Norwegian Medicines Agency

Single technology assessment

ID2022_020 Axicabtagene ciloleucel (Yescarta) 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

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Norwegian Medicines Agency

Preface

The regional health authorities (RHF) are responsible for *Nye* metoder, *the National System for the Managed Introduction of New Health Technologies* within the specialist health service. The principles for prioritization which *Nye Metoder* operates by are set out in the white paper on priority setting in the Norwegian health care sector (Meld. St. 34 (2015-2016)) by the Ministry of Health and Care Services. The *Nye Metoder* system has been legislated since 2019 and allows health technologies relevant for the specialist health service to be assessed in a systematic way, to ensure efficient allocation of resources within the health services. More details about the system can be found on the *Nye Metoder* website at nyemetoder.no.

As part of *Nye Metoder*, the Norwegian Medicines Agency has been given the responsibility to perform single technology assessments (STA). STA is a methodological framework for comparing the costs and benefits of a single (new) technology to the standard of care for the indication of interest. The severity of the disease in question is also considered. The objective of STAs is to inform decision-making through an overall evaluation of whether the new method meets the three principles for priority setting in health care: the benefit criterion, the resource criterion, and the severity criterion. The benefit and resource use associated with a health technology is assessed by estimating the additional cost for each "year of life spent in good health" the technology offers compared to the current standard of care. A “year of life spent in good health", indicates a year spent in "perfect" health, in other words without illness or any pain nor discomfort. "Perfect" health in a STA is defined as a quality-adjusted life-year (1 QALY), which is a standardized unit of measure allowing one to compare the benefit of different treatments across indications. The Norwegian Medicines Agency does not evaluate the risk-benefit ratio; this is assessed by the European Medicines Agency (EMA) during the marketing authorization process.

The pharmaceutical company holding the marketing authorization for the health technology in question is obligated to submit documentation for the STA. More specifically, the company submits a health economic model which is used for estimating the relationship between benefit and cost, expressed as the cost for an additional QALY. The Norwegian Medicines Agency can provide guidance for this. Subsequentially, the Norwegian Medicines Agency assesses the assumptions made in the submitted model by examining if the model reflects Norwegian clinical practice. If required, the Norwegian Medicines Agency may request additional information from the company, clinical experts and/or patients to perform additional calculations of the costs and cost-effectiveness using the submitted model.

A Decision Forum comprised of the four CEOs (one for each regional health authority) decides whether to introduce the method or not within the specialist health service through an overall assessment of the criteria for priority-setting. The Norwegian Medicines Agency does not have decision-making authority in the system of *Nye Metoder*, but the STA reports by the Norwegian Medicines Agency are used to inform decision-making. Sykehusinnkjøp HF negotiates the price of the new health technology in the system of *Nye Metoder*. How much society is willing to pay for a QALY is related to the severity of the disease. In addition, STAs associated with high uncertainty, low quality of available evidence, and/or with large budgetary consequences may be given a lower priority by the Decision Forum.

Some of the information in the Norwegian Medicines Agency's reports may be confidential. The Norwegian Medicines Agency assesses requests for exemption from public access by the pharmaceutical company and decides whether the information should be confidential (section 13.1 of the Public Administration Act, guideline in Norwegian can be found here). All HTA evaluation reports are published and are publicly available on the Norwegian Medicines Agency's website at www.legemiddelverket.no.

Executive summary

Scope

A single technology assessment (STA) of Yescarta (axicabtagene ciloleucel, axi-cel) has been conducted. The Norwegian Medicines Agency (NoMA) has assessed the criteria for priority-setting (the benefit criterion, the resource criterion, and the severity criterion) when using axi-cel in accordance with the request from Ordering Forum (Bestillerforum, request number ID2022_020: *En hurtig metodevurdering med en kostnad-nytte vurdering (løp C) gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til behandling av voksne pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) som får tilbakefall innen 12 måneder etter fullføring av, eller som er refraktære overfor, førstelinje kjemoimmunterapi. Prisnotat utarbeides av Sykehusinnkjøp HF, LIS*), and the approved summary of product characteristics (SmPC). NoMAs´s assessment is primarily, but not exclusively, based on the documentation presented by Gilead.

Axi-cel has previously been assessed and introduced for the treatment of patients with relapsed or refractory diffuse large B-cell lymphoma (r/r DLBCL) and primary mediastinal large B-cell lymphoma (r/r PMBCL), following two or more lines of systemic therapy (see Nye Metoder ID2017_105, ID2019_143).

Patient population in Norway

Approximately 400 de novo diffuse large B-cell lymphoma (DLBCL) patients (including high grade B-cell lymphoma (HGBL)) are diagnosed every year in Norway. Of these approximately 70 % (280 patients) are cured with first-line treatment and 40 patients are not treated with a curative intent. The remaining patients will eventually relapse or be refractory to first-line treatment. According to a clinical expert consulted by Gilead, approximately 22 patients have relapsed/refractory (r/r) DLBCL within <12 months and are expected to be treated with axi-cel in the target indication each year in Norway. This estimate is in line with that provided by the clinical experts consulted by NoMA, who estimated that around 20-25 patients with r/r DLBCL will be eligible for treatment with axi-cel each year in Norway. The Norwegian clinical experts highlighted that the estimated patient number is uncertain and will be dependent on the selection criteria eventually implemented in clinical practice.

Severity and absolute shortfall

Patients with primary refractory or early relapsing DLBCL or HGBL have a severe prognosis with limited treatment options according to the clinical experts consulted by NoMA. The willingness to pay for a quality-adjusted life year (QALY) depends on the severity of the disease, estimated as absolute shortfall (AS). NoMA estimates the AS among the target population for this STA (i.e. patients with r/r DLBCL and HGBL eligible for treatment with salvage chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT) in chemotherapy sensitive patients) to be about 13 QALYs.

Treatment of r/r DLBCL/HGBL in Norwegian clinical practice

Standard of care (SOC) second line therapy in the curative setting is comprised of rituximab and salvage chemotherapy (i.e., R-IME, R-ICE, R-GDP or R-DHAP), followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT) in chemotherapy sensitive patients. While HDT-ASCT has a curative potential, only half of patients respond to second-line salvage chemotherapy and are able to proceed to ASCT. Outcomes are particularly poor for patients who have primary refractory disease or early relapse after first-line therapies.

Clinical efficacy

The efficacy and safety of axi-cel in adult patients with r/r DLBCL/HGBL was demonstrated in a phase 3 randomised, open-label, multicenter study (ZUMA-7). In total, 359 patients were randomised in a 1:1 ratio to receive a single infusion of axi-cel or SOC (2 to 3 cycles of standard chemoimmunotherapy followed by HDT-ASCT in those with disease response).

Axi-cel was superior to SOC with respect to the primary endpoint, event-free survival (EFS), with a median EFS time of 8.3 months (95 % CI: 4.5, 15.8 months) vs. 2.0 months (95 % CI: 1.6, 2.8 months), respectively (stratified HR of 0.398 (95 % CI: 0.308, 0.514)). The secondary endpoints were supportive of the primary outcome measure. Overall response rate (ORR) was 81 % and complete response (CR) was 68 % in patients treated with axi-cel compared with 42 % and 23 % respectively in the SOC arm. The median progression free survival (PFS) in the axi-cel arm was 14.7 months (95 % CI: 5.4, NE) compared with 3.7 months (95 % CI: 2.9, 5.3) in the SOC arm (HR: 0.490 (95 % CI: 0.368, 0.652)). Consistent efficacy was observed across relevant subgroups. At a pre-specified interim analysis at the time of the primary analysis of EFS, the overall survival (OS) data were not mature. Updated OS data using a data cut-off date of 25 January 2023 became available during the assessment. After a median follow-up time of 47 months and 45.8 months for the axi-cel arm and SOC arm, respectively, the median OS was not reached for axi-cel and was 31.1 months for SOC (HR = 0.726 (95% CI: 0.540, 0.977, stratified log-rank 1-sided p-value = 0.017).

This is the first approved indication for a CAR-T in the r/r DLBCL setting where the marketing authorization is based on a randomized controlled trial. The randomized controlled trial design is considered appropriate to establish the clinical efficacy of axi-cel vs. SOC. Nevertheless, substantial uncertainty remains regarding the true magnitude of the Yescarta relative effect size. Under the primary EFS definition, the key driver of benefit for axi-cel was the larger proportion of new anti-lymphoma therapy (NALT) events in the SOC arm compared to the axi-cel arm (n=63 (35 %) for SOC and n=11 (6 %) for axi-cel). Events of disease progression and death, on the other hand, were slightly more frequent with axi-cel compared to SOC (46 % vs. 42 % and 6 % vs. 3 %, respectively). In an open-label trial, initiation of new anti-cancer therapy prior to adjudicated disease progression is likely to be informative. A closer examination of NALT events, established that 35/63 events in the SOC arm were due to “premature” initiation of NALT (i.e. initiation of NALT in responding patients, patients who had SD following only 1 cycle of salvage chemotherapy and patients who received a new therapy without having received the randomized treatment). Thus, an

apparent perceived lack of efficacy for SOC in the context of the open-label trial design, is considered to have biased the primary outcome measure in favour of axi-cel.

To explore the impact of such bias, an EFS sensitivity analysis was requested by NoMA, where the "premature" NALT events were to be followed until disease progression. Gilead declined to send the requested analysis, stating that it was not defined in the protocol. NoMA therefore elected to use a similar sensitivity analysis previously conducted by the FDA. The two EFS definitions (i.e. the primary definition of EFS and the EFS definition from the FDA sensitivity analysis) constitute the basis for the two NoMA cost-effectiveness analyses (see below).

The OS analysis is also biased, due to the premature NALT events. Nevertheless, the bias is likely reduced as the overall clinical course would be less sensitive to the impact of "premature" treatment switch (mostly to CAR-T). Although the updated OS analyses establish an OS benefit with axi-cel, the long-term magnitude of this benefit, and the proportion of patients for which axi-cel may lead to a cure is uncertain.

Safety

Serious side effects occurred in most patients, both with axi-cel and with SOC. No new major safety concerns were identified within the new population. The most significant and frequently occurring adverse reactions reported with axi-cel in the ZUMA-7 trial were cytokine release syndrome (CRS, 92 %), encephalopathy (49 %), and infections (45 %). Serious adverse reactions occurred in 54 % of patients, of which CRS and encephalopathy were the most common (reported in 17 % and 16 % respectively). Both higher-grade CRS and neurotoxicity can be life threatening and may require care in an intensive care unit (ICU), as may infections, an adverse event associated with both axi-cel and SOC. The safety profile is manageable with good clinical routines for handling such events being implemented at all treatment centres.

Efficacy and safety of axi-cel are well documented, however, the exact magnitude of the effect size compared to best SOC cannot be reliably established based on the submitted data. Furthermore, there is a lack of evidence of the long-term effect, and therefore the proportion of patients for which axi-cel may lead to a cure cannot be verified.

Cost-effectiveness

NoMA has assessed the analysis and the assumptions used in the economic model submitted by Gilead. NoMA considers that there is substantial uncertainty regarding the true magnitude of axi-cel's relative effect size compared with SOC because of issues related to the EFS definition in the context of the open-label design. Therefore, NoMA has conducted two main analyses based on different definitions of EFS:

- *Analysis 1* is based on the primary definition of EFS and OS results as per randomised population (as per Gilead's main analysis). This analysis is considered anti-conservative as the benefit of axi-cel is driven by the higher number of premature NALT events in the SOC arm, rather than the progression-/death- events.

- *Analysis 2* is based on an alternative definition of EFS (as per FDA's sensitivity analysis). In this analysis, patients in the SOC arm who received NALT prematurely (i.e. while still in response as defined by the blinded independent review committee, in SD following only one salvage chemotherapy cycle, or who never received the randomized treatment) were followed until progression/stable disease at day 150 occurred. This analysis is considered conservative as it generates over-optimistic EFS in the SOC arm, due to the added benefit of a second salvage therapy (likely primarily axi-cel) being included in the EFS event time.

The results from NoMA's analysis 1 and 2 are shown in the tables below. There is a rather large difference in the ICER produced by the two analyses. Partly this is explained by a small decline in the incremental QALY benefit in analysis 2 compared to analysis 1 (1,15 vs 1,38 QALYs). The main driver of the difference in ICER, however, is related to the cost of subsequent treatment, as the time patients spend in EFS has impact on the proportion of patients receiving subsequent CAR-T therapy in the SOC arm. The time the patients spend in EFS also impacts other healthcare costs.

Table 1: Results from NoMA's main analysis 1 (primary definition of EFS). Based on maximum PRPs without VAT. Per patient. Discounted.

NoMA's analysis 1 – primary definition of EFS			
	Axi-cel	SOC	Difference
Total costs	4 309 734	3 646 583	663 150
Total QALYs Total life years	6,93 8,90	5,55 7,39	1,38 1,51
Incremental cost per QALY gained Incremental cost per life year gained			480 150 438 698

Table 2: Results from NoMA's main analysis 2 (alternative definition of EFS, as per FDA's sensitivity analysis). Based on maximum PRPs without VAT. Per patient. Discounted.

NoMA's analysis 2 – alternative definition of EFS (as per FDA's sensitivity analysis)			
	Axi-cel	SOC	Difference
Total costs	4 309 734	2 834 002	1 475 732
Total QALYs Total life years	6,93 8,90	5,78 7,39	1,15 1,51
Incremental cost per QALY gained Incremental cost per life year gained			1 286 026 976 250

The incremental cost (estimated using maximum PRPs without VAT) of axi-cel compared with SOC is:

- 480 000 NOK per QALY gained in NoMA's analysis 1 (primary definition of EFS)
- 1 290 000 NOK per QALY gained in NoMA's analysis 2 (alternative definition of EFS, as per FDA's sensitivity analysis)

Both analyses have major limitations.

Analysis 1 overestimates incremental QALY gain due to investigator-driven early initiation of 3L treatment, mainly axi-cel, in the SOC arm. Early initiation of NALT also underestimates incremental costs due to higher 3L treatment costs in the SOC arm than would be expected. Therefore, the true ICER is expected to be higher than 480 000 NOK.

Analysis 2 is based on aggregated published Kaplan Meier curves and the lack of access to individual patient level data is a considerable restriction in this analysis. Furthermore, NoMA considers the resulting EFS in the SOC arm to be overoptimistic due to the added benefit of a second salvage therapy (likely primarily axi-cel) being included in the EFS event time. Hence the true ICER is expected to be lower than 1 290 000 NOK. In *analysis 2* NoMA aligns the time of initiating the 3L treatment with the EFS curve in the SOC arm. This results in a lower proportion of 2L SOC patients eligible for (expensive) 3L treatment resulting in lower overall costs of the SOC arm, therefore increasing incremental costs and the ICER as compared to *analysis 1*. NoMA has not adjusted the distribution of, nor the type of 2L and 3L treatments in *analysis 2,* as this would be based on assumptions rather than empirical data.

Taking into consideration NoMA's anti-conservative analysis 1 and NoMA's conservative analysis 2, the ICER is believed to lie somewhere between 480 000 and 1 290 000 NOK. The difference in the ICERs is to some extent driven by a reduced EFS treatment effect (i.e. decreased QALY incremental benefit) but mainly due to the reduced costs for subsequent treatment (i.e. increased cost increment) in the SOC arm.

The costs of the subsequent treatment in the SOC arm have a large impact on the ICER. A scenario analysis was conducted excluding axi-cel costs for 20 patients who received NALT while in BIRC assessed ongoing response. Of these, 15 patients were in response pre-ASCT and had the cost of ASCT added (these patients should have proceeded to ASCT as per the study protocol). This analysis increased the ICER from 480 000 to 772 378 in NoMA's analysis 1. Note that this scenario did not adjust the effects accordingly i.e. the ICER may not have increased to the same extent if the benefit of ASCT was reduced compared to CAR-T in these patients. Similarly, a scenario analysis in which the proportion of patient receiving axi-cel as a subsequent treatment among patients receiving a 3rd line treatment in the SOC arm (120/180) decreased from 81% (97/120 based on ZUMA-7) to 70% or 60% (based on the input from Norwegian clinical experts) increased the ICER.

Axi-cel and some of the other drugs that are included in the analyses have a discounted price. These prices are confidential and not available to the general public. The confidential ICERs and budget impact are presented in a separate attachment (not included here).

Gilead's main analysis

The results from Gilead's main analysis are presented in the table below.

Table 3: Results from Gilead's main analysis. Based on maximum PRPs without VAT. Per patient. Discounted.

	Axi-cel	SOC	Difference
Total costs	4 317 061	3 762 174	554 887
Total QALYs Total life years	6.95 8.91	5.58 7.39	1.38 1.51
Incremental cost per QALY gained Incremental cost per life year gained			403 151 366 548

Budget impact

Budget impact for the pharmaceutical budget for specialist health services:

Based on data and assumptions, NoMA estimates the annual budget impact of introducing Yescarta (axi-cel) for the eligible patient population as described in this STA to be around 91 million NOK including VAT in year 5. The pharmaceutical budget impact for specialist health services is based on drug costs for Yescarta and SOC in the second line only and does not consider a transfer of the costs of axi-cel from the third to the second line of treatment. The presented budget impact estimates are uncertain and simplified.

Budget impact for the total budget of specialist health services:

Based on data and assumptions, NoMA estimates the total annual budget impact of introducing Yescarta (axi-cel) for the eligible patient population as described in this STA to be around 28 – 43 million NOK including VAT in the year with the largest budget impact after introduction. These calculations include costs for third-line CAR-T treatment, after SOC. The presented budget impact estimates are uncertain and simplified.

