.5	809.1	839.7	849.3
Lognormal	791.9	801.4	819.6	829.1
Loglogistic	778.6	788.2	805.0	814.6
Gamma	787.2	796.8	815.1	824.6
Generalised gamma	787.8	800.6	814.3	827.0
Spline models				
One knot odds	787.8	797.3	822.1	831.7
Two knots odds	771.7	784.5	802.9	815.6
Three knots odds	765.6	781.5	802.6	818.5
One knot hazard	785.1	794.7	815.7	825.3
Two knots hazard	775.2	788.0	806.5	819.3
Three knots hazard	764.5	780.5	801.6	817.5
One knot normal	803.3	812.9	851.4	861.0
Two knots normal	770.6	783.4	802.6	815.3
Three knots normal	774.1	790.1	803.8	819.8

Source: Survival_parameters sheet and spline parameters sheet in model.
Abbreviations: TTNT: Time to next therapy, AIC: Akaike information criterion, BIC: Bayesian information criteria, Axi-cel: axicabtagene ciloleucel, SoC: Standard of care.

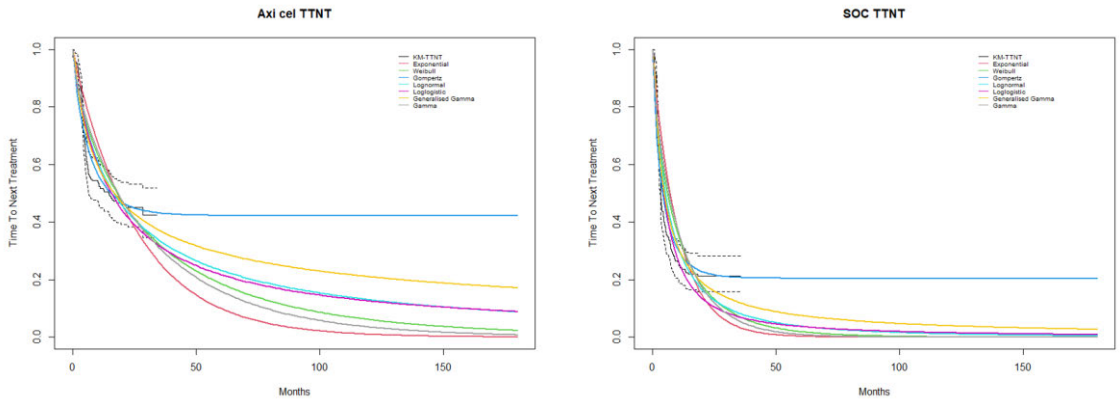


Figure 39: Parametric distribution models: Non-proportional hazards models of TTNT for axi-cel and SoC

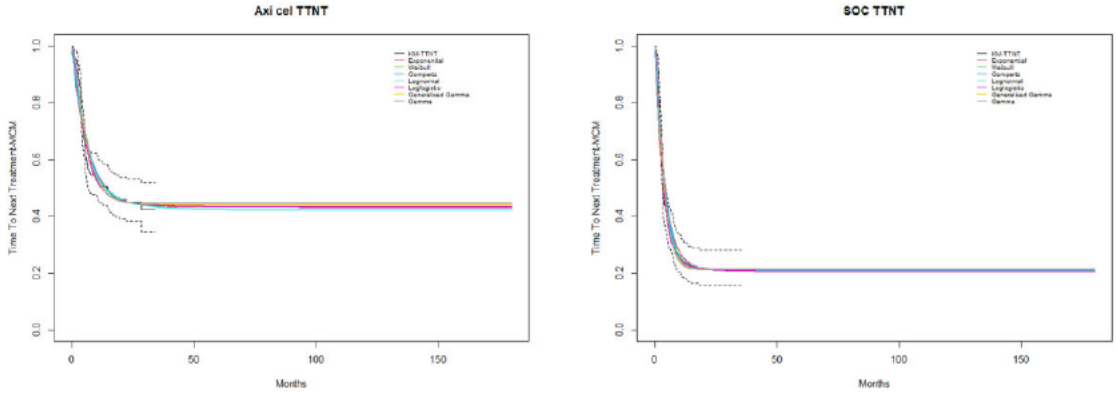


Figure 40: MCMs of partitioned survival: Non-proportional hazards models of TTNT for axi-cel and SoC