NoMA's overall assessment

The input values in the economic model are based on the randomised open-label ZUMA-7 study. As described above, the definition and the assessment of the primary EFS endpoint is a key source of uncertainty regarding the true magnitude of the axi-cel effect size. NoMA believes that the relative effect for EFS of HR=0.398 (used in NoMA's analysis 1) is biased in favour of axi-cel, and that an analysis that explores the impact of an alternative HR of 0.7 (used in NoMA's analysis 2) is important to demonstrate the uncertainty in the ICER. Analysis 2 is based on EFS survival curves reconstructed from KM curves based on a sensitivity analysis performed by FDA. The lack of patient level data is a considerable limitation of analysis 2, mainly in terms of EFS extrapolation. The OS analysis is also biased due to the early initiation of NALT. Nevertheless, compared to EFS, the impact of bias on OS results may be more limited, as the administration of NALT (mostly CAR-Ts) pre-progression is less likely to have substantially altered the overall clinical course. The original OS analysis was immature. Updated OS results demonstrate a statistically significant OS benefit. This is particularly encouraging considering the high proportion of treatment-switch to CAR-T in the SOC arm. Still, whereas the curative potential of ASCT in the second line setting is generally considered well established, the follow-up time is not sufficient to verify the cure fraction estimated for axi-cel.

NoMA considers the ICER of 480 000 as obtained from analysis 1 as anti-conservative (i.e. it produces over-optimistic relative treatment effect of axi-cel), whereas the ICER of 1 290 000 obtained from analysis 2 is conservative (i.e. it produces over-pessimistic relative treatment effect for axi-cel). Even though there is an uncertainty related to the EFS results, the differences in the two analyses are mainly driven by costs associated to subsequent treatment, and other costs in the SOC arm. Assumptions about the proportion of patients receiving a subsequent therapy and the distribution of such patients to CAR-T vs. alternative SOC options have a major bearing on the costs in the model. These assumptions are highly uncertain, precluding a precise estimate of the ICER.

Sammendrag

Formål

Dette er en metodevurdering av legemiddelet Yescarta (axicabtageneciloleucel, axi-cel). Legemiddelverket har vurdert prioriteringskriteriene nytte, ressursbruk og alvorlighet, samt usikkerheten og budsjettvirkningene i henhold til godkjent preparatomtale og bestilling ID2022_020: *axicabtagene ciloleucel (Yescarta) til behandling av voksne pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) som får tilbakefall innen 12 måneder etter fullføring av, eller som er refraktære overfor, førstelinje kjemoimmunterapi.* Vurderingen er først og fremst, men ikke utelukkende, basert på dokumentasjon sendt inn av Gilead.

Bakgrunn

Yescarta er CAR-T celleterapi, en type avansert behandling der pasientens egne T-celler reprogrammeres ved hjelp av et transgen som koder for en kimær antigenreseptor (CAR) slik at de blir i stand til å identifisere og eliminere celler som uttrykker CD19. Antigenet CD19 finnes kun på B-celler, inkludert kreftceller med opphav fra B-celler, som for eksempel ved DLBCL og PMBCL. Når axi-cel gis til pasienten, vil de modifiserte T-cellene gjenkjenne og drepe kreftcellene, og dermed bidra til å fjerne kreftsykdommen.

Den kliniske prosessen starter med leukaferese, hvor pasientens egne mononukleære celler, inkludert T-celler, høstes fra perifert blod. Cellene sendes deretter til et sentralt produksjonslaboratorium hvor CAR-T cellene blir laget ved å bruke et retrovirus til å sette DNA-et for det kimære proteinet inn i DNA-et til pasientens T-celler. De modifiserte cellene blir deretter stimulert og ekspandert, for så å bli fryst ned og sendt tilbake til behandlingsstedet. Pasientene venter vanligvis 3-4 uker mens behandlingen lages. Axi-cel er en engangsbehandling som gis som infusjon. Før infusjonen får pasientene en kur med lymfodepleterende kjemoterapi (fludarabin i kombinasjon med syklofosfamid) for å redusere antallet konkurrerende T-celler.

Axi-cel er tidligere metodevurdert og innført til behandling av pasienter med residivert eller refraktært diffust storcellet B-cellelymfom (r/r DLBCL) og primært mediastinalt storcellet B-cellelymfom (r/r PMBCL), etter to eller flere linjer med systemisk behandling (se Nye Metoder ID2017_105, ID2019_143).

Pasientgrunnlag i Norge

Medisinske fageksperter Legemiddelverket har kontaktet anslår at om lag 20-25 pasienter vil være aktuelle for behandling med axi-cel hvert år, men de understreker at dette estimatet er usikkert og vil være avhengig av seleksjonskriterier som eventuelt implementeres i klinisk praksis.

Alvorlighet og prognosetap

Pasienter med primær refraktær eller tidlig relapserende DLBCL og HGBL har en alvorlig prognose med få tilgjengelige behandlingsalternativer ifølge medisinske fageksperter. Alvorlighetsgraden kan påvirke om kostnadene vurderes å stå i rimelig forhold til nytten av behandlingen. Legemiddelverket har beregnet at aktuell pasientpopulasjon behandlet med dagens standardbehandling har et absolutt prognosetap (APT) på ca. 13 QALYs.

Behandling i norsk klinisk praksis

Behandling av pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) følger Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer fra Helsedirektoratet. Rundt 60-70 % av pasientene blir kurert ved dagens førstelinjebehandling med rituksimab kombinert med syklofosfamid, doksorubicin, vinkristin og prednisolon (R-CHOP). Standardbehandling (SOC) ved andre behandlingslinje i kurativ setting består av rituksimab kombinert med kjemoterapi (R-IME, R-ICE, R-GDP or R-DHAP) etterfulgt av høydose kjemoterapi (HDT) og autolog stamcelletransplantasjon (ASCT) for de som responderer på kjemoterapi og som er egnet for ASCT. Selv om HDT-ASCT har et kurativt potensial, vil kun halvparten av pasientene respondere på kjemoterapi i andre linje og være i stand til å få ASCT. Utsiktene er særlig dårlig hos pasienter som har primær refraktær sykdom eller som får tidlig tilbakefall etter førstelinjebehandling.

Effekt

Klinisk effekt og sikkerhet for axi-cel hos voksne pasienter med r/r DLBCL eller HGBL er vist i en fase 3 randomisert åpen studie kalt ZUMA-7. Totalt 359 pasienter ble randomisert 1:1 til å motta engangsbehandling med infusjon av axi-cel eller SOC. SOC bestod av 2 til 3 sykluser av kjemoimmunterapi etterfulgt av HDT-ASCT hos de som responderte. Primærendepunktet i studien var hendelsesfri overlevelse (EFS). Ved en median oppfølgingstid på 24,9 måneder var median EFS 8,3 måneder (95 % CI: 45 – 15,8 måneder) i axi-cel armen sammenlignet med 2,0 måneder (95 % CI: 1,6 – 2,8 måneder) i placebo armen (stratifisert hasard ratio (HR) på 0,398 (95 % CI: 0,308 – 0,514)). Sekundærendepunktene støttet primærutfallsmålet. Total responsrate (ORR) var på 81 % og komplett respons (CR) var på 68 % hos pasienter behandlet med axi-cel sammenlignet med henholdsvis 42 % og 23 % hos pasienter behandlet med SOC. Median progresjonsfri overlevelse (PFS) var 14,7 måneder (95 % CI: 5,4 - NE) i axi-cel armen sammenlignet med 3,7 måneder (95 % CI: 2,9 – 5,3) i SOC armen. Observert effekt var konsistent hos relevante subgrupper. Ved den prespesifiserte interim analysen av EFS var data for totaloverlevelse (OS) umodne. Under metodevurderingen ble oppdaterte OS data ved et datakutt fra 25. januar 2023 ettersendt av Gilead. Etter en median oppfølgingstid på 47 måneder og 45,8 måneder for henholdsvis axi-cel armen og SOC armen var median OS ikke nådd for axi-cel og 31,1 måneder for SOC armen (HR = 0,26 (95 % CI: 0,540 – 0,977, stratifisert log-rank 1-sidig p-verdi = 0,017).

Legemiddelverkets vurdering av effekt

Dette er den første godkjente indikasjonen for CAR-T behandling til r/r DLBCL, der markedsføringstillatelsen er basert på data fra en randomisert kontrollert studie. Det randomiserte kontrollerte studiedesignet til ZUMA-7 er egnet for å etablere klinisk effekt av axi-cel sammenlignet med SOC. Det er imidlertid stor usikkerhet knyttet til den faktiske effektstørrelsen. Ved den primære definisjonen av EFS, var hoveddriveren av gevinsten av axi-cel knyttet til en større andel som fikk ny anti-lymfombehandling (NALT) i SOC armen (35 %) sammenlignet med axi-cel armen (6 %). På den annen side, oppstod sykdomsprogresjon og død mer hyppig hos pasienter behandlet med axi-cel sammenlignet med SOC (henholdsvis 46 % versus 42 % og 6 % versus 3 %). I en åpen studie vil en beslutning om initiering av ny kreftbehandling før sykdomsprogresjon sannsynligvis være såkalt informativ (dvs. gi systematiske skjevheter/bias). Ved en nærmere vurdering av NALT hendelsene, fant vi at over halvparten (35/63) av hendelsene i SOC armen var «for tidlig» initiering av NALT, dvs. initiering av NALT hos pasienter som responderte på SOC, pasienter som hadde stabil sykdom etter kun én syklus av kjemoterapi og pasienter som mottok ny behandling før de hadde mottatt studiebehandlingen. Følgelig ser det ut til at en manglende tro på effekten av SOC i sammenheng med det åpne studiedesignet, har ført til skjevhet (bias) i relativ effekt i favør av axi-cel.Legemiddelverket etterspurte en sensitivitetsanalyse som utforsker innvirkningen denne biasen har på EFS, hvor «for tidlig» NALT hendelser ble fulgt frem til sykdomsprogresjon. Gilead har ikke sendt inn en slik analyse, med begrunnelse om at dette ikke var definert i protokollen til ZUMA-7. Legemiddelverket valgte derfor å bruke en lignende sensitivitetsanalyse tidligere utført av FDA (USAs mat- og legemiddelkontroll). De to EFS definisjonene, den primære definisjonen av EFS og FDA sin sensitivitetsanalyse av EFS, er grunnlaget for Legemiddelverkets to hovedanalyser presentert under.

OS er også utsatt for bias på grunn av «for tidlig» NALT hendelser. Skjevheten er trolig ikke like stor som for EFS siden det kliniske forløpet er mindre sensitivt til innvirkningen av «for tidlig» behandlingsbytte (stort sett CAR-T).

Sikkerhet

Alvorlige bivirkninger forekom hos de fleste pasientene, både med axi-cel og med standard behandling. Ingen nye, viktige sikkerhetsproblemer ble identifisert i den nye populasjonen. De mest hyppige bivirkningene hos pasienter behandlet med axi-cel rapportert i ZUMA-7 studien var cytokinfrigjøringssyndrom (CRS), encefalopati og infeksjoner. I overkant av halvparten av pasientene fikk alvorlige bivirkninger, hvorav CRS og nevrotoksisitet var vanligst. Både CRS og nevrotoksisitet kan være livstruende og kreve behandling i intensivavdeling på sykehus. Infeksjoner kan også være en livstruende bivirkning både av axi-cel og av standardbehandling.

Effekt og sikkerhet av axi-cel er godt dokumentert, men et sikkert estimat på effektstørrelsen sammenlignet med SOC kan ikke etableres basert på innsendt dokumentasjon. Videre er det utfordrende å anslå andelen pasienter som kan bli kurert på behandling med axi-cel.

Kostnadseffektivitet

Legemiddelverket har vurdert innsendt helseøkonomisk analyse fra Gilead og forutsetningene for denne. Legemiddelverket mener det er stor usikkerhet knyttet til størrelsen på relativ effekt av axi-cel sammenlignet med SOC grunnet definisjonen av EFS i det åpne studiedesignet. Legemiddelverket har derfor utført to hovedanalyser:

- *Analyse 1* er basert på den primære definisjonen av EFS og OS resultater fra hele studiepopulasjonen i ZUMA-7 (som Gilead sin grunnanalyse). Denne analysen er vurdert som for optimistisk siden nytten av axi-cel er drevet av et høyt antall «for tidlige» ny anti-lymfombehandling (NALT) hendelser i SOC armen, fremfor hendelser som progresjon eller dødelighet.

- *Analyse 2* er basert på en alternativ definisjon av EFS basert på FDA sin sensitivitetsanalyse. I denne analysen er pasientene som mottok «for tidlig» NALT fulgt til progresjon eller stabil sykdom ved dag 150. Denne analysen er vurdert som for konservativ siden den genererer en EFS som er for optimistisk i SOC armen, siden de fleste pasientene mottok CAR-T som NALT.

Legemiddelverkets inkrementelle kostnadseffektivitetsbrøk (IKER) for axi-cel sammenlignet med SOC i de to analysene er:

- Analyse 1: 480 000 NOK (maksimal AUP uten mva.) per kvalitetsjusterte leveår (QALY)
- Analyse 2: 1 290 000 NOK (maksimal AUP uten mva.) per kvalitetsjusterte leveår (QALY)

Det er en ganske stor forskjell mellom IKER presentert i de to analysene. Dette kan delvis forklares av en liten reduksjon i nytte i analyse 2 sammenlignet med analyse 1 (1,15 versus 1,38 QALYs). Hoveddriveren for forskjellene i IKER er imidlertid relatert til kostnader for etterfølgende behandling, siden tiden pasientene er i EFS påvirker andelen pasienter som mottar CAR-T etter standardbehandling i SOC armen. Tiden pasientene er i EFS påvirker også kostnader knyttet til andre helsetjenester.

Axi-cel og andre legemidler inkludert i analysene har rabatterte konfidensielle priser. Konfidensielle resultater vil bli presentert i et separat dokument.

Begge analysene har begrensninger og usikkerheter.

Analyse 1 overestimerer de inkrementelle QALY gevinstene på grunn av «for tidlig» NALT, hovedsakelig CAR-T, i SOC armen. «For tidlig» NALT underestimerer også de inkrementelle kostnadene på grunn av høye kostnader knyttet til CAR-T behandling enn hva man kunne forvente seg hvis pasientene hadde fortsatt på SOC frem mot sykdomsprogresjon. Derfor er det forventet at reell IKER er høyere enn 480 000 NOK.

Analyse 2 er basert på aggregerte publiserte Kaplan Meier kurver og vi mangler tilgang på individuelle pasientdata, som er en stor begrensning i denne analysen. Legemiddelverket anser at denne analysen gir en EFS i SOC armen som er for optimistisk fordi tid-til EFS hendelsen måler nytten av to etterfølgende SOC behandlinger i senere linje (hovedsakelig CAR-T). Følgelig er det ventet at reell IKER vil være lavere enn 1 290 000 NOK. I analyse 2 er tiden for initiering av tredjelinjesbehandling satt lik som EFS-kurven for SOC armen. Dette resulterer i at en lavere andel pasienter i SOC armen mottar kostbar tredjelinjesbehandling som fører til lavere totalkostnader i SOC armen og dermed øker de inkrementelle kostnadene og IKER sammenlignet med analyse 1. Legemiddelverket har ikke justert for fordelingen av, eller type andre- og tredjelinjesbehandling i analyse 2 siden dette vil være basert på antagelser fremfor empiriske data.

Tatt i betrakting Legemiddelverkets optimistiske hovedanalyse 1 og konservative hovedanalyse 2, tror vi at reell IKER ligger et sted mellom 480 000 NOK og 1 290 000 NOK. Forskjellen mellom disse analysene er til en viss grad drevet av en reduksjon i redusert relativ effekt for EFS for axi-cel sammenlignet med SOC (redusert inkrementell QALY gevinst i analyse 2 sammenlignet med analyse 1), men hovedsakelig av reduserte behandlingskostnader i SOC armen (reduserte kostnader i SOC armen i analyse 2 sammenlignet med analyse 1).

Kostnadene knyttet til påfølgende behandling i SOC armen har stor innvirkning på IKER i begge analysene. En scenarioanalyse ble gjennomført der kostnadene for axi-cel ble ekskludert for 20 pasienter som fikk NALT mens de fremdeles var i respons i ZUMA-7. Femten av disse pasientene var i respons før ASCT og fikk kostnader for ASCT lagt til (disse pasientene skulle ha gått videre til ASCT iht. studieprotokollen). I denne analysen økte IKER med 300 000 NOK i Legemiddelverkets analyse 1. Merk at dette scenariet ikke har justert effekten tilsvarende og at IKER ville ikke ha økt i like stor grad dersom det hadde vært mulig å justere for effekten. I scenarioanalyser som justerer ned andelen pasienter i SOC armen som mottar CAR-T behandling som påfølgende behandling i 3. linje fra 81 % (basert på ZUMA-7) til 70 % og 60 % (basert på input fra norske medisinske fageksperter) øker også IKER.

<u>Gileads hovedanalyse</u>

Gileads inkrementelle kostnadseffektivitetsbrøk (IKER) for axi-cel sammenlignet med SOC er 403 151 NOK (maksimal AUP uten mva.) per kvalitetsjusterte leveår (QALY).