Of the standard parametric models, the Gompertz model provided the best statistical fit for both axi-cel and SoC. Of the MCMs, the loglogistic model provided the best fit for both axi-cel and SoC. Overall, the MCM provided the best statistical fit, with long-term TTNT extrapolations aligned with feedback from clinical expert consulted in the development phase of the model. The clinical plausibility of the curves in Figure 40 was discussed with the consulted Danish clinical expert, who informed that all curves were clinically plausible for axi-cel. However, for SoC, the clinical expert informed that the loglogistic and Weibull curves could be excluded. The other curves were almost identical and were clinically plausible. Thus, the loglogistic model was used for axi-cel, and the second-best fit for SoC OS, gamma, was used in the base case scenario.

Appendix H – Literature search for HRQoL data

HRQoL data was included in the ZUMA-7 trial and thus, we have not conducted a systematic literature search.

Appendix I Mapping of HRQoL data

Not applicable.

Appendix J Probabilistic sensitivity analyses

Table 82 presents an overview of all the parameters included in the PSA. All parameters relevant for the present analysis were included in the PSA. The assumptions and data for the PSA can be found in the model on the 'Parameters' sheet.

Table 82: Data used in the PSA

Variable	Applied value	SE	Distribution
Female	34%	0.025001393	Beta
Mean age (years)	57	0.638613575	Normal
Mean body weight (kg)	84	1.168169508	Normal
Mean BSA (m^2)	1.97	0.098623759	Lognormal
HR SoC OS to axi-cel OS (ZUMA-7)	2.40	1.096028183	Lognormal

Outpatient visits (months 1 to 6) PES (units per cycle): axi-cel	2.0	0.1	Gamma
Outpatient visits (months 1 to 6) PES (units per cycle): SoC	2.0	0.1	Gamma
Outpatient visits (months 7 to 24) PES (units per cycle): axi-cel	2.0	0.1	Gamma
Outpatient visits (months 7 to 24) PES (units per cycle): SoC	2.0	0.1	Gamma
Outpatient visits (years 2 to 3) PES (units per cycle): axi-cel	2.0	0.1	Gamma
Outpatient visits (years 2 to 3) PES (units per cycle): SoC	2.0	0.1	Gamma
Outpatient visits (years 4 to 5) PES (units per cycle): axi-cel	2.0	0.1	Gamma
Outpatient visits (years 4 to 5) PES (units per cycle): SoC	2.0	0.1	Gamma
Utility: on-treatment axi-cel	0.85	0.015911146	Beta
Utility: on-treatment SoC	0.84	0.01671258	Beta
Utility: off-treatment pre-event	0.86	0.010905505	Beta
Utility: post-event	0.79	0.029081633	Beta
Utilities: time on axi-cel	1.00	0.05	Lognormal
Utilities: time on SoC	3.00	0.15	Lognormal
Population norm male: 18-29	0.87	0.04355	Beta
Population norm male: 30-39	0.85	0.0424	Beta
Population norm male: 40-49	0.83	0.0417	Beta
Population norm male: 50-59	0.82	0.0409	Beta
Population norm male: 60-69	0.82	0.0409	Beta
Population norm male: 70-79	0.81	0.04065	Beta
Population norm male: 80+	0.72	0.03605	Beta
Population norm female: 18-29	0.87	0.04355	Beta
Population norm female: 30-39	0.85	0.0424	Beta
Population norm female: 40-49	0.83	0.0417	Beta
Population norm female: 50-59	0.82	0.0409	Beta