Budsjettkonsekvenser

Legemiddelverket har estimert at de årlige budsjettvirkningene av å innføre axi-cel hos aktuell pasientpopulasjon vil være omtrent 91 millioner NOK (maksimal AUP med mva.) for spesialisthelsetjenestens legemiddelbudsjett. Beregningene er usikre og forenklede, de inkluderer kun legemiddelkostnader for axi-cel og SOC i andre behandlingslinje. Det betyr at budsjettberegningene for

spesialisthelsetjenestens legemiddelbudsjett ikke tar hensyn til en forflytning av kostnader av axi-cel fra tredje til andre behandlingslinje.

Ved å ta hensyn til spesialisthelsetjenesten totalbudsjett har Legemiddelverket estimert årlige budsjettvirkninger til 28 – 43 millioner NOK (maksimal AUP med mva.) ved en eventuell innføring av axi-cel. Disse beregningene inkluderer kostnader for CAR-T behandling i tredje linje, etter SOC.

Legemiddelverkets totalvurdering

Parametere som inngår i den helseøkonomiske modellen baserer seg hovedsakelig på den randomiserte åpne studien ZUMA-7. Som beskrevet over, er hovedkilden til usikkerhet den primære definisjonen av EFS som har ført til skjevhet i estimatet på relativ effekt av axi-cel. Legemiddelverket vurderer at den relative effekten for EFS anvendt i Legemiddelverkets hovedanalyse 1 (HR = 0,4) er biased i favør av axi-cel på grunn av «for tidlig» initiering av NALT. På den andre side er den alternative EFS analysen basert på aggregerte Kaplan Meier kurver fra FDA sin sensitivitetsanalyse anvendt i Legemiddelverkets hovedanalyse 2 (HR = 0,7) biased i disfavør av axi-cel. Mangelen på data på pasientnivå er en betydelig begrensning i analyse 2, hovedsakelig for ekstrapoleringen av EFS og totalkostnadene ved SOC. Også i analysen av total overlevelse vil det være skjevhet pga. for tidlig start av NALT. Sammenliknet med EFS analysen vurder Legemiddelverket imidlertid at denne skjevheten vil være mer begrenset, da NALT administrering (primært CAR-T) før progresjon i mindre utstrekning vil påvirke det totale kliniske forløpet. Den opprinnelige OS analysen var umoden. Oppdaterte OS resultater viser en statistisk signifikant fordel for axi-cel. Dette er spesielt oppmuntrende med tanke på den høye andelen av etterfølgende axi-cel behandling i SOC armen. Mens det kurative potensiale av ASCT anses veletablert, er imidlertid oppfølgingstiden fremdeles for kort for å kunne verifisere kur-fraksjonen estimert for axi-cel.

Legemiddelverket vurderer at IKER på 480 000 i analyse 1 er for optimistisk fordi den estimerer en for stor relativ effekt av axi-cel, mens IKER på 1 290 000 i analyse 2 er for konservativ fordi den estimerer en for liten relativ effekt av axi-cel. Selv om det er usikkerhet knyttet til EFS resultatene, er forskjellen mellom de to analysene drevet av kostnader knyttet til etterfølgende behandling og andre kostnader i SOC armen. Antagelser rundt andelen pasienter som mottar etterfølgende behandling og fordelingen av CAR-T versus annen standardbehandling har stor innvirkning på kostnadene i modellen. Disse antagelsene er svært usikre og gjør det vanskelig å etablere et presist estimat på IKER.

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Logg

Bestilling:	*ID2022_020: En hurtig metodevurdering med en kostnad-nytte vurdering (løp C) gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til behandling av voksne pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) som får tilbakefall innen 12 måneder etter fullføring av, eller som er refraktære overfor, førstelinje kjemoimmunterapi. . Prisnotat utarbeides av Sykehusinnkjøp HF, LIS.*
Forslagstiller:	Statens legemiddelverk
Legemiddelfirma:	Kite Pharma (Gilead)
Preparat:	Yescarta
Virkestoff:	Aksikabtagenciloleucel
Indikasjon:	Yescarta er indisert til behandling av voksne pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) som får tilbakefall innen 12 måneder etter fullføring av, eller som er refraktære overfor, førstelinje kjemoimmunterapi.
ATC-nr:	L01X X70

Prosess

Tidspunkt for MT for legemiddelet evt. Indikasjonsutvidelsen	14-10-2022
Dokumentasjon bestilt av Legemiddelverket	14-02-2022
Fullstendig dokumentasjon mottatt hos Legemiddelverket	16-01-2023 (første innsendelse som ble mottatt 04.11.2022 var ikke komplett)
Saken tildelt saksutreder(e)	14-11-2022
Klinikere kontaktet for første gang	11-01-2023

LIS kontaktet for første gang av Legemiddelverket	10-03-2023
Tid i påvente av opplysninger fra legemiddelfirma:	66 dager
Rapport ferdigstilt:	30-06-2023
Saksbehandlingstid:	155 dager. Dette innebærer 34 dager i kø i påvente av tildeling til saksutreder(e).
Saksutredere:	Helga Haugom Olsen Kristie van Lieshout Ania Urbaniak Solveig Bryn
Medisinske fageksperter:	Anne Turid Bjørnevik Unn Merete Fagerli Julian Hamfjord
Medisinske fageksperter har bidratt med avklaringer av sentrale forutsetninger i analysen (bl.a. sammenlignende behandling, pasientgrunnlag og overførbarhet av studiedata til norsk klinisk praksis). Legemiddelverket er ansvarlig for rapportens innhold. Medisinske fageksperter har ikke vært involvert i noen konsensusprosess eller hatt noen «peer-review» funksjon ved utarbeidelse av rapporten.	

Glossary

AE	Adverse event
AIC	Akaike information criterion
AS	Absolute shortfall
ASCT	Autologous stem cell transplant
BEAM	carmustine, etoposide, cytarabine and melphalan
BIC	Bayesian information criteria
BIRC	Blinded independent review committee
BSA	Body surface area
CAR	Chimeric antigen receptor
CMH	Cochran-Mantel-Haenszel
CNS	Central nervous system
COD	Cut-off date
CR	Complete response
CRS	Cytokine release syndrome
CUA	Cost-utility analysis
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
EBMT	The European Group for Blood & Marrow Transplantation
EBV+	Epstein Barr virus positive
ECOG	Eastern cooperative oncology group
EFS	Event-free survival
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
FL	Follicular lymphoma

HDT	High-dose therapy
HGBL	High-grade B-cell lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
ICU	Intensive care unit
IPCW	Inverse probability of censoring weights
IPI	International prognostic index
IVIG	Intravenous infusions of immunoglobulins
ITT	Intention-to-treat
KM	Kaplan-Meier
LBCL	Large B-cell lymphoma
LIS	Sykehusinnkjøp HF
MA	Marketing authorization
MCM	Mixture cure model
MMRM	Mixed model with repeated measures
NALT	New anti-lymphoma therapy
NHL	Non-Hodgkin lymphoma
NICE	National Institute for Health and Care Excellence
NOK	Norwegian kroner
NoMA	Norwegian Medicines Agency
NOS	Not otherwise specified
ORR	Overall response rate
OS	Overall survival
PartSA	Partitioned survival

PFS	Progression free survival
PH	Proportional hazard
PMBCL	Primary mediastinal large B-cell lymphoma
PO	Orally
PPP	Pharmacy purchase price
PR	Partial response
PRP	Pharmacy retail price
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life-year
QoL	Quality of life
RHF	Regional health authorities
RPSFT	Rank preserving structural failure time
R-CHOP	Rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone
R-CHOEP	Rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, etoposide, and prednisone
R-ESHAP	Rituximab plus etoposide, solu-medrone, high dose cytarabine, and cisplatin
R-DHAP/R-DHAX	Rituximab plus dexamethasone, cytarabine, and cisplatin
R-GDP	Rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin
R-ICE	Rituximab plus ifosfamide, carboplatin, and etoposide
R-IME	Rituximab plus ifosfamide, mixantrone, and etoposide
r/r	Relapsed/refractory
sAAIPI	Second-line age-adjusted International Prognostic Index
SAE	Serious adverse event
SD	Stable disease
SMR	Standardised mortality rate
SmPC	Summary of product characteristics

SOC	Standard of care
STA	Single technology assessment
TEAE	Treatment emergent adverse event
TTNT	Time to next treatment
VAS	Visual analogue scale
VAT	Value added tax
WHO	World Health Organization
95 % CI	95 % confidence interval

1. Background

1.2 Scope

This single technology assessment (STA) concerns treatment with the CAR-T cell therapy axicabtagene ciloleucel (axi-cel, Yescarta) 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 in Norway.

Health care interventions are to be evaluated against the three prioritisation criteria in Norway – the benefit criterion, the resource criterion and the severity criterion. In this STA, axi-cel is compared to chemotherapy (standard of care – SOC) in a cost-utility analysis (CUA). NoMA's assessment is primarily, but not exclusively, based on the documentation presented by Gilead.

1.3 Relapsed and refractory (r/r) DLBCL/HGBL

Non-Hodgkin lymphoma (NHL) comprises a heterogeneous group of cancers originating primarily in B lymphocytes and, to a lesser extent, in T lymphocytes and natural killer cells. Large B-cell lymphoma (LBCL) is an aggressive subset of B-cell NHL, representing 30 % to 40 % of NHL cases. The most common LBCL subtype is diffuse large B-cell lymphoma (DLBCL) (including DLBCL not otherwise specified [NOS]), which accounts for more than 80 % of LBCL cases). Other disparate DLBCL entities include primary cutaneous DLBCL, leg type; Epstein Barr virus positive (EBV+) DLBC; DLBCL associated with chronic inflammation; T cell/histiocyte-rich LBCL and DLBCL arising from follicular lymphoma (FL). In 2016, the World Health Organization (WHO) introduced high-grade B-cell lymphoma (HGBL) as a new category of LBCL. HGBL comprises 2 subcategories: 1) HGBL with MYC, BCL2, and/or BCL6 rearrangements, which is also known as double- or triple-hit lymphoma and excludes FL or lymphoblastic lymphoma; and 2) HGBL NOS, which includes LBCL that are "high-grade" and would be previously characterized as B cell lymphoma unclassifiable, and lack genetic features of double- or triple hit lymphomas. HGBL represents up to 13 % of LBCL cases.

The clinical manifestations of LBCL vary and depend on the site of disease involvement. Rapidly growing tumours may present as masses, causing symptoms when they infiltrate tissues or organs. Pain may occur due to rapid or invasive tumour growth, and is often the first sign of this illness, sometimes associated with "B-symptoms" of fever, drenching night sweats, and weight loss. Generalized pruritus may also be present.

The DLBCL and HGBL populations relevant to this STA consist of patients who have relapsed within 12 months from completion of, or are refractory to, first-line chemoimmunotherapy. This is a less chemotherapy-sensitive population with a particularly severe prognosis. Approximately 400 de novo DLBCL patients are diagnosed every year in Norway. Of these approximately 70% (280 patients) are cured with first line treatment. The remaining patients will eventually relapse or be refractory to first-line

treatment. According to the clinical experts consulted by NoMA, approximately 20-25 patients with r/r DLBCL will be eligible for treatment with Yescarta each year in Norway. The Norwegian clinical experts highlighted that the estimated patient number is uncertain and will be dependent on the selection criteria eventually implemented in clinical practice.

1.4 Severity and shortfall

The prognosis in patients with primary refractory or early relapsed DLBCL and HGBL is poor.

The degree of severity affects whether the costs are considered to be reasonable relative to the benefit of the treatment. NoMA uses a quantitative method (see Appendix 2 Severity and shortfall) for estimating the level of severity based on absolute shortfall (AS).

NoMA estimates the absolute shortfall based on current standard care with chemotherapy followed by high-dose therapy (HDT) and autologous stem cell transplant (ASCT) in responding patients, to be approximately 13 QALYs.

1.5 Treatment of R/R DLBCL/HGBL

1.5.1 Treatment with axi-cel

- *Therapeutic indication*

Axi-cel (Yescarta) 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.

Axi-cel is also indicated in adult patients with relapsed or refractory (r/r) DLBCL and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy, as well as in r/r FL after three or more lines of systemic therapy.

- *Mechanism of action*

Axi-cel is an autologous, immunocellular cancer therapy that involves reprogramming patient's own T cells with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19 expressing cells. When axi-cel is given to the patient, the modified T cells attach to and kill the cancer cells, thereby helping to clear the cancer from the body.

CD19 is a transmembrane protein expressed on B cells from early development until differentiation into plasma cells, but that is not present on pluripotent blood stem cells and most normal tissues other than B cells. This makes CD19 a suitable target for therapeutic intervention in B cell leukaemia and lymphoma. 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.

- *Posology*

Axi-cel is to be administered after a 3-day lymphodepleting chemotherapy regimen consisting of fludarabine 30 mg/m^2/day and cyclophosphamide 500 mg/m^2/day, followed by 2 rest days. Axi-cel is then administered as a single intravenous infusion at a target dose of 2 x 10^6 anti CD19 CAR T cells/kg (minimum dose of 1 x 10^6 anti CD19 CAR T cells/kg; for subjects weighing > 100 kg, the maximum flat dose was 2 x 10^8 anti CD19 CAR T cells).

Following axi-cel administration, patients must be monitored daily for the first 10 days for signs and symptoms of potential cytokine release syndrome (CRS), neurologic events and other toxicities. After the first 10 days following the infusion, the patient is to be monitored at the physician's discretion. Patients should remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

- *Undesirable effects*

CAR-T cells proliferate and kill tumour cells, concomitantly releasing inflammatory cytokines in order to enhance an effective immune response. The release of pro-inflammatory cytokines can induce CRS with symptoms of high fevers, low blood pressure, and respiratory distress. Another common and severe side effect of CAR T-cell therapy is neurotoxicity.

Both higher-grade CRS and neurotoxicity can be life threatening and may require care in an intensive care unit. A detailed CRS management algorithm is given in the Summary of product characteristics (SmPC).

The most significant and frequently occurring adverse reactions reported in the ZUMA-7 trial were cytokine release syndrome (CRS, 92%), encephalopathy (49%), and infections (45%). Serious adverse reactions occurred in 54% of patients. The most common (≥ 5%) serious adverse reactions included CRS (17%), encephalopathy (16%), unspecified pathogen infections (8%), fever (6%) and viral infection (5%).

See the SmPC of Yescarta for more information (1).

1.5.2 Treatment guidelines

Treatment of adult patients with DLBCL is described in national guidelines from The Norwegian Directorate of Health: "Nasjonalt handlingsprogram med retningslinjer for diagnostikk behandling og oppfølging av maligne lymfomer" (2).

The current standard of care for the first-line treatment is a regimen of rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). For patients <60 years, etoposide can be added (R-CHOEP). The optimal therapy for the first-line treatment of patients with HGBL has not been established. While R-CHOP has improved outcomes for patients with DLBCL overall, about 10 % to 15 % of patients have primary refractory disease and a further 20 % to 40 % of patients have disease that relapses.

Standard second-line therapy in the curative setting for LBCL is comprised of rituximab and salvage chemotherapy (i.e., R-IME, R-ICE, R-GDP or R-DHAP), followed by high-dose therapy (HDT) and autologous stem cell transplant (auto SCT or ASCT) for those who are eligible. While HDT-ASCT has curative potential, only half of patients respond to second-line salvage chemotherapy and are able to proceed to ASCT. Outcomes are particularly poor for patients who have primary refractory disease or early relapse after first-line therapies, due to the more chemotherapy-resistant disease. Outcomes are also poor for patients with higher second-line age-adjusted International Prognostic Index (sAAIPI) scores.

1.5.3 Comparator: treatment with salvage chemotherapy followed by ASCT

Axi-cel is intended as a treatment option for adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy.

The currently available treatment option for these patients is rituximab and salvage chemotherapy (i.e., R-IME, R-ICE, R-GDP or R-DHAP), followed by HDT and ASCT for those who are eligible.

NoMA considers different chemotherapy combinations with rituximab, followed by ASCT in eligible patients, to be a relevant comparator for this STA.

2 Submitted documentation to prove the relative efficacy

Axi-cel was granted an extension of the indication to include second-line treatment of adult patients with early relapsed or refractory (r/r) diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma (HGBL) in Norway on 14.10.2022. The main evidence for the extension of the indication comes from a Phase 3, randomized, open-label study (ZUMA-7) evaluating the efficacy and safety of axi-cel versus standard of care therapy (SOC) in transplant eligible subjects with early (within 12 months) relapsed or primary refractory DLBCL or HGBL.

2.2 Overview of relevant Clinical Studies

NoMA considers the ZUMA-7 study to be the relevant clinical evidence for this STA. An overview of the ZUMA-7 study is given in Table 4 and Figure 1.

Table 4: Main characteristics of the ZUMA-7 trial. Source: (Adapted from Gilead submission).