Population norm female: 60-69	0.82	0.0409	Beta
Population norm female: 70-79	0.81	0.04065	Beta
Population norm female: 80+	0.72	0.03605	Beta
Rate of CRS: axi-cel	0.06	0.018867013	Lognormal
Unit cost of CRS	52,165.80	2,608.29	Gamma
Rate of Neurologic events: axi-cel	0.21	0.031336951	Lognormal
Rate of neurologic events: SoC	0.01	0.005934639	Lognormal
Unit cost of Neurologic events	26,440.40	1322.02	Gamma
Axi-cel: % receiving leukapheresis	0.99	0.007774245	Beta
Axi-cel: % receiving axi-cel	0.94	0.017701224	Beta
Axi-cel: % receiving bridging therapy	0.36	0.035798743	Beta
Axi-cel: % receiving conditioning chemotherapy	0.96	0.015286886	Beta
Axi-cel: unit cost of CT scans (pre-treatment)	3,753.00	187.65	Gamma
Axi-cel: unit cost of CT scans (midway treatment)	3,753.00	187.65	Gamma
Axi-cel: unit cost of CT scans (post-treatment)	3,753.00	187.65	Gamma
Unit cost of leukapheresis	9,580.00	479	Gamma
Unit cost: follow-up: 0-6 mths: outpatient visits	3,225.00	161.25	Gamma
Unit cost: follow-up: 0-6 mths: blood test	230.00	11.5	Gamma
Unit cost: follow-up: 6-12 mths: outpatient visits	3,225.00	161.25	Gamma
Unit cost: follow-up: 6-12 mths: blood test	230.00	11.5	Gamma
Unit cost: follow-up: 12-24 mths: outpatient visits	3,225.00	161.25	Gamma
Unit cost: follow-up: 12-24 mths: blood test	230.00	11.5	Gamma
Unit cost: follow-up: 2-5 years: outpatient visits	3,225.00	161.25	Gamma
Unit cost: follow-up: 2-5 years: blood test	230.00	11.5	Gamma
SoC SCT eligible: % receiving R-DHAP	0.33	0.03523434	Beta
SoC SCT eligible: % receiving R-ICE	0.67	0.035236189	Beta
SoC SCT eligible: % receiving high-dose chemotherapy	0.63	0.036185046	Beta
SoC SCT eligible: % receiving ASCT	0.63	0.036185046	Beta
SoC SCT eligible: % receiving stem cell harvest	0.73	0.033374044	Beta
CT scans (pre-treatment) unit cost	3,753.00	187.65	Gamma

CT scans (midway treatment) unit cost	3,753.00	187.65	Gamma
CT scans (post-treatment) unit cost	3,753.00	187.65	Gamma
Unit cost of stem cell harvest	18,391.00	919.55	Gamma
ASCT procedure cost	111,255.00	5,562.75	Gamma
Unit costs: follow-up: 0-6 mths: outpatient visits	3,225.00	161.25	Gamma
Unit costs: follow-up: 0-6 mths: blood test	230.00	11.5	Gamma
Unit costs: follow-up: 6-12 mths: outpatient visits	3,225.00	161.25	Gamma
Unit costs: follow-up: 6-12 mths: blood test	230.00	11.5	Gamma
Unit costs: follow-up: 12-24 mths: outpatient visits	3,225.00	161.25	Gamma
Unit costs: follow-up: 12-24 mths: blood test	230.00	11.5	Gamma
Unit costs: follow-up: 2-5 years: outpatient visits	3,225.00	161.25	Gamma
Unit costs: follow-up: 2-5 years: blood test	230.00	11.5	Gamma
Axi-cel: acquisition cost	2,440,000.00	122,000	Normal
Bendamustine formulation 1 acquisition cost	73.40	3.67	Normal
Bendamustine formulation 2 acquisition cost	234.80	11.74	Normal
Carboplatin formulation 1 acquisition cost	84.00	4.2	Normal
Carboplatin formulation 2 acquisition cost	203.00	10.15	Normal
Carmustine formulation 1 acquisition cost	3,945.00	197.25	Normal
Cisplatin formulation 1 acquisition cost	100.00	5	Normal
Cisplatin formulation 2 acquisition cost	200.00	10	Normal
Cyclophosphamide formulation 1 acquisition cost	61.04	3.052	Normal
Cyclophosphamide formulation 2 acquisition cost	153.75	7.6875	Normal
Cyclophosphamide formulation 3 acquisition cost	307.50	15.375	Normal
Cytarabine formulation 1 acquisition cost	100.00	5	Normal
Cytarabine formulation 2 acquisition cost	150.00	7.5	Normal