ZUMA-7 (3), NCT03391466	
Design	Phase 3, randomized (1:1), open-label, multicentre study, stratified by response to first-line therapy (primary refractory, vs relapse ≤ 6 months of first-line therapy vs relapse > 6 and ≤ 12 months of first-line therapy) and second-line age-adjusted IPI (0 to 1 vs 2 to 3) as assessed at the time of screening
Key eligibility criteria	• Adult patients with histologically proven LBCL including DLBCL not otherwise specified, HGBL with or without MYC and BCL2 and/or BCL6 rearrangement, DLBCL arising from follicular lymphoma, T-cell/histiocyte rich LBCL, DLBCL associated with chronic inflammation, primary cutaneous DLBCL, leg type, Epstein-Barr virus+ DLBCL. • Relapsed or refractory disease after first-line chemoimmunotherapy. - Relapsed disease defined as complete remission to first line therapy followed by biopsy proven disease relapse ≤ 12 months of therapy. - Refractory disease defined as no complete remission to first line therapy; subjects who were intolerant to first-line therapy were excluded. • Received adequate first-line therapy including at a minimum: - Anti-CD20 monoclonal antibody unless the investigator determined the tumour was CD20 negative, and - An anthracycline containing chemotherapy regimen. • Intended to proceed to HDT-ASCT if there was a response to second-line therapy. • 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. • Adequate renal, hepatic, cardiac, and pulmonary function.

Intervention	Lymphodepleting chemotherapy regimen consisting of fludarabine 30 mg/m2/day and cyclophosphamide 500 mg/m2/day, for 3 days followed by 2 rest days. A single infusion of axi-cel administered intravenously at a target dose of 2 x 10^6 anti CD19 CAR T cells/kg (minimum dose of 1 x 10^6 anti CD19 CAR T cells/kg; for subjects weighing > 100 kg, the maximum flat dose was 2 x 10^8 anti CD19 CAR T cells). Bridging therapy with corticosteroids (e.g., dexamethasone at a dose of 20 to 40 mg or equivalent, either orally [PO] or IV daily for 1 to 4 days) was allowed prior to lymphodepleting chemotherapy at the discretion of the investigator.
Comparators	R-ICE, R-DHAP/R-DHAX, R-ESHAP, or R-GDP as selected by the investigator, administered every 2 to 3 weeks for 2 to 3 cycles. • R-ICE: rituximab plus ifosfamide, carboplatin, and etoposide • R-DHAP/R-DHAX: rituximab plus dexamethasone, cytarabine, and cisplatin • R-ESHAP: rituximab plus etoposide, solu-medrone, high dose cytarabine and cisplatin • R-GDP: rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin Subjects responding to salvage chemotherapy after 2 or 3 cycles were to proceed with HDT-ASCT per institutional or regional standards. Subjects not responding to salvage chemotherapy could receive additional treatment off protocol.
Primary endpoint	Event-free survival (EFS): defined as the time from randomisation to the earliest date of disease progression according to the Lugano classification, 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. The primary analysis of EFS was conducted on the full analysis set (FAS), defined as all randomized subjects, and according to the randomized treatment regardless of whether study treatment was received, when all subjects had the opportunity to be followed for the Month 9 disease assessment (i.e., the Month 9 timepoint had passed for all subjects) and 250 EFS events by blinded central assessment had been observed.
Main secondary endpoints	Key secondary: - Objective response rate (ORR) per blinded central assessment - Overall survival (OS) Other secondary: - EFS (with progression and censoring events) based on investigator disease assessments - Progression-free survival (PFS) (with progression and censoring events) based on investigator disease assessments - Duration of response (DOR) by blinded central assessments

<table>
<tr><td></td><td>
- Changes from screening in the global health status QoL scale and the physical functioning domain of the EORTC QLQ-C30a
- Changes from screening in the EQ-5D-5L index and VAS scores

Disease response and progression were evaluated per the Lugano classification.
</td></tr>
<tr><td>Sample size</td><td>
A total of 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 of care (SOC) group.
<table>
<tr><th></th><th>Axi-cel (N = 180)</th><th>Standard of Care (N = 179)</th><th>Overall (N = 359)</th></tr>
<tr><td>Full analysis set, n (%)</td><td>180 (100)</td><td>179 (100)</td><td>359 (100)</td></tr>
<tr><td>Safety analysis set, n (%)</td><td>170 (94)</td><td>168 (94)</td><td>338 (94)</td></tr>
<tr><td>Safety analysis set - ASCT, n (%)</td><td>NA</td><td>62 (35)</td><td>62 (17)</td></tr>
<tr><td>QoL analysis set, n (%)</td><td>165 (92)</td><td>131 (73)</td><td>296 (82)</td></tr>
<tr><td>Retreatment analysis set, n (%)</td><td>9 (5)</td><td>NA</td><td>9 (3)</td></tr>
</table>
</td></tr>
<tr><td>Follow-up</td><td>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.</td></tr>
</table>

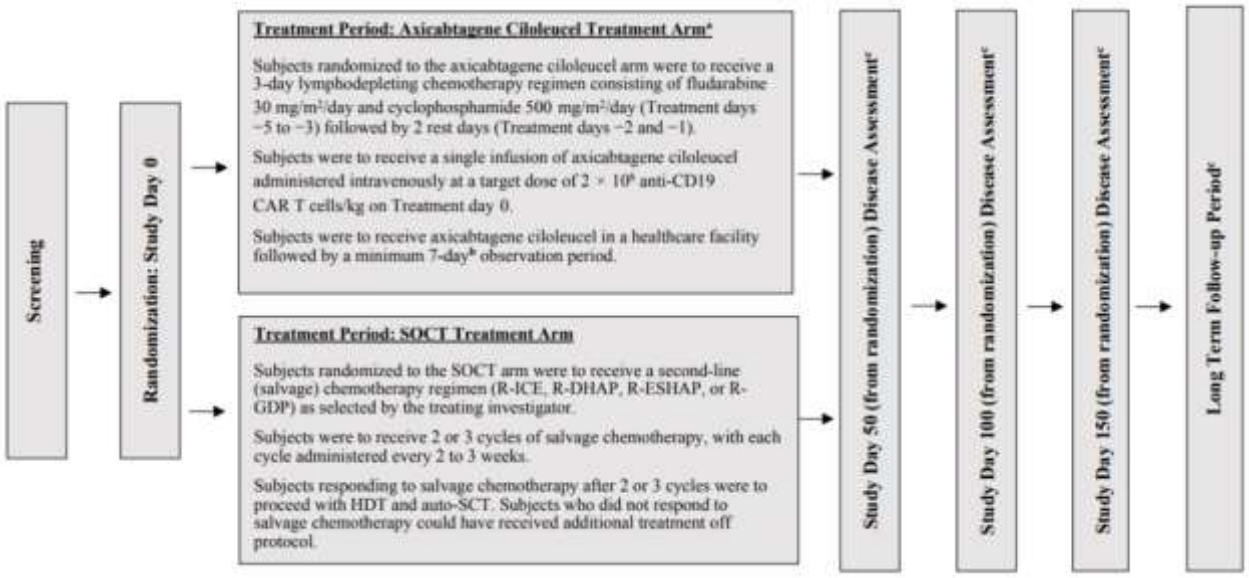


Figure 1: ZUMA-7 study design. Source: (Gilead submission).

NoMA's assessment of the submitted evidence

This is the first randomized controlled trial of axi-cel in the r/r DLBCL indication. The randomized ZUMA-7 study, pivotal to the marketing authorization (MA), is considered appropriate to evaluate the relative efficacy and safety of axi-cel versus SOC in the target population, and thereby acceptable for use in the health economic model.

A main limitation of the study, is the open-label trial design, combined with the definition of the primary endpoint (EFS), where the initiation of new anti-lymphoma therapy (NALT) was a defined event left at the discretion of the investigator. In an open-label trial, initiation of new anti-cancer therapy prior to adjudicated disease progression is likely to be informative and thus may bias the primary outcome measure. The impact of such bias has been explored by NoMA by performing two cost-utility analyses with different EFS definitions (see chapter 3 for more information).

For specific comments regarding the patient population, comparator, intervention and outcome measures, please refer to the relevant subsections in chapter 3.

3 PICO[1]

3.2 Patient Population

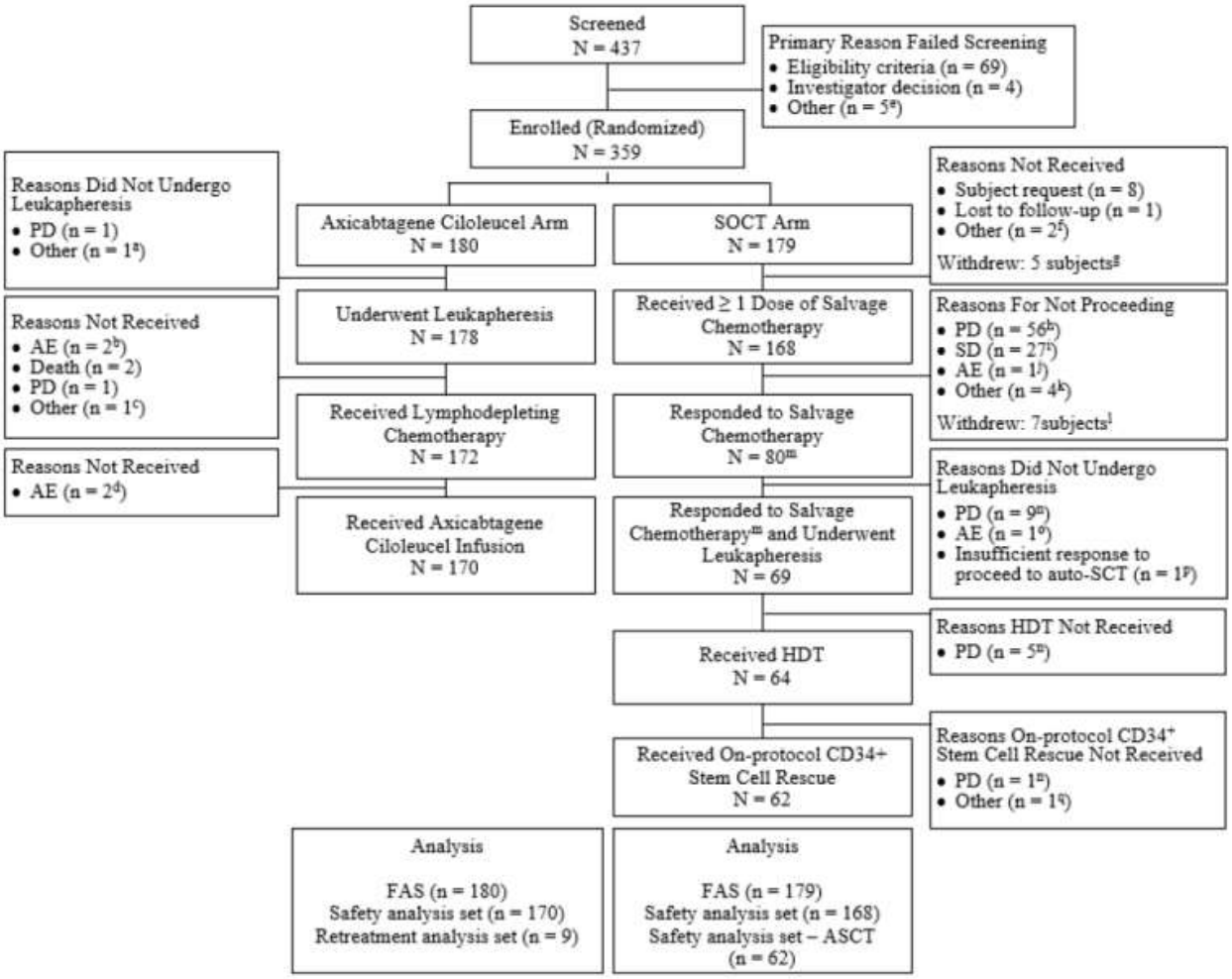
The patient population in the Norwegian setting
Axi-cel is intended for the second-line treatment of patients with early relapse (within 12 months) or primary refractory DLBCL/HGBL. This constitutes a broader population than that included in the ZUMA-7 trial, which was restricted to patients that were intended for transplant only. In Norwegian clinical practice it is anticipated that the selection criteria for CAR-T therapy will be broadly in line with the criteria implemented for ASCT. Although, with increased experience, criteria may be somewhat broadened in terms of age, ECOG and/or co-morbidities, the populations are expected to be largely overlapping. Whereas the ZUMA-7 trial also included patients >70 years, patients older than 70 years are not usually transplant-intended in Norway.

According to a clinical expert consulted by Gilead, approximately 22 patients have r/r (relapsed/refractory) DLBCL within <12 months and are eligible for ASCT in Norway each year. These patients are expected to be treated with axi-cel in the target indication each year in Norway. This is overall in line with the projections of the clinical experts consulted by NoMA, who provided estimates ranging from approximately 20 – 25 adult patients per year. The Norwegian clinical experts highlighted that the estimated patient number is uncertain and will depend on the selection criteria eventually implemented in clinical practice.

The patient population in the submitted clinical study
A total of 437 patients were screened for the study and 359 patients were randomized in ZUMA-7. Of the 180 patients randomized to axi-cel, 170 patients received infusion. Of the 179 patients randomized to SOC, 168 patients received at least one dose of salvage chemotherapy and 62 patients proceeded to ASCT.

Participant flow in ZUMA-7 is presented in Figure 2 below.

[1] Patients, Intervention, Comparator, Outcome.



Abbreviations: AE, adverse event; ALT, alanine aminotransferase; auto-SCT, autologous stem cell transplant; CVA, cerebrovascular accident; FAS, full analysis set; HDT, high-dose therapy; PD, progressive disease; PET-CT, positron emission tomography – computed tomography; PR, partial response; R-EPOCH, rituximab plus etoposide, doxorubicin, vincristine, cyclophosphamide, and prednisolone; R-DHAP, rituximab plus dexamethasone, cytarabine, and cisplatin; R-GDP, rituximab plus gemcitabine, dexamethasone, and cisplatin/carboplatin; R-ICE, rituximab + ifosfamide, carboplatin, and etoposide; SOCT, standard of care therapy; SD, stable disease; TBI, total body irradiation.

a. Subject was ineligible.
b. One subject had an AE of ALT increased; 1 subject had an AE of hyperbilirubinemia.
c. Subject in false progression at baseline; reassessment showed he was not progressing.
d. One subject had an AE of CVA; 1 subject had an AE of small intestinal perforation.
e. Three subjects because of reasons related to insurance; 1 subject due to rapid progression, and 1 subject opted out.
f. One subject had a negative disease biopsy; 1 subject had a false positive PET-CT and no refractory DHL after R-EPOCH x 5.
g. Withdrawals: 5 subjects withdrew with full consent due to subject request. Subjects are also included in the categories of reasons not received.
h. Includes 4 subjects with PD who were leukapheresed. PD represents best response to salvage chemotherapy.
i Includes 1 subject with SD who was leukapheresed. SD represents best response to salvage chemotherapy.
j. Subject had an AE of acute kidney injury.
k. Includes 1 subject with lack of response to salvage chemoimmunotherapy with R-ICE; 1 subject who did not tolerate RGDP and switched to R-ICE; 1 subject who changed treatment after 1 cycle of R-DHAP due to renal impairment; and 1 subject with insufficient overall response) to proceed to ASCT per investigator.
l. Withdrawals: Subjects withdrew with full consent; 4 subjects completed therapy but no response; 3 subjects with PD. Subjects are also included in the categories of reasons for not proceeding.
m. As determined by the investigator.
n. PD represents disease progression after an initial response to salvage chemotherapy.
o. Subject had an AE of blood stem cell harvest failure.
p. As determined by the investigator.
q. Subject was inadvertently enrolled on an alternative protocol.

Figure 2: Participant flow in the ZUMA-7 trial. Source: (4).

Patient baseline characteristic from the ZUMA-7 trial are presented in Table 5.

Table 5: Baseline characteristics of patients included in the ZUMA-7 trial. Source: (Gilead submission).

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 (48)	79 (44)	164 (46)
Disease stage – no. (%)			
I or II	41 (23)	33 (18)	74 (21)
III or IV	139 (77)	156 (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 (/)
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 (79)	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) mm2§§	2123 (181-22,538)	2069 (251-20,117)	2118 (181-22,538)

* Patients were randomly assigned to receive axi-cel (axi-cel) or standard of 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 2Lage-adjusted International Prognostic Index (IPI) at randomisation, which were similar to the 2Lage-adjusted IPI according to the investigator as entered into the clinical database. The 2Lage-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 of 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 of 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, which made further classification of the subtype impossible. Diffuse large B-cell lymphoma, not otherwise specified, according to the World Health Organization 2016 definition 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 and was assessed by the central laboratory.

The patient population in the health economic model

The patient population in the model was based on the patient population in the ZUMA-7 trial. The variables that are used directly in the health economic model are shown in the table below.

Table 6: Patient characteristics that serve as input in the health economic model.

	Input variable	Source
Mean age at model start	57.2 years	ZUMA-7
Share of females	34.0 %	ZUMA-7
Mean body weight	84.3 kg	ZUMA-7
Mean body surface area (BSA)	1.97 m^2	ZUMA-7

Body weight and BSA are used to calculate drug costs. The starting age in the model influences the age adjustment of utilities, with gradually reduced utilities the older the patients in the model become. The mean age at model start also impacts which age-matched general Norwegian population utility value is being implemented after five years (see chapter 3.4.3 for more information). Gender distribution, together with starting age, is relevant for calculating background mortality.

NoMA´s evaluation of the patient population
The ZUMA-7 study enrolled a transplant-eligible patient population, with refractory or early relapsed disease. A total of 74 % were primary refractory, and in the SOC arm only 35 % proceeded to ASCT. This is consistent with a chemotherapy resistant patient population.

In general, the two treatment arms were well balanced in terms of demographic and disease characteristics. The median age of 59 years (mean age 57.2 years) is younger than the median age of DLBCL /HGBL patients in Norwegian clinical practice (70 years) but reflects the expected age in a transplant eligible population. The mean body weight of 84.3 kg in ZUMA-7 might be somewhat higher than that expected in Norwegian clinical practice, but this model parameter does not influence the ICER particularly. Thus, the mean age and mean body weight from the study is accepted as input data for the health economic model.

In terms of external validity, in line with other CAR-T developments, the study implemented fairly restrictive eligibility criteria. Furthermore, the ZUMA-7 study provide limited (or no) data from certain LBCL subpopulations, patients with CNS involvement and patients with CD19 negative disease. Patients with an ABC subtype were underrepresented in the study compared to the general Norwegian DLBCL population (<10 % vs ~35-40 %). This is probably reflective of the high-risk population enrolled, with a larger proportion of patients having HGBL which is primarily of GCB subtype. Also, the study did not allow bridging chemotherapy and patients with a tumour mass effect requiring rapid treatment were excluded, thus limiting the applicability of the data in such patients.

As per inclusion criteria, all patients in the ZUMA-7 study had to be intended for ASCT, whereas the approved indication allows patients eligible for CAR-T, independent of their eligibility for transplant. Due to the waiting period between leukapheresis and infusion, the need for lymphodepleting chemotherapy and the risk of serious adverse events (SAEs), candidates for CAR-T therapy still need to be sufficiently fit prior to infusion. Hence, although CAR-T therapy may be considered for a somewhat broader patient population in terms of age, performance status and/or co-morbidities, it is expected that the patient population in Norwegian clinical practice will to a large extent be overlapping with the ZUMA-7 study population.

The clinical experts consulted by NoMA noted that the ZUMA-7 study population included patients with an age range up to 81 years, whereas patients >70 years are usually not transplant intended in Norwegian clinical practice. Apart from this, the experts verified that the study population in ZUMA-7 is sufficiently representative for the relevant population in Norwegian clinical practice.

NoMA accepts Gilead's modelling of the patient population.

3.3 Intervention

Intervention in the Norwegian setting
The SmPC states that axi-cel must be administered in a qualified treatment centre. It is assumed that the posology in the SmPC for lymphodepleting chemotherapy and axi-cel infusion will be followed in Norwegian clinical practice (please refer to section 1.4.1). Corticosteroid bridging therapy can be administered to patients with high disease burden.

According to the clinical experts consulted by NoMA, patients receiving CAR-T would be expected to be in hospital for approximately 6 days before axi-cel infusion related to leukapheresis, preparatory investigations and lymphodepletion chemotherapy. Following CAR-T administration patients are hospitalized for a minimum of 15 days and should hereafter stay in close proximity (within a 2-hour drive) of the hospital for 14 days, either at home or in a patient hotel. There is limited data available on re-treatment with CAR-T cell therapy, and the clinical experts consulted by NoMA did not expect re-treatment to be implemented in Norwegian clinical practice.

Intervention in the submitted clinical study
Axi-cel administration requires the sequential treatment phases of leukapheresis, bridging corticosteroid therapy (optional), lymphodepletion and axi-cel infusion. The posology for the lymphodepleting chemotherapy and the axi-cel infusion is described in section 1.5.1.

Among the patients in the axi-cel group in ZUMA-7, 99 % underwent leukapheresis, 96 % received lymphodepletion chemotherapy and 94 % (n=170/180) received axi-cel. A total of 36 % also received bridging therapy with glucocorticoids. Axi-cel was successfully manufactured for all the patients who underwent leukapheresis, with a median time from leukapheresis to product release (i.e., when the product passed quality testing and was made available to the investigator) of 13 days.

Axi-cel was infused in an inpatient setting, where subjects were monitored at a healthcare facility for a minimum of 7 days. Five of the 170 infused subjects (3 %) were planned as outpatient infusion with subsequent elective submission to a hospital for observation. All 170 treated subjects were eventually hospitalized with a median duration of hospitalization of 16 days (range: 5 to 103 days). A total of 98 % of patients administered axi-cel, received within +/- 10 % of the planned dose. For the 137 subjects who received axi-cel and weighed ≤ 100 kg, the median weight-adjusted dose was 2×10^6 anti-CD19 CAR T-cells/kg (range: 1.0 to 2.1×10^6cells/kg), and for the 33 subjects who weighed > 100 kg, all received the planned flat dose of 200×10^6cells.

Overall, 9 subjects were retreated with axi-cel. After retreatment, 5 subjects had a response per central assessment, with all 5 subjects achieving a complete response (CR).

Intervention in the health economic model
In the model, the proportion of patients receiving leukapheresis, bridging chemotherapy, lymphodepletion chemotherapy and axi-cel were informed by the ZUMA-7 trial. Patients received one infusion of axi-cel, and re-treatment was not permitted in the health economic model (as compared to ZUMA-7 where 9 subjects were retreated with axi-cel). The posology for the lymphodepleting chemotherapy and the axi-cel infusion is as recommended in the SmPC. The applied bridging therapy in the model was based on the bridging therapy that was given in the ZUMA-7 trial, namely dexamethasone.

NoMA´s evaluation of the intervention
NoMA considers the expected use of axi-cel in a Norwegian clinical setting, the ZUMA-7 study, and health economic model as aligned.

NoMA accepts Gilead's modelling of the intervention.

3.4 Comparator

Comparator in the Norwegian setting
According to the national lymphoma guidelines from The Norwegian Directorate of Health, transplant-intended patients in a first relapse/refractory disease setting receive salvage chemotherapy in combination with rituximab, followed by high-dose therapy (HDT) and ASCT in responding patients (2). The clinical experts consulted by NoMA gave somewhat divergent estimates of the most commonly used chemotherapy regimens in Norwegian clinical practice, probably reflecting local treatment practices and lack of documented differences in efficacy. Overall, the regimens and their estimated distribution (range) were as follows:

- R-ICE (rituximab, ifosfamide, carboplatin, etoposide): 10 % - 40 %
- R-GDP (rituximab, gemcitabine, dexamethasone, cisplatin): 10 % - 25 %
- R-DHAP (rituximab, dexamethasone, cytarabine, cisplatin): 15 % - 40 %
- R-IME (rituximab, ifosfamide, mixantrone, etoposide): 20 % - 50 %

The experts further expected that the majority of patients would receive at least 3 cycles of induction therapy, while some treatment centres would offer 4 induction cycles or more (up to a maximum of 6 cycles). Stable disease (SD) as best response to induction therapy would be considered a treatment failure which would warrant the initiation of a second induction regimen, usually following at least 2 treatment cycles.

Comparator in the submitted clinical study
In the ZUMA-7 SOC arm, patients were to receive salvage chemotherapy, administered every 2 to 3 weeks for 2 to 3 cycles. Subjects responding to salvage chemotherapy after 2 or 3 cycles were to proceed with HDT and ASCT per institutional or regional standards. Subjects not responding to salvage chemotherapy could receive additional treatment off protocol.

Salvage treatment consisted of a platinum-based induction chemotherapy regimen as selected by the treating investigator from several protocol defined options. The induction regimens administered were distributed as follows: R-ICE (50 %), R-GDP (25 %), R-ESHAP (3 %) and R-DHAP/R-DHAX (22 %). Among the 179 patients randomized to the SOC arm, 168 subjects (94 %) received a SOC regimen (safety analysis set). Of these, 90 % received 2 or 3 cycles as directed by the protocol, and 10 % received 1 cycle of salvage chemotherapy. The average number of cycles received was 2.3. A total of 62 patient (35 %) went on to receive HDT and ASCT.

Comparator in the health economic model
Salvage (induction) chemotherapy in combination with rituximab, followed by ASCT for those who were eligible, is the comparator in the submitted health economic analysis. This is considered to be the standard of care (SOC) in clinical practice.

The treatment costs in the health economic model are based on the following distribution:

- R-ICE: 20 %
- R-GDP: 30 %
- R-DHAP: 30 %
- R-IME: 30 %

Gilead has based this distribution on input from a Norwegian clinical expert. Based on information from the clinical expert, a mean number of 3.5 cycles was calculated for all four regimens included in the model. The proportion of patients receiving stem cell harvesting, HDT and ASCT in the model were informed by the ZUMA-7 trial, and are respectively 41 %, 36 % and 35 %.

Note that the effect data in the model is based on the chemotherapy distribution and share of patients that were eligible for HDT and ASCT as observed in ZUMA-7.

NoMA´s evaluation of the comparator
Salvage chemotherapy followed by HDT and ASCT as administered in the ZUMA-7 trial is representative for SOC also in Norwegian clinical practice. There is some variation in the individual salvage chemotherapy regimens used in the study and in Norway. Particularly this concerns R-IME, which was not used in the ZUMA-7 trial but is used in up to 50 % of patients in Norwegian clinical practice. Furthermore, there appears to be some local variation with regards to the distribution of different salvage chemotherapy regimens used across Norwegian treatment centres/regions. However, in randomized studies, no salvage chemotherapy has been demonstrated to be superior (5-7) and as such the salvage chemotherapy regimens and their distribution in the ZUMA-7 trial are considered to be sufficiently representative for Norwegian clinical practice in terms of deriving relative efficacy estimates.

In terms of drug costs per salvage chemotherapy treatment regime, there is only little variation between them, and varying the patient shares in the model in accordance with the input received from clinical experts only has a minor impact on the ICER. Hence, NoMA accepts the distribution of treatment regimens in the SOC arm as modelled by Gilead.

The average number of cycles of chemotherapy received was 2.3 in ZUMA-7. According to the U.S. Food and Drug Administration (FDA) clinical review (8), the purpose of awaiting the day 150 assessment before considering SD as an EFS event, was to allow for completion of the third cycle of chemotherapy in the SOC arm and to allow for deepening of response (conversion of SD to CR/PR) prior to declaring an event in the axi-cel arm. Since SD that does not convert to CR or PR by day 150 does not represent a clinical benefit,

the timing of the event was clocked back to when SD was first determined to avoid a trial design error that would allow time to event to be extended beyond the actual event time. Nevertheless, due to an apparent perceived lack of efficacy in the SOC arm, 10 % of patients received only 1 treatment cycle prior to proceeding with off-protocol new-anti lymphoma therapy, and only 36 % of patients actually received 3 treatment cycles. This is lower than what would be expected in Norwegian clinical practice, where responding patients would receive at least 3 treatment cycles, whereas for patients in SD normally 2 treatment cycles would be administered, although in certain circumstances treatment switch would be considered also after 1 cycle.

To ensure consistency between the efficacy input and cost input in the model, NoMA has changed the average number of treatment cycles in the model from 3.5 to 2.3 in our main analyses. This change only affects the costs in the health economic model. A scenario analysis shows the effect of including treatment costs for 3.5 cycles.

A total of 35 % of patients in the SOC arm eventually proceeded to HDT and ASCT. According to the clinical experts consulted by NoMA, this transplant rate is considered representative for Norwegian clinical practice, taking into account the requirement for patients to be refractory or early relapsed to their first treatment line.

NoMA accepts Gilead's modelling of the comparator, but changes the average number of treatment cycles in the model from 3.5 to 2.3 in our main analyses.

3.5 Outcomes

3.5.1 Efficacy

Submitted clinical studies
Clinical efficacy results of axi-cel versus SOC were obtained from the phase III ZUMA-7 study. The data cut-off used for the efficacy analysis was 18 March 2021, with a median follow-up time of 24.9 months. Updated overall survival (OS) data were also provided with a data cut-off date of 25 January 2023. A total of 359 patients were enrolled and randomized 1:1 to axi-cel or SOC.

Primary endpoint EFS
The primary endpoint, EFS, was defined as the time from randomization to the earliest date of disease progression (according to the Lugano classification), 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 (D150) assessment after randomization. Blinded central review of progression events and censoring times was implemented, whereas initiation of new anti-lymphoma therapy (NALT) was at the discretion of the investigator.

The primary analysis of EFS was conducted on the full analysis set (FAS), defined as all randomized subjects, and according to the randomized treatment regardless of whether study treatment was received, when all subjects had the opportunity to be followed for the month 9 disease assessment (i.e., the month 9 timepoint had passed for all subjects) and 250 EFS events by blinded central assessment had been observed.

Kaplan-Meier (KM) estimates were provided for EFS and a hazard ratio (HR) with 95 % confidence interval (CI) was calculated from a Cox proportional-hazards model with stratification according to the randomization stratification factors.

At the time of the data cut-off (18 March 2021), 252 EFS events by blinded central assessment had occurred for 108 subjects (60 %) in the axi-cel arm and 144 subjects (80 %) in the SOC arm. Axi-cel was superior to SOC, with a stratified HR of 0.398 (95 % CI: 0.308, 0.514; stratified log-rank p < 0.0001). The KM median EFS time for the axi-cel and SOC arm were 8.3 months (95% CI: 4.5, 15.8 months; range: 0 to 31 months with censoring [+]) and 2.0 months (95% CI: 1.6, 2.8 months; range: 0 [+] to 33 [+] months), respectively.

EFS per blinded central assessment is presented in Table 7, whereas the KM plot for EFS is presented in Figure 3.

Table 7: EFS per Blinded Central Assessment from the ZUMA-7 trial (Full Analysis Set). Source: (4).

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N = 179)**
Number of subjects	180	179
Events, n (%)	108 (60)	144 (80)
Censored[a], n (%)	72 (40)	35 (20)
Stratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), stratified	0.398 (0.308, 0.514)	NA
Stratified (derived) log-rank p-value	<.0001	NA
Hazard ratio (95% CI), stratified (derived)	0.406 (0.313, 0.525)	NA
Unstratified log-rank p-value	<.0001	NA
Hazard ratio (95% CI), unstratified	0.423 (0.328, 0.544)	NA
KM median (95% CI) EFS time (months)	8.3 (4.5, 15.8)	2.0 (1.6, 2.8)
Min, Max EFS time (months)	0, 31+	0+, 33+
Event		
Disease progression, n (%)	82 (46)	75 (42)
Best response of SD up to and including Day 150 assessment post-randomization, n (%)	4 (2)	0 (0)
New lymphoma therapy[b], n (%)	9 (5)	63 (35)
Axicabtagene ciloleucel retreatment, n (%)	2 (1)	0 (0)
Death from any cause, n (%)	11 (6)	6 (3)
Censoring reason		
Response ongoing, n (%)	72 (40)	28 (16)

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Response assessed but no disease at baseline and post-baseline, n (%)	0 (0)	3 (2)
No post-baseline disease assessment, n (%)	0 (0)	1 (1)
Full withdrawal of consent, n (%)	0 (0)	1 (1)
Lost to follow up, n (%)	0 (0)	2 (1)
Event-free rate, % (95% CI) by KME		
3 month	80.6 (74.0, 85.6)	40.5 (33.2, 47.8)
6 month	51.1 (43.6, 58.1)	26.6 (20.2, 33.3)
9 month	49.4 (42.0, 56.5)	19.4 (13.8, 25.6)
12 month	47.2 (39.8, 54.3)	17.6 (12.3, 23.6)
15 month	43.9 (36.5, 50.9)	17.0 (11.8, 23.0)
18 month	41.5 (34.2, 48.6)	17.0 (11.8, 23.0)
21 month	41.5 (34.2, 48.6)	16.3 (11.1, 22.2)
24 month	40.5 (33.2, 47.7)	16.3 (11.1, 22.2)
27 month	40.5 (33.2, 47.7)	16.3 (11.1, 22.2)
30 month	37.2 (28.0, 46.3)	16.3 (11.1, 22.2)
33 month	NE (NE, NE)	16.3 (11.1, 22.2)
Median (95% CI) follow-up time (months) (reverse KM approach)	23.0 (20.9, 24.0)	21.2 (20.4, 23.7)

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; EFS, event-free survival; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; SCT, stem cell transplant; SD, stable disease.

Notes: EFS is defined as the time from randomization to the earliest date of disease progression per Lugano Classification, commencement of new lymphoma therapy (including SCT in the axicabtagene ciloleucel arm without axicabtagene ciloleucel-induced response or retreatment of axicabtagene ciloleucel), or death from any cause. The stratification factors are 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 International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. The derived stratification factors are based on data collected on case report forms. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. The Breslow method is used to handle the ties for the Cox regression models. One-sided p-value from log-rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

a. Only 8 subjects (all in the standard of care therapy arm) of a total of 359 subjects were censored before Month 12 (m5.3.5.1, ZUMA 7 Primary Analysis CSR, Listing 16.2.1.1).

b. A total of 12 subjects (2 in the axicabtagene ciloleucel arm and 10 in the standard of care therapy arm) initiated a new lymphoma therapy in the absence of any post-baseline evaluable disease assessment (m5.3.5.1, ZUMA 7 Primary Analysis CSR, Listings 16.2.1.1 and 16.2.1.2) and had EFS event dates imputed as the randomization date as predefined in the statistical analysis plan.