Dexamethasone formulation 1 acquisition cost	5.19	0.2596	Normal
Dexamethasone formulation 2 acquisition cost	2.16	0.10785	Normal
Epirubicin formulation 1 acquisition cost	110.60	5.53	Normal
Epirubicin formulation 2 acquisition cost	442.76	22.138	Normal
Etoposide formulation 1 acquisition cost	71.37	3.5685	Normal
Etoposide formulation 2 acquisition cost	278.72	13.936	Normal
Fludarabine formulation 1 acquisition cost	1,310.15	65.5075	Normal
Fludarabine formulation 2 acquisition cost	3,275.25	163.7625	Normal
Gemcitabine formulation 1 acquisition cost	350.00	17.5	Normal
Gemcitabine formulation 2 acquisition cost	370.00	18.5	Normal
Gemcitabine formulation 3 acquisition cost	385.00	19.25	Normal
Gemcitabine formulation 4 acquisition cost	420.00	21	Normal
Ifosfamide formulation 1 acquisition cost	330.00	16.5	Normal
Lenalidomide formulation 1 acquisition cost	1,309.52	65.47619048	Normal
Lenalidomide formulation 2 acquisition cost	1,390.48	69.52380952	Normal
Lenalidomide formulation 3 acquisition cost	1,580.95	79.04761905	Normal
Lenalidomide formulation 4 acquisition cost	1,523.81	76.19047619	Normal
Melphalan formulation 1 acquisition cost	4,500.00	225	Normal
Prednisone formulation 1 acquisition cost	0.56	0.02819	Normal

Prednisone formulation 2 acquisition cost	2.08	0.103835	Normal
Rituximab formulation 1 acquisition cost	1337.90	66.895	Normal
Rituximab formulation 2 acquisition cost	6,687.00	334.35	Normal
Rituximab formulation 3 acquisition cost	12,377.73	618.8865	Normal
Nivolumab formulation 1 acquisition cost	3,690.69	184.5345	Normal
Nivolumab formulation 2 acquisition cost	9,168.23	458.4115	Normal
Nivolumab formulation 3 acquisition cost	22,003.74	1,100.187	Normal
Pembrolizumab formulation 1 acquisition cost	23204.61	1160.2305	Normal
Unit cost: Chemotherapy OP admin. simple parenteral 1st	3,225.00	161.25	Gamma
Unit cost: Chemotherapy OP admin. more complex parenteral 1st	3,225.00	161.25	Gamma
Unit cost: Chemotherapy OP admin. complex 1st	3,225.00	161.25	Gamma
Unit cost: chemotherapy OP admin. subsequent in cycle	3,225.00	161.25	Gamma
Unit cost: chemotherapy IP admin.	10,106.00	505.3	Gamma
3L axi-cel arm: % receiving R-Chemo	0.89	0.0445	Beta
3L axi-cel arm: % receiving Nivolumab	0.03	0.00125	Beta
3L axi-cel arm: % receiving Pembrolizumab	0.03	0.00125	Beta
3L axi-cel arm: % receiving Radiotherapy	0.27	0.0135	Beta
3L axi-cel arm: % receiving ASCT	0.05	0.0025	Beta
3L SoC arm: % receiving Nivolumab	0.03	0.00125	Beta
3L SoC arm: % receiving Pembrolizumab	0.03	0.00125	Beta
3L SoC arm: % receiving R-Lenalidomide	0.10	0.005	Beta
3L SoC arm: % receiving R-Benda	0.10	0.005	Beta
3L SoC arm: % receiving Prednisone	0.35	0.0175	Beta
3L SoC arm: % receiving Allo-SCT	0.05	0.0025	Beta
3L: allo-SCT - unit cost	747,851.00	37,392.55	Gamma