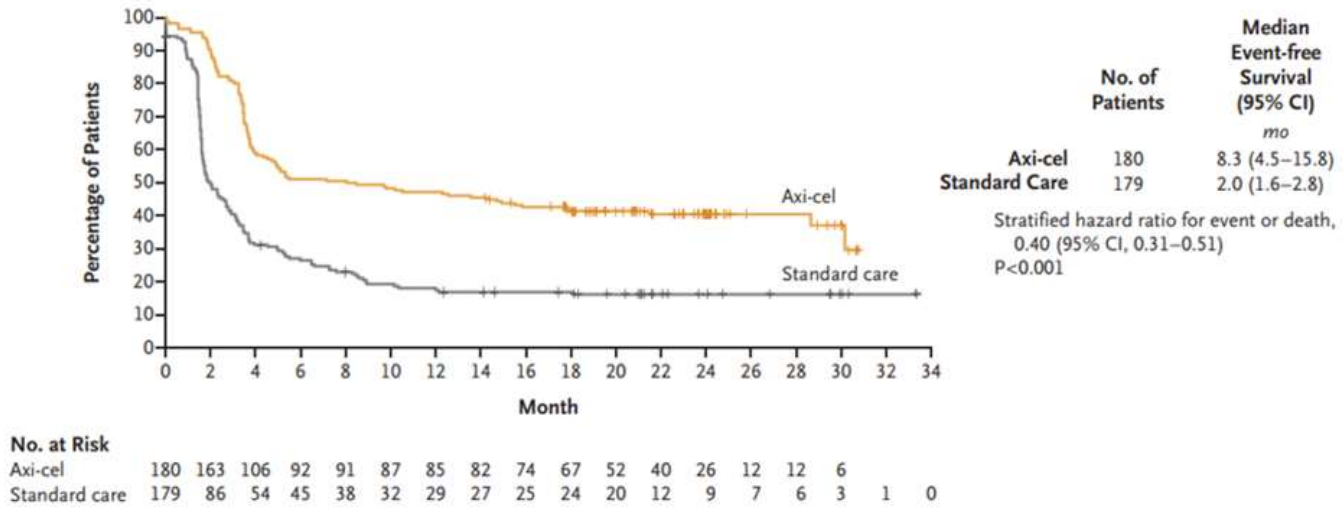


Figure 3: Kaplan-Meier plot for EFS from the ZUMA-7 trial (FAS). Source: (Gilead submission).

Key secondary endpoints

- ORR (objective response rate) per blinded central assessment

ORR was higher in the axi-cel arm (83 %) than in the SOC arm (50 %), with a statistically significant difference between treatment arms of 33.1% (95 % CI: 23.2 %, 42.1 %; stratified Cochran-Mantel-Haenszel (CMH) p < 0.0001). The CR rate was also numerically higher in the axi-cel arm (65 %) compared to the SOC arm (32 %). A summary of ORR and best ORR per blinded central assessment is provided in Table 8.

Table 8: Summary of ORR and Best Overall Response per Blinded Central Assessment (Full Analysis Set). Source: (4).

Response Category	**Axicabtagene Ciloleucel (N = 180)**	**Standard of Care (N = 179)**
Number of objective responders (CR + PR), n (%)	150 (83)	90 (50)
95% CI for ORR	(77.1, 88.5)	(42.7, 57.8)
Difference in ORR (95% CI)	33.1 (23.2, 42.1)	NA
Stratified CMH test p-value	<.0001	NA
Complete response, n (%)	117 (65)	58 (32)
95% CI for response rate	(57.6, 71.9)	(25.6, 39.8)
Partial response, n (%)	33 (18)	32 (18)
95% CI for response rate	(13.0, 24.8)	(12.6, 24.3)
Stable disease, n (%)	5 (3)	33 (18)
95% CI for response rate	(0.9, 6.4)	(13.0, 24.9)
Progressive disease, n (%)	21 (12)	38 (21)
95% CI for response rate	(7.4, 17.3)	(15.5, 28.0)

Response Category	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)
Undefined/ no disease, n (%)	0 (0)	4 (2)
95% CI for response rate	(0.0, 2.0)	(0.6, 5.6)
Not evaluable, n (%)	0 (0)	0 (0)
95% CI for response rate	(0.0, 2.0)	(0.0, 2.0)
Not done, n (%)	4 (2)	14 (8)
95% CI for response rate	(0.6, 5.6)	(4.3, 12.8)

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; CR, complete response; NA, not applicable; ORR, objective response rate; PR, partial response.

Notes: 95% CI for rate is from the Clopper-Pearson method, and the 95% CI for the difference in ORR (standard of care therapy arm as reference group) is from Wilson's score method with continuity correction. Response assessments per Lugano Classification. The stratification factors are 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 International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. One sided p value from CMH test is presented. “Undefined/no disease” include subjects who were found to have no disease at baseline or follow up by central assessment but had disease by investigator assessment. “Not evaluable” disease assessments were performed but no conclusion could be made.

A summary of concordance between Central Assessment and Investigator Assessment on objective response is presented in Table 9 below.

Table 9: Summary of concordance between Central Assessment and Investigator Assessment on Objective Response (Full Analysis Set). Source: (Gilead submission).

	Axicabtagene Ciloleucel (N = 180)	Standard of Care (N = 179)	Overall (N = 359)
Number of subjects evaluable for concordance	180	179	359
Objective responder concordance, n (%)	169 (94)	151 (84)	320 (89)
Central assessment responder and investigator assessment responder, n (%)	144 (80)	71 (40)	215 (60)
Central assessment non-responder and investigator assessment non-responder, n (%)	25 (14)	80 (45)	105 (29)
Objective responder discordance, n (%)	11 (6)	28 (16)	39 (11)
Central assessment responder and investigator assessment non-responder, n (%)	6 (3)	19 (11)	25 (7)
Central assessment non-responder and investigator assessment responder, n (%)	5 (3)	9 (5)	14 (4)
Overall concordance, %	94	84	89
Kappa coefficient	0.78	0.69	0.76
95% confidence interval	(0.66, 0.91)	(0.58, 0.79)	(0.69, 0.83)

Data cutoff date = 18MAR2021
Note: Overall concordance is the percentage of subjects whose central assessment match investigator assessment.
Note: Response assessments per Lugano Classification (Cheson et al, 2014).

- Overall survival (OS)

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. 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 was updated (with the same data cut-off date of 18 March 2021) to include the updated information for the 8 subjects. Stratified Cox regression models were used to provide the estimated OS HR and 95 % confidence intervals.

At the time of the data cut off, 72 subjects (40 %) in the axi-cel arm and 81 subjects (45 %) in the SOC arm had died. In the axi-cel arm the KM estimated median OS had not been reached with a median follow-up time for OS (reverse KM approach) of 24.7 months (95 % CI: 23.3, 26.0). In the SOC arm the KM estimated

median OS was 25.7 months with a median follow-up time for OS of 24.4 month (95 % CI:22.5, 25.7). Overall survival data are presented in Table 10, whereas the KM plot for OS is presented in Figure 4.

Table 10: Overall survival from the ZUMA-7 study (full analysis set). Source: (4).

	Axicabtagene Ciloleucel (N = 180)	**Standard of Care (N = 179)**
Number of subjects	180	179
Death from any cause, n (%)	72 (40)	81 (45)
Alive, n (%)	108 (60)	98 (55)
Full consent withdrawn	0 (0)	9 (5)
Lost to follow up	2 (1)	2 (1)
End of study due to investigator decision	0 (0)	1 (1)
End of study due to other reason	0 (0)	0 (0)
Stratified log-rank p-value	0.0270	NA
Hazard ratio (95% CI), stratified	0.730 (0.530, 1.007)	NA
Unstratified log-rank p-value	0.0442	NA
Hazard ratio (95% CI), unstratified	0.759 (0.553, 1.043)	NA
KM median (95% CI) OS time (months)	NR (28.3, NE)	35.1 (18.5, NE)
Min, Max OS time (months)	1, 38+	0+, 37+
Survival rate % (95% CI) by KME		
3 month	96.7 (92.7, 98.5)	97.7 (93.9, 99.1)
6 month	90.0 (84.6, 93.6)	87.1 (81.0, 91.3)
9 month	83.9 (77.6, 88.5)	74.1 (66.9, 80.1)
12 month	76.0 (69.1, 81.6)	64.7 (57.0, 71.4)
15 month	67.6 (60.3, 74.0)	59.4 (51.6, 66.3)
18 month	64.8 (57.3, 71.3)	58.2 (50.4, 65.2)
21 month	63.6 (56.1, 70.2)	53.2 (45.2, 60.5)
24 month	60.7 (52.8, 67.7)	52.1 (44.0, 59.5)
27 month	59.4 (51.2, 66.7)	50.6 (42.2, 58.3)
30 month	53.1 (43.1, 62.2)	50.6 (42.2, 58.3)
33 month	53.1 (43.1, 62.2)	50.6 (42.2, 58.3)
36 month	53.1 (43.1, 62.2)	33.7 (10.0, 59.9)
Median (95% CI) follow-up time (months) (reverse KM approach)	24.7 (23.3, 26.0)	24.1 (22.1, 25.1)

Data cutoff date = 18MAR2021.

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; KME, Kaplan-Meier estimation; Max, maximum; Min, minimum; NA, not applicable; NE, not estimable; NR, not reached; OS, overall survival.

Notes: OS is defined as the time from the randomization date to the date of death from any cause. Subjects who have not died by the analysis data cutoff date will be 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 will be censored at the data cutoff date. The stratification factors are 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 International Prognostic Index (0 to 1 versus 2 to 3) as collected via interactive voice/web response system. Stratified (or unstratified) Cox regression models are used to provide the estimated hazard ratio and 2-sided 95% CIs for axicabtagene ciloleucel relative to standard of care therapy. One-sided p-value from log rank test is presented. Censored times are represented with "+"; censoring is indicated regardless of whether any uncensored events occurred at the same time. Event/censoring time was calculated as event/censoring date – randomization date + 1 (= days) / 30.4375 (= months).

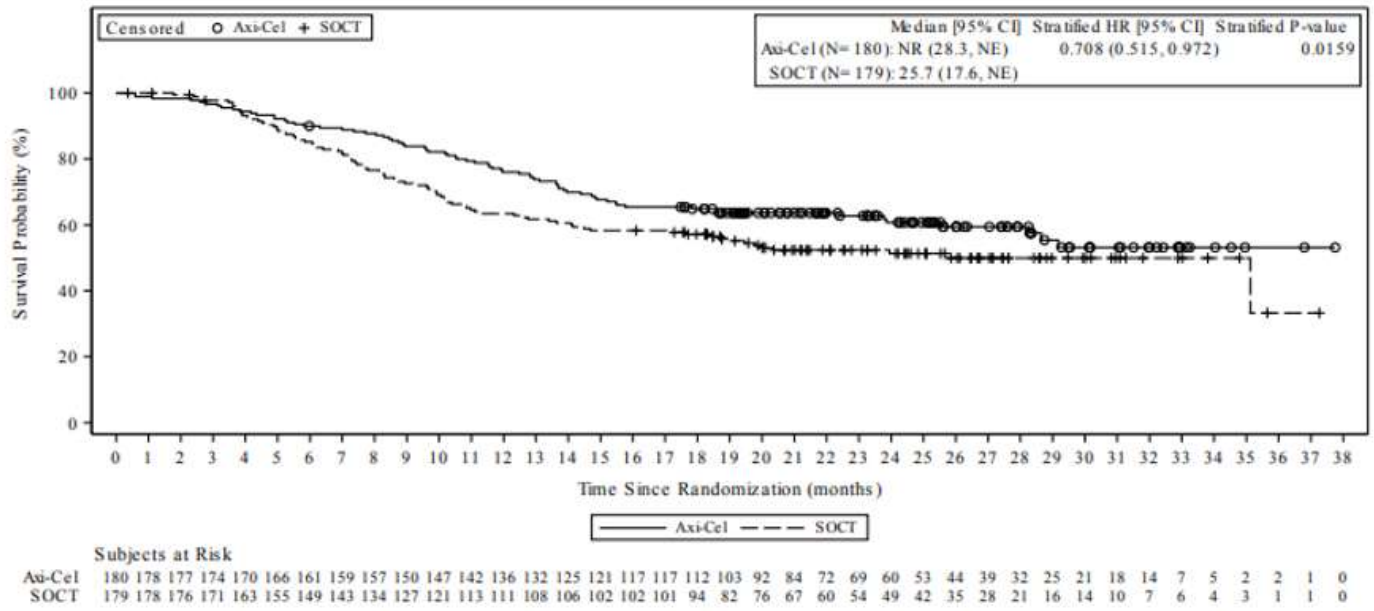


Figure 4: Kaplan-Meier plot for OS from the ZUMA-7 trial (FAS), data cut-off 18 Mar 2021. Source: (4).

During the assessment procedure, data from the primary OS analysis became available. The data cut-off date for the updated analysis was 25 January 2023, with a median follow-up time of 47 months and 45.8 months for the axi-cel arm and SOC arm, respectively. The median OS was not reached for the axi-cel arm and was 31.1 months for the SOC arm. There was a statistically significant difference between treatment arms (HR = 0.726 (95% CI: 0.540, 0.977), stratified log-rank 1-sided p-value = 0.0168) (Figure 5).

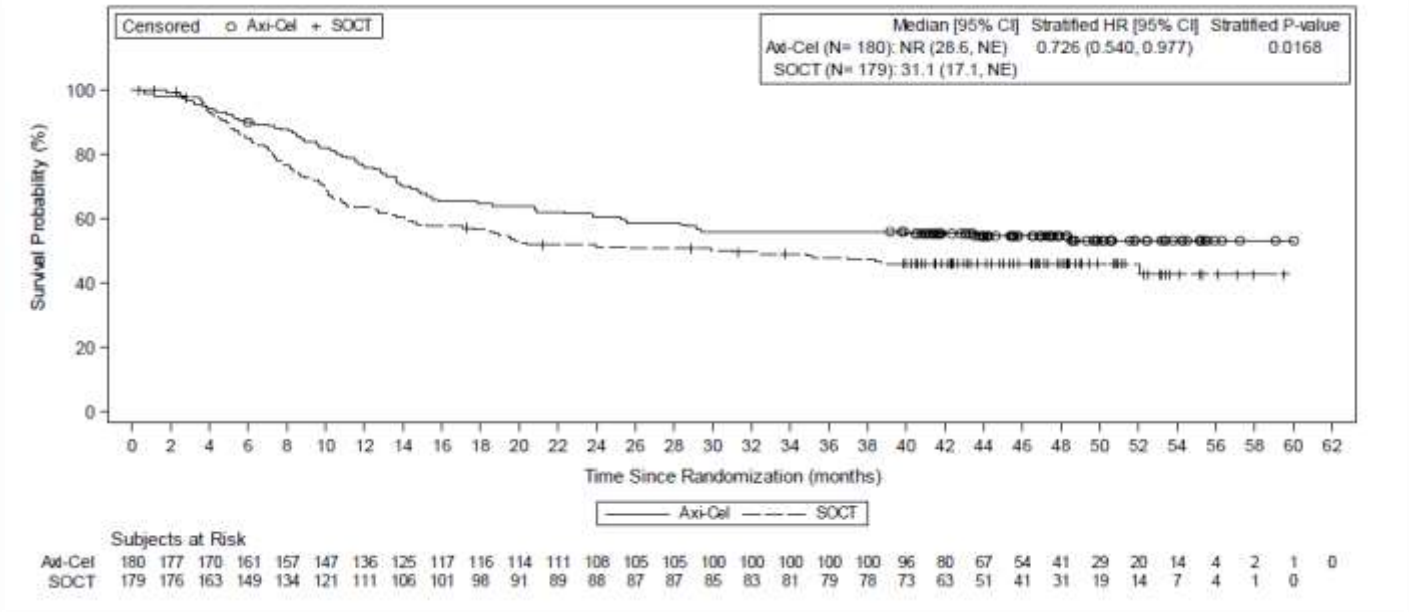


Figure 5: Kaplan-Meier plot for OS from the ZUMA-7 trial (FAS) based on the primary OS analysis, data cut-off 25 Jan 2023. Source: Gilead submission.

- 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 CAR-T cell therapy at some time after SOC. A sensitivity analysis of OS was included in the interim analysis of OS (data cut-off 18 March 2021) to address the confounding effects of this treatment switching in the SOC group. Two crossover adjustment methods were explored: 1) the rank preserving structural failure time (RPSFT) model with g-estimation by Robins et al (9), and 2) inverse probability of censoring weights (IPCW) adjustment methods (10). These sensitivity analyses were also updated to include the additional survival data for discontinued subjects. Only the RPSFT method is presented below. This method estimates survival times that would have been observed had treatment switching not occurred (i.e., counterfactual survival times) (11), and 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.

The KM plot from the sensitivity analysis using the RPSFT model is presented in Figure 6.