3L: radiotherapy unit cost	8,604.00	430.2	Gamma
3L: radiotherapy (palliative) unit cost	34,020.00	1,701	Gamma
Palliative care unit cost: End-of-life care	193,320.0	9,666	Gamma
Outpatient visits (months 1 to 6) unit cost	3,225	161.25	Gamma
Outpatient visits (months 7 to 24) unit cost	3,225	161.25	Gamma
Outpatient visits (years 2 to 3) unit cost	3,225	161.25	Gamma
Outpatient visits (years 4 to 5) unit cost	3,225	161.25	Gamma
Nurse visits unit cost	441.0	22.05	Gamma
Specialist nurse visits unit cost	441.0	22.05	Gamma
Inpatient days unit cost	2,185.0	109.25	Gamma
Blood test unit cost	230.0	11.5	Gamma
PET-CT unit cost	8,949.0	447.45	Gamma
District nurse unit cost	441.0	22.05	Gamma
CT scans unit cost	3,753.0	187.65	Gamma
SoC EFS- MCM: exponential Theta	-1.64	0.21	Multivariate normal
SoC EFS- MCM: exponential rate	-1.05	0.09	
Axi-cel OS- MCM: generalised_gamma Theta	0.10	0.27	Multivariate normal
Axi-cel OS- MCM: generalised_gamma Mu	2.72	0.16	
Axi-cel OS- MCM: generalised_gamma Sigma	-0.37	0.23	
Axi-cel OS- MCM: generalised_gamma Q	0.89	0.41	
Axi-cel OS- MCM: gamma Theta	0.03	0.26	
Axi-cel OS- MCM: gamma shape	0.58	0.20	
Axi-cel OS- MCM: gamma rate	-2.14	0.34	
Axi-cel EFS- MCM: Gompertz Theta	-0.56	0.23	Multivariate normal
Axi-cel EFS- MCM: Gompertz shape	-0.04	0.03	
Axi-cel EFS- MCM: Gompertz rate	-1.66	0.14	
Axi-cel TTNT- MCM: loglogistic Theta	-0.28	0.16	Multivariate normal
Axi-cel TTNT- MCM: loglogistic shape	0.75	0.10	
Axi-cel TTNT- MCM: loglogistic scale	1.57	0.08	
SoC TTNT- MCM: generalised_gamma Theta	-1.32	0.19	Multivariate normal
SoC TTNT- MCM: generalised_gamma Mu	1.27	0.09	
SoC TTNT- MCM: generalised_gamma Sigma	-0.30	0.06	
SoC TTNT- MCM: generalised_gamma Q	0.43	0.16	
SoC TTNT- MCM: gamma Theta	-1.32	0.19	

SoC TTNT- MCM: gamma shape	0.68	0.11
SoC TTNT- MCM: gamma rate	-0.69	0.13

Appendix K – Company response regarding ZUMA-7 updated primary OS analysis and CE model update (June 26th 2023)

Confidential – contains unpublished data

[redacted]

Update of ZUMA-7 primary Overall Survival (OS) analysis results (data cut January 25th 2023)

The original application submitted to DMC on October 7th, 2022, was based on the on the interim analysis (data cut-off 18th March 2021) of ZUMA-7. Updated primary OS analysis results were published in Westin et al., (2023) on June 5th, 2023, based on data cut-off 25th January 2023. This document (Appendix K) outlines the key outcomes from ZUMA-7 with median follow-up time of 47.0 months (axi-cel) and 45.8 months (SoC arm) and maximum follow up time of 60 months in the axi-cel arm, adding an additional 22 months of FU data.