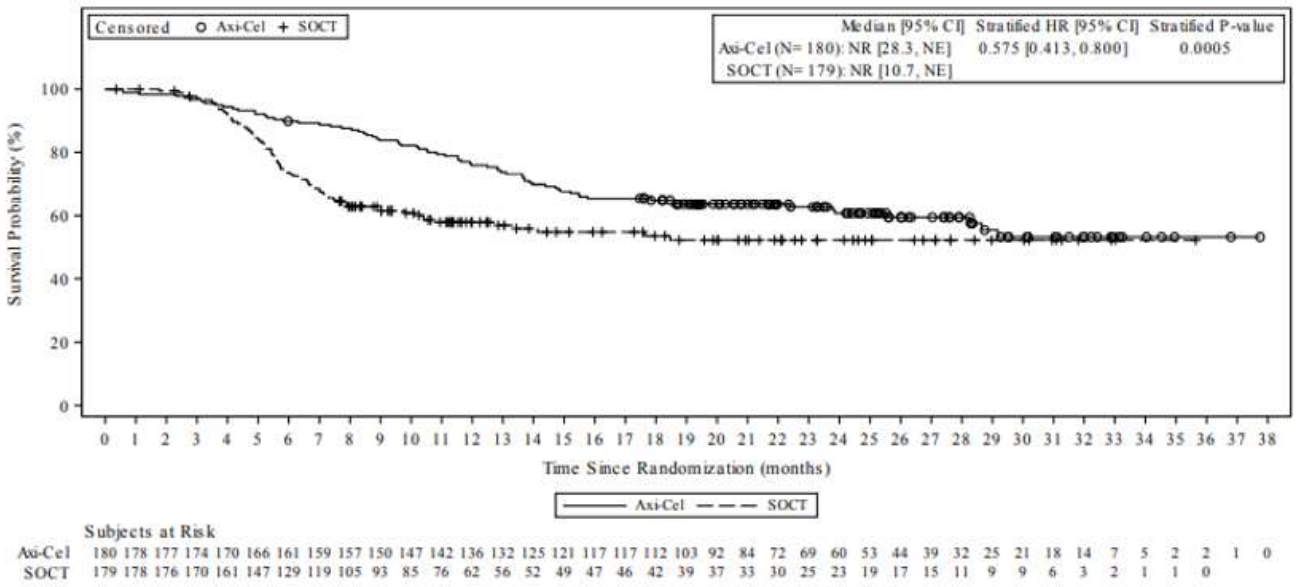


Figure 6: Kaplan-Meier plot for OS from the RPFST sensitivity analysis of OS (data cut-off 18 March 2021) from ZUMA-7 (FAS). Source: (Gilead submission).

Secondary endpoints

- PFS per Investigator Assessment

PFS was defined as the time from randomisation to disease progression per the Lugano Classification (12), as determined by investigator assessment or death from any cause. At the time of the data cut off, 96 subjects (53 %) in the axi-cel arm and 103 subjects (58 %) in the SOC arm had experienced a PFS event. The KM median PFS time based on the investigator assessment was longer in the axi-cel arm compared with the SOC arm (14.7 months (95% CI: 5.4, not estimable) versus 3.7 months (95% CI: 2.9, 5.3)) (stratified HR of 0.490 (95% CI: 0.368, 0.652)). A total of 5 patients (3 %) in the axi-cel arm compared to 37 patients (21 %) in the SOC arm received subsequent new lymphoma therapy (with the exception of HDT, total body irradiation (TBI) for HDT, and ASCT while in a protocol therapy-induced response) without having had a documented disease progression event prior to the NALT initiation. These patients had their last evaluable disease assessment date censored before the commencement of the subsequent new lymphoma therapy. The KM plot for PFS is presented in Figure 7.

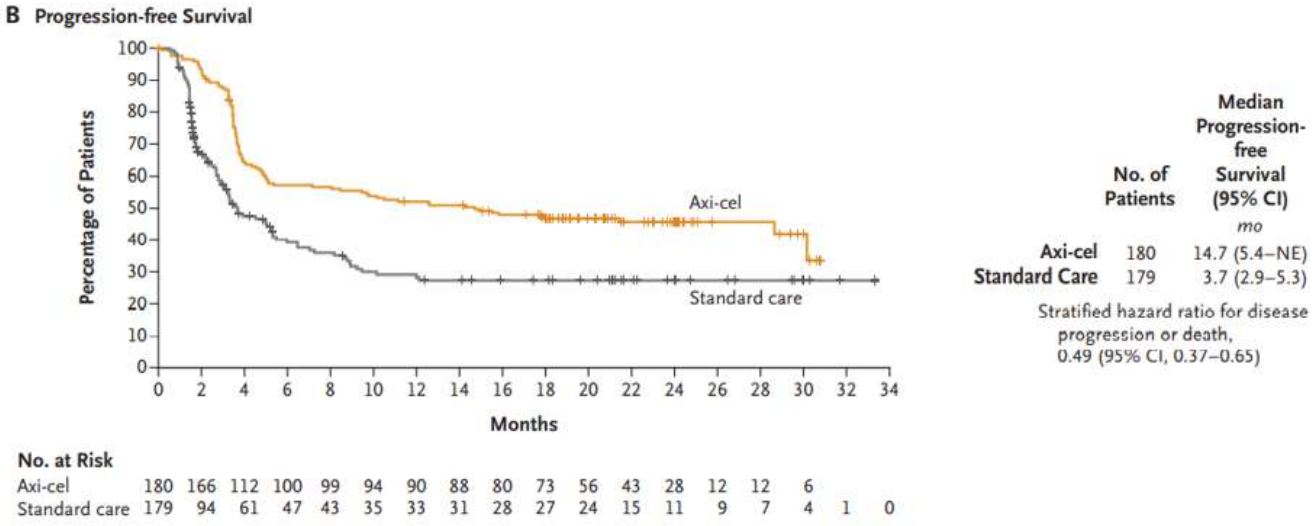


Figure 7: Kaplan-Meier plot for PFS (investigator assessed) from the ZUMA-7 trial (FAS). Source: (Gilead submission).

Exploratory endpoints

- Time to next treatment (TTNT)

TTNT was an exploratory outcome in the ZUMA-7 trial and defined as the time from the randomisation date to the start of the subsequent new lymphoma therapy (including retreatment (5 % of patients in ZUMA-7) or subsequent SCT for subjects in the axi-cel group) or death from any cause.

TTNT events occurred for 99 subjects (55 %) in the axi-cel arm and 135 subjects (75 %) in the SOC arm. The KM median TTNT was 14.7 months (95% CI: 6.5, not estimable) in the axi-cel arm and 3.4 months (95% CI: 3.1, 4.4) in the SOC arm. The KM estimate of the percentage of subjects with events in the axi-cel arm 24 months from randomisation was 45 % (95 % CI: 37.6 %, 52.2 %) in the axi-cel arm and 21 % (95 % CI: 15.4 %, 27.6 %) in the SOC arm. The KM TTNT curves for axi-cel and SOC are presented in Figure 8. The stratified HR was 0.43 (95 % CI: 0.33, 0.56 and log-rank p-value: <0.0001).

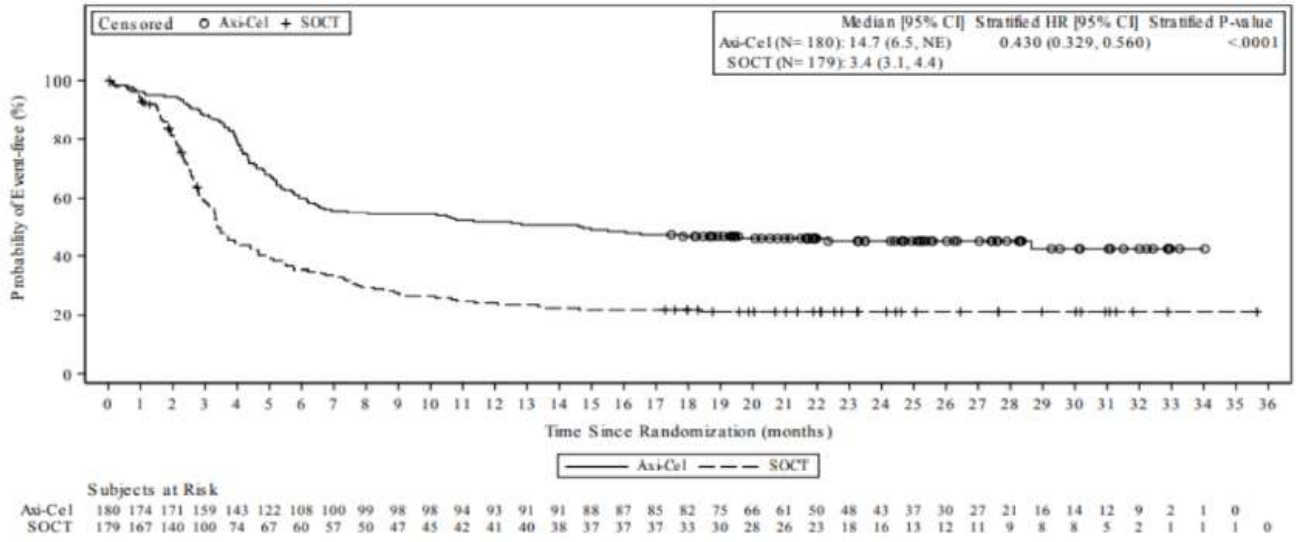


Figure 8: Kaplan-Meier plot for TTNT from the ZUMA-7 trial (FAS). Source: (Gilead submission).

NoMA´s evaluation of efficacy

ZUMA-7 demonstrated superior efficacy of axi-cel compared to SOC as a second-line therapy in adult subjects with primary refractory or early relapsed transplant intended DLBCL. A significant benefit was observed both in terms of the primary endpoint (EFS) and the key secondary endpoint of ORR. For the interim analysis of OS, there was a numerical trend in favour of axi-cel, but data were immature (43 % of patients having had an event) and median OS was not reached in the axi-cel arm. Updated OS data using a data cut-off date of 25 January 2023 became available during the procedure, demonstrating a statistically significant benefit in favour of axi-cel (HR = 0.73 (95% CI: 0.54, 0.99).

This is the first approved indication for a CAR-T in the r/r DLBCL setting where the marketing authorization is based on a randomized controlled trial. The randomized, controlled trial design is considered appropriate for defining the relative benefit of axi-cel over SOC. Nevertheless, substantial uncertainty remains regarding the true magnitude of the axi-cel effect size. For the primary EFS endpoint, the initiation of new anti-lymphoma therapy (NALT) was a defined event left at the discretion of the investigator. In an open-label trial, initiation of new anti-cancer therapy prior to adjudicated disease progression is likely to be informative and thus may bias the primary outcome measure.

As evident by the distribution of EFS events across arms, the key driver of benefit for axi-cel was the larger proportion of NALT events in the SOC arm compared to the axi-cel arm (n=63 (35 %) for SOC and n=11 (6 %) for axi-cel). Events of disease progression and death, on the other hand, were slightly more frequent with axi-cel compared to SOC (46 % vs. 42 % and 6 % vs. 3 %, respectively).

Further classification of NALT events as extracted from the FDA clinical report (8), indicate that the imbalance across study arms is largely driven by: 1) a greater discordance in response assessments

between blinded independent review committee (BIRC) and investigators for the SOC arm compared to the axi-cel arm (i.e. patients were judged to be in response by BIRC and in progression by investigator, thus prompting initiation of NALT), 2) a larger number of patients achieving SD as their best response in the SOC arm compared to the axi-cel arm, triggering initiation of NALT prior to the protocol defined D150 assessment, and 3) the larger number of patients in the SOC arm who did not receive protocol specified therapy followed by NALT. Thus, an apparent perceived lack of efficacy for SOC in the context of the open-label trial design, is considered to have biased the primary outcome measure. To explore the impact of such bias, the analysis described below was requested by NoMA but not submitted by Gilead.

Table 11: Categorisation of EFS events of NALT in ZUMA-7 and an analysis requested by NoMA

EFS events of NALT	***Axi-cel (n=11)***	***SOC (n=63)***	***Analysis requested by NoMA***	***Rationale for the request***
NALT while in BIRC CR/PR	*8*	***24***	*Exclude as EFS event and follow until progression event/end of study.*	*Patients are still in response to their initial therapy.* *The requested EFS analysis is also consistent with the OS definition where patients are followed for survival irrespectively of receival of a 3rd line treatment.*
NALT while in SD after 1 tx cycle		***7***	*Exclude as EFS event and follow until progression event/end of study.*	*As per study protocol and in line with clinical practice, normally 2 cycles should be administered prior to initiating NALT for "treatment failure".*
NALT while in SD after 2-3 tx cycles	*1 (no. of cycles N/A)*	*22*	*Include as EFS event.*	*SD after 2-3 cycles is considered a treatment failure an initiation of NALT is clinically justified.*
NALT w/o study treatment	*2*	***6***	*Exclude as EFS events and censor at randomization.*	*Subjects never received study treatment and as such cannot be considered a "treatment failure".*
NALT due to not tolerating tx		*3*	*Include as EFS event.*	*Subjects can be considered a "treatment failure" due to not tolerating the randomized therapy.*
NALT w/o evaluable disease progr.		*1*	*Exclude as EFS event and censor at randomization.*	*Inadequate post treatment response assessment cannot be classified as a "treatment failure".*

BIRC: Blinded independent review committee. CR: complete response. EFS: event free survival. N/A: not applicable. NALT: new anti-lymphoma therapy. NoMA: Norwegian Medicines Agency. PR: partial response. SD: stable disease. SOC: standard of care. Tx: treatment. w/o: without. In **bold** are categories addressed in the FDA analysis. Note: Four additional subjects in the SOC arm who were in response post-HSCT per central and investigator assessment received consolidative radiation therapy which constituted events in the ZUMA-7 primary analysis. These remained events in the FDA sensitivity analysis but were to be excluded in the NoMA requested analysis as consolidative radiation therapy while in response is not considered a treatment failure.

A similar sensitivity analysis was, however, conducted by the FDA (8): in total, 35 subjects in the SOC arm were excluded as EFS events and instead treated as ongoing responders and censored at the time of data cut off or randomization. Nineteen subjects that were administered NALT based on investigator determined lack of response or PD while in IRC determined response and 7 subjects that were

administered NALT while in IRC-determined SD after one cycle of chemotherapy were considered ongoing responders and censored at data cut off in the sensitivity analysis. Two subjects had partially responded (PR) to chemotherapy but were not taken for transplantation and one additional subject was inadvertently enrolled on a different protocol with receipt of off protocol stem cells were included. In addition, 6 subjects randomized to the SOC arm who did not receive any protocol specified therapy and subsequently received anti-lymphoma therapy with no post-baseline disease assessment, considered events at randomization in the primary analysis were also excluded as events and instead censored at randomization in the sensitivity analysis. The updated EFS analysis resulted in a HR of 0.7 (95%CI: 0.535-0.916), compared to the original HR of 0.398 (95% CI: 0.308- 0.514) (Figure 9).

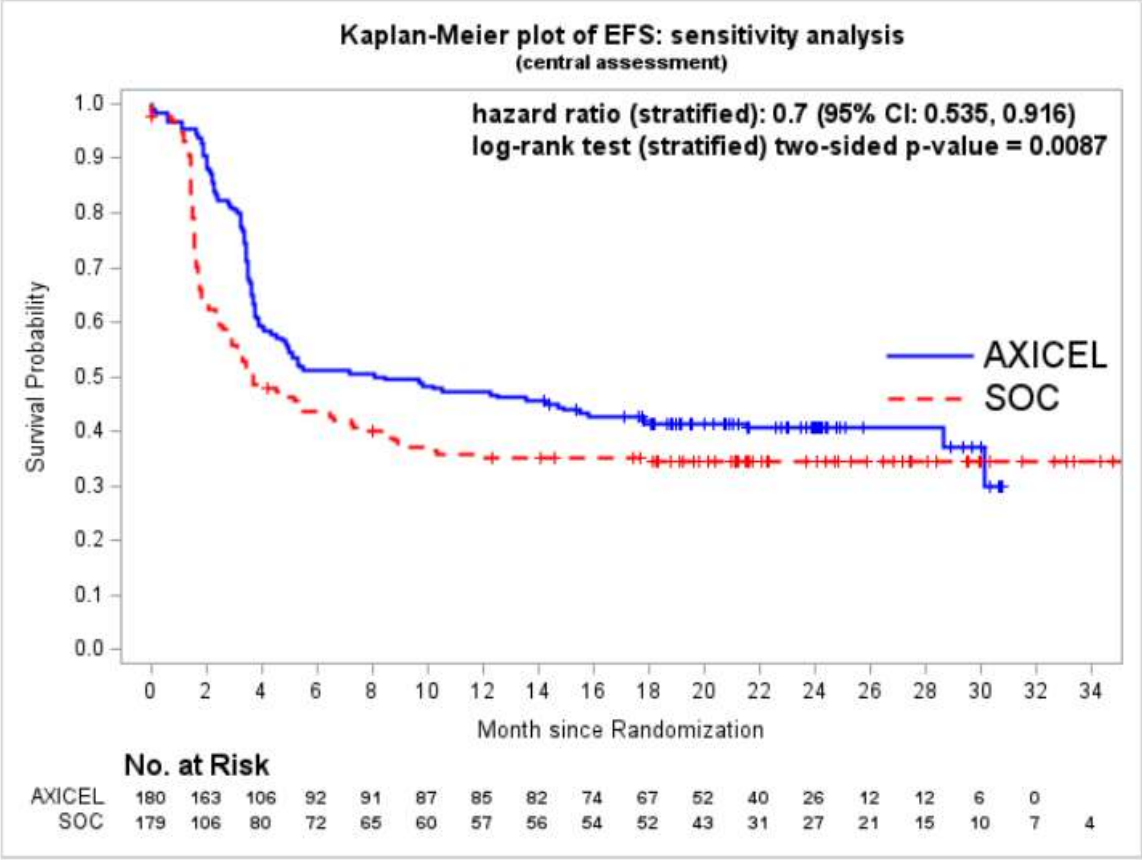


Figure 9: FDA KM-plot of EFS, sensitivity analysis. Source: (8).

Although this sensitivity analysis is conservative, the HR of 0.7 remains in favour of axi-cel, which confirms the robustness of the EFS outcome. Nevertheless, the analysis illustrates that bias introduced by the open-label trial design may potentially have had a rather large impact on the magnitude of the EFS effect size.