Overall survival

At the time of the data cut-off date for the primary OS analysis (25 January 2023), 177 OS events (ie, deaths) were observed with a median follow-up time of 47.0 months (range, 39.8 to 60.0) and 45.8 months for the axi-cel arm and SoC arm, respectively, using the reverse Kaplan Meier (KM) method. The median OS was not reached for the axi-cel arm and was 31.1 months for the SoC arm. For this intent-to-treat primary analysis of OS with the allocated 1-sided significance level of 2.49% (ie, efficacy boundary), there was a statistically significant difference between treatment arms (hazard ratio [HR] = 0.73 [95% confidence interval (CI): 0.54, 0.98], stratified log-rank 1-sided p-value = 0.0168).

OS sensitivity analysis to adjust for treatment switching

The drop-in rate (ie, subjects randomized to the control arm who received commercially available or investigational cellular immunotherapy after non-response to or relapse after the SoC therapy [treatment switching]) is 57%, which is a 1% increase since the time of primary analysis of EFS. Drop-in on the SoC arm may lead to an underestimate of the treatment effect of axi-cel. The HRs with 95% CIs from the exploratory sensitivity analyses of OS to address the confounding effect from treatment switching are [redacted]) and [redacted], using the Rank Preserving Structural Failure Time Model and Inverse Probability of Censoring Weights, respectively.

All in all, data from the ZUMA-7 primary OS analysis show that axi-cel intended as a definitive therapy is highly effective as a second-line treatment of r/r DLBCL and is superior to historical SoC. At a median follow-up of 47.2 months, axi-cel as second-line treatment for patients with early relapsed or refractory large B-cell lymphoma resulted in significantly longer overall survival than standard care.

Response to DMC regarding appropriate modelling of SoC OS in presence of treatment switching (primary OS data)

Summary of DMC's request

DMC proposes that Gilead submits an updated CE model using the primary OS data (4-year follow-up from ZUMA-7) and that SoC survival is modelled using the crossover-adjusted analysis presented in the Westin et al 2023 supplementary materials (RPSFTM with partial recensoring of switchers only Figure S2). DMC further proposes that independently fitted parametric models are

used instead of the proportional hazard model used in the company base case. The rationale provided by DMC is that utilizing independently fitted models will result in reduced uncertainty since follow-up is longer in the updated analysis. DMC further voices concerns regarding the large difference in long term OS in the company extrapolation of the SoC arm compared to the updated adjusted SoC curve presented in Westin et al supplementary materials.

Gilead's response

The ZUMA-7 model was developed in accordance with the NICE technical support document guidance (TSD 14, 16 and 21) (Latimer 2011; Latimer & Abrams 2014; Rutherford et al. 2020). With regards to independently modelling of OS extrapolations, TSD 14 was followed. In the NICE guidance document, the decision to extrapolate time to event data beyond the trial is contingent on the following criteria:

1. Does the proportional hazards assumption hold?
2. How do the model fit compared to the hazard functions?
3. Internal validity with regards to statistical fit
4. And external validity vs other studies

For the modelling of SoC OS using the ZUMA-7 primary analysis OS data, criteria number four is strongly violated because the resultant OS curves using RPSFTM with partial recensoring lack clinical face validity. When adjusting for crossover, we attempt to remove the confounding effect on OS of all subsequent cellular therapies, meaning the resultant curve should represent the outcomes in a world where 3L+ CAR T does not exist. Thus, the only remaining curative treatment in the SOC arm is SCT. In ZUMA-7, 34.6% of SoC patients received intended SCT, thus in the best case, if all these patients were cured, we would expect the SoC arm to plateau at around 35% (Westin et al., 2023). We see from the updated switching analysis that the KM curves for RPSFTM partial and no recensoring results in a plateau of around [redacted] (Figure 1) which is a result of heavy censoring and loss of FU information due to recensoring of patients in the RPSFTM. The different RPSFTM adjusted KM curves (Figure 1) are very similar during the time period up to around 15m when the number at risk was reasonably large for all three recensoring approaches. Between months 10 and 15 in Figure 1, the number of patients at risk in the RPSFTM with partial recensoring goes from 99 to 44.

Care should be taken not to over-interpret the tails of the curves when few patients are at risk, since a single event can have a large impact on the positioning of the tail. What the RPSFTM analyses show is that adjusting for the confounding effect of 3L+ CAR-T will result in a directionally lower hazard ratio (larger treatment effect), but accurately determining the magnitude of the treatment effect based solely on the RPSFTM analyses is associated with high degree of uncertainty. The RPSFTM recensoring approaches are sensitive to a range of assumptions and conditions, including the complexity of the survivor function, the size of the treatment effect and the proportion of switchers, which are all likely even more pronounced for potentially curative treatments like CAR-T.

Given this uncertainty, we need to look to other sources of data to understand what outcomes we might expect in a setting without CAR-T available in 3L+ (external validity). A Swedish study by Harryson et al (2022) using data from 736 R/R DLBCL patients treated during the pre-CAR-T period 2007-2014 showed that early relapse, defined as relapsing within ≤12m from primary diagnosis, was strongly associated with selection of less intensive treatment and poor survival (2-year OS of around 20%). Among patients of at most 70 years of age, 63% started intensive second-line treatment and 34% received autologous stem cell transplantation (ASCT). Two-year OS among transplanted patients was 56% (early relapse ≤12 months 40%, late relapse >12 months 66%). A minority of patients not older than 76 years (n = 178/506, 35%) fitted CAR-T trial criteria, of which ZUMA-7 was one of the trials. The 2-year OS for those patients who fitted the CAR-T trial criteria was 27% (95% CI: 18–36), i.e. not consistent with the adjusted SoC OS curve from Westin et al (2023).

Finally, Figure 2, shows the SoC KM OS curve for the RPSFTM with full recensoring alongside KM curves from the ORCHAARD (2y OS ~30%) and SCHOLAR-1 (2y OS ~20%) trials as well as the updated parametric curves fitted to the primary OS data (RPSFTM full recensoring). We see that

independently modelled SoC OS using MCMs (green) leads to externally invalid results, whereas using the HR approach (yellow) or using independently fitted (red) SoC OS using the best fitting standard parametric fit (gen gamma) provide clinically plausible results. Thus, we recommend using the HR ratio approach (yellow) in the first instance, or use the best fitting independently modelled generalised gamma model standard parametric curve (red).

In summary, based on the proportion of patients completing SCT in ZUMA-7 and outcomes demonstrated in external data sources, it is clinically implausible to assume an OS plateau of >35% when accounting for switching to 3L+ CAR-T. Fitting mixture cure or standard parametric models to RPSFTM partial recensoring data would result in implausible long-term survival for the SoC arm. Hence, we propose to instead use the RPSFTM with full recensoring to adjust for the confounding effect of treatment switching.

Gilead's updated base case

In the updated model we include time-to-event data (EFS, OS, TTNT) from the latest data cut-off (Jan 25, 2023) for both arms of ZUMA-7. The model is flexible to fit a range of parametric models to either ITT or the RPSFTM with full recensoring KM data for the SoC arm. We present two updated scenarios:

1. Gilead's original base case updated with the new RPSFTM (full recensoring) hazard ratio. The updated hazard ratio for RPSFTM with full recensoring is [redacted]) (Table 3). This hazard ratio was applied to the axi-cel MCM gamma curve used in the original base case. The resultant model curves are displayed in Figure 3 and the updated cost-effectiveness results are presented in Table 1. With the updated RPSFTM hazard ratio the ICER [redacted] from DKK 501,397 to [redacted]

Figure 3 Model curves for EFS and OS (data cut-off 25 Jan, 2023) – HR: [redacted] for RPSFTM with full recensoring applied to the axi-cel MCM OS curve (gamma)

2. DMC's preferred approach of best fitting standard parametric model (generalised gamma) fitted to the RPSFTM (full recensoring) data.

Figure 4 shows the resultant model curves when we fit a standard parametric (generalised gamma) model to the SoC RPSFTM curve with full recensoring.

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The updated cost-effectiveness results for Scenario 2 (Table 2) shows an ICER of DKK

References for Appendix K

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