According to Gilead's clinical expert, the study design (requiring a CR or PR for ASCT and a minimum of two salvage chemotherapy cycles prior to adjudicating a SD) is not in line with clinical practice, where patients may be considered a treatment failure if achieving SD after 1 cycle or a "poor" PR after two salvage cycles. "Premature" NALT events in ongoing responders in the SOC arm could thereby be due to a "poor" PR as best overall response (BOR), and as such the primary EFS analysis would be externally valid. NoMA acknowledges that this might be the case, however, no data supporting this claim was provided. Rather, in ZUMA-7 the imbalance in "premature" NALT events between study arms was mainly due to the larger discordance between investigator and BIRC assessed responses in the SOC arm compared to the axi-cel arm. In addition, more patients in the SOC arm started NALT before ever having received the randomized treatment despite the longer pre-treatment waiting period required for axi-cel (bridging was not allowed). This may well suggest that bias on the part of the investigator in the context of the open-label trial design influenced treatment decisions in the SOC arm.

Ensuring a study with externally valid decision rules for EFS is ultimately the responsibility of the company. If different decision rules are eventually implemented across the two study arms (as appears to be the case in ZUMA-7), the internal validity of the EFS analysis is severely compromised. There is no satisfactory way to correct for this bias, which ideally should have been minimised by adequate study design and conduct. It seems reasonable, however, to assume that the "true" effect size would lie somewhere in between that reported in the primary analysis of ZUMA-7 and the FDA sensitivity analysis. Compared to external studies (see section 3.4.2) the SOC EFS estimate from the FDA sensitivity analysis appears rather optimistic. This is in line with the conservative approach taken (i.e., treating patients receiving NALT as on-going responders in the analysis), particularly considering most patients may have received a CAR-T as their subsequent line (data not provided).

In the PFS analysis, events of NALT were censored. Again, such informative censoring likely biased the outcome measure in favour of axi-cel. According to the FDA analysis (8), 16 of the 35 patients who were prematurely switched to NALT in the SOC arm, were in ongoing response pre-ASCT, but were not taken for transplant. Mostly this was due to the patients being assessed as non-responders/PDs by the investigator. If correctly adjudicated, these patients could have proceeded to ASCT in line with the study protocol, thus potentially increasing the transplant rate in the SOC arm. In the FDA assessment (8), PFS by central review was also presented, increasing the HR from 0.490 (0.368, 0.652, investigator assessed) to 0.562 (0.414, 0.762, central assessment). Whereas this analysis allows for assessment of efficacy without investigator bias, it does not compensate for informative censoring introduced by the imbalance in "premature" NALT events across arms. Thus, the true magnitude of the PFS benefit cannot be reliably established.

The OS analysis is also biased due to the early initiation of NALT. Nevertheless, compared to the EFS and PFS analyses, the impact of bias on OS results may be more limited. Among the 35 patients who prematurely initiated NALT in the SOC arm, a proportion could have been long-term responders to SOC, whereas the remaining patients would have eventually received a subsequent treatment, albeit at a later time point. The initiation of NALT (mostly CAR-T) pre-progression in these patients is considered less likely to have substantially altered the overall clinical course. It is therefore anticipated that the OS outcome

may more closely reflect the true effect size of axi-cel positioned in the second line. The original OS analysis was immature. Updated OS results demonstrate a statistically significant OS benefit. This is particularly encouraging considering the high proportion of treatment-switch to CAR-T in the SOC arm. Still, whereas the (although somewhat limited) curative potential of ASCT in the second line setting is generally considered well established, the follow-up time is not sufficient to verify the cure fraction estimated for axi-cel.

In the SOC arm, the majority of patients who went on to receive a third line therapy (i.e. 97 of 120) received CAR-T as their next treatment (81 %). Treatment-switch adjusted analyses of OS were submitted and presented (Figure 6). However, in Norway axi-cel is reimbursed in the third line. The clinical experts consulted by NoMA provided different estimates for the proportion of transplant-eligible patients receiving SOC in the second line who would receive a CAR-T therapy in the third line in Norwegian clinical practice (ranging from 50 % to 80 % of patients). Based on this, NoMA considers that treatment-switch adjustment for OS is not appropriate as it is not reflective of Norwegian clinical practice. It is acknowledged, however, that the rate of CAR-T as a subsequent treatment as seen in ZUMA-7 (and used in the economic model) might be an overestimation. A scenario analysis is therefore conducted to show the impact of third line treatment on the ICER (see Table 39).

NoMA´s evaluation of efficacy - conclusion

In conclusion, given that substantial uncertainty remains regarding the true magnitude of the axi-cel effect size, NoMA has conducted two main analyses:

- *Analysis 1* is based on the primary definition of EFS and OS results as per randomised population (as per Gilead's main analysis). This analysis is considered anti-conservative as the benefit of axi-cel is driven by the higher number of premature NALT events in the SOC arm, rather than the progression-/death- events.
- *Analysis 2* is based on an alternative definition of EFS (as per FDA's sensitivity analysis). In this analysis, patients in the SOC arm who received NALT prematurely (i.e. while still in response as defined by the blinded independent review committee, in stable disease following only one salvage chemotherapy cycle, or who never received the randomized treatment) were followed until progression/stable disease occurred. This analysis is considered conservative as it generates over-optimistic EFS in the SOC arm, primarily due to the receipt of CAR-Ts as NALT.

Sections below describe NoMA's choice of extrapolation functions based on:

1. The primary EFS and OS definitions (Section 3.5.2) – *NoMA's analysis 1*
2. EFS in the FDA's sensitivity analysis and primary OS definition (Section 3.5.3) – *NoMA's analysis 2*

3.5.2 Extrapolation of efficacy (based on the primary EFS and OS definitions) – NoMA's analysis 1

Submitted health economic model

The clinical trial data from the FAS population from ZUMA-7 with a median follow-up of 24.9 months (cut-off date 18 March 2021) were used in the economic model. To extrapolate EFS (primary definition, as assessed by blinded central review), OS and TTNT over the model time horizon, the survival data were first parameterized. 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 were based on the algorithm by Royston and Parmar (13), where one-, two-, and three-knot restricted cubic spline models using hazard, odds and normal scales were explored.

According to Gilead, MCMs take into account the long-term remission observed in some patients with DLBCL and are suitable for extrapolation. MCMs assume 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 KM curve, which allows for a change in the hazard of death over time (14). The "cured" population in the model has a slightly higher mortality than the general population (standardised mortality rate (SMR) of 1.09), and "non-cured" patients are subjected to an additional risk of excess mortality related to the disease (15). The cure fractions for EFS and OS obtained by fitting various MCMs independently to each arm are presented in Table 12.

Table 12: Cure fractions from the MCMs for EFS and OS. Source: (Gilead submission).

Distribution	Axi-cel		SOC	
	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 %
Generalized gamma	39 %	53 %	16 %	42 %

The proportional hazard (PH) assumption was evaluated statistically and graphically using the log cumulative hazard plot, a Schoenfeld residuals plot and the proportional hazards test as outlined by

Grambsch and Therneau (16). The decision in terms of the preferred extrapolation method considered both the best statistical fit and the 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 (KM plots). This was followed by validation of long-term survival estimates based on feedback from the consulted Norwegian clinical expert to determine the clinical plausibility.

Gilead's process of selecting parametric functions to extrapolate EFS, OS and TTNT over the economic model time horizon is described in detail in Appendix 3.

Summary of Gilead's base case parametric curves

Gilead's base case extrapolations are presented in Figure 10. Gilead chose to fit independent parametric curves to each arm as the log cumulative hazard plots showed crossing curves for EFS, OS and TTNT. EFS was extrapolated with MCM loglogistic in the axi-cel arm and MCM exponential in the SOC arm resulting in the modelled median EFS of 7 and 2 months, respectively. The cure proportion for EFS was 38 % for axi-cel and 14 % for SOC. OS was extrapolated with MCM generalized gamma in both arms resulting in the modelled median OS of 98 and 25 months for axi-cel and SOC, respectively. The cure proportion for OS was 53 % for axi-cel and 42 % for SOC. TTNT was extrapolated with MCM loglogistic in both arms.

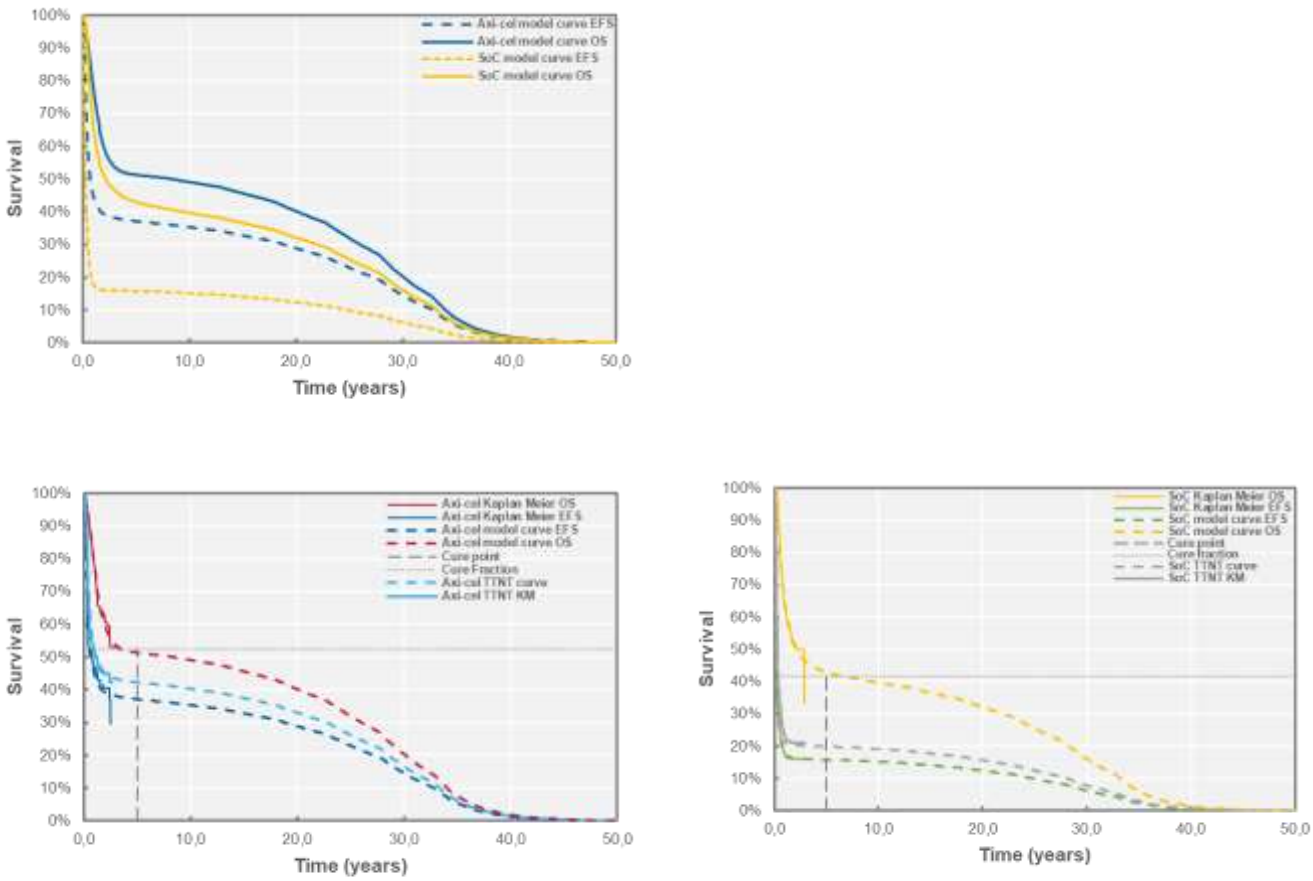


Figure 10: Gilead's base case extrapolations with MCMs for EFS, OS and TTNT. The curves have been corrected for background mortality with a SMR to general population of 1.09. The top graph shows a relative position of parametric curves for EFS and OS in both arms. The bottom graphs show a relative position of parametric curves for EFS, OS and TTNT for axi-cel (left) and SOC (right), together with their fit to the KM curves from ZUMA-7. Source: (Gilead submission).

NoMA's assessment

<u>General comments</u>

A wide selection of parametric curves was available in the economic model. Gilead chose to fit parametric functions independently to each arm despite inconclusive results of the PH diagnostics (see Appendix 3). Especially for EFS, the log cumulative hazard plot shows parallel lines for most of the follow-up time with convergence at the end. Due to high censoring rate and few patients at risk in the tail, it is difficult to conclude that the loss of proportionality occurs at that point. NoMA has, however, accepted independent modelling per arm as a constant treatment effect of axi-cel over the entire (economic model) time horizon is unlikely to be clinically plausible. In addition, NoMA has explored PH modelling in a scenario analysis, but the parametric curve based on the hazard ratio of 0.4 applied to the SOC arm for EFS was not aligned with the KM curves (not shown here).

The fit of standard parametric curves for EFS, TTNT and OS extrapolation was generally poor, except for the Gompertz function for EFS in the SOC arm (see Appendix 3). NoMA has therefore considered parametrization with mixture cure models (MCMs) and spline models. Best fitting spline models and MCMs provided a similar visual fit to the EFS and OS KM curves. From a purely mathematical and visual perspective, NoMA judged that spline models to be considered further were 3-knot hazard and 3-knot odds for EFS in both arms. For OS, all the spline models provided a similar mathematical and visual fit. External validation was therefore critical for the selection of the most plausible model.

Gilead chose to use mixture cure models to extrapolate EFS, OS and TTNT in their base case. Kearns et al., Grant et al., and Othus et al. (17-19) have shown that the performance of cure modeling methods is heavily dependent on the maturity of the data. Evidence of a sustained plateau might be indicative of statistical cure. Nevertheless, if data are heavily censored (e.g., 60 % in the axi-cel arm for OS in ZUMA-7) and the sample size is small, the visual inspection can be misleading (20). At the cut-off date March 2021, the follow-up time in ZUMA-7 is deemed insufficient to reliably estimate statistical cure. This is reflected in the broad spread of cure fractions for OS (Table 12) ranging from 24 % to 54 % for axi-cel and 32 % to 50 % for SOC. The emergence of a plateau is also questioned as EFS and OS events are still observed at the end of the follow-up time and the censoring rate is high from month 16 indicating high uncertainty around the tail of the KM curves. NoMA concludes that the ZUMA-7 data are too immature for the MCMs to reliably estimate the cure fraction. The acceptance of MCMs over the preferred spline models will therefore be guided by/subject to external validation.

During the assessment process, updated OS data from ZUMA-7 (from DCO 25 January 2023) became available. However, Gilead has not provided the CUA model with MCM curves based on the updated KM data. These show an emerging plateau from around Month 38 (maximum follow-up in the previous DCO of 18 March 2021) to Month 60. However, the vast majority of 98 (54%) censored events in the axi-cel arm and of 84 (47%) censored events in the SOC arm occurred between Month 38 and 60. Therefore, although fitting MCMs to the updated KM data would certainly increase the confidence in the extrapolations (and decrease the variability in the cure fractions between different MCMs), the empirical data would still be judged to be too immature to reliably estimate the cure fraction.

External validation

In theory, the mixture cure modelling seems clinically plausible as a cohort of primary refractory/early relapse DLBCL patients who receive HDT-ASCT are expected to be cured in clinical practice. The Norwegian clinical experts that NoMA consulted estimated that about 15-40 % of patients that received ASCT would be cured whereas patients that do not receive ASCT are normally not cured. A paper by Harryson et al. (2022) showed that in r/r DLBCL patients ≤70 years who underwent ASCT mainly in the second line, the 10-year survival is about 22 % in those who relapsed within 12 months from primary diagnosis (21). NoMA uses the above estimates as the lower survival benchmark for the SOC arm as 56 % of patients received

cell therapy in the subsequent line (mainly CAR-T's), and thus survival is expected to be higher in the SOC arm of ZUMA-7. The 5-year survival for axi-cel infused patients (mITT population) in the ≥3-line r/r DLBCL is 43 % according to the latest cut-off date in ZUMA-1 (22). In the corresponding HTA for axi-cel in ≥3-line r/r DLBCL, NoMA's base case projection of 10- and 20- year survival was 40 % and 34 % (mITT), respectively (23, 24). Those projections are similar in the ITT population (39 % and 33 %). These estimates might serve as another lower benchmark of expected survival in the SOC arm in the current assessment.

To validate EFS in the SOC arm, which is not affected by the effect of subsequent axi-cel therapy, NoMA has identified a number of external studies, but their use was limited due to the maximum follow-up time of 4 years (Table 13). Furthermore, based on the submitted documentation the similarity of the external studies and the ZUMA-7 trial could not be readily ascertained. Heterogeneity in response rates to salvage chemotherapy indicate the distribution of prognostic variables might indeed differ between studies. For extrapolation of EFS in the axi-cel arm (based on ZUMA-7), it was deemed reasonable to validate the estimates against ZUMA-1 results. In ZUMA-1, only PFS was reported for axi-cel, with a progression-free proportion at 24 months of 36.1 % (ITT). The extrapolated 10-year proportion of progression-free was 35 % (in NoMA's base case (23)). In ZUMA-7, the progression-free proportion at 24 months was 46 % (ITT), which is unsurprisingly higher (+10 %) than in the later treatment line. The event-free proportion at 24 months was 41 % (ITT), which is predictably lower (-5 %) as the EFS outcome definition was more comprehensive than PFS. Given that a 10-year EFS in the second line should be higher than the PFS in the third line (+10 %), but also slightly lower due to a different event definition (-5 %), NoMA expects that a 10-year extrapolated EFS proportion in the second line axi-cel arm should be around 40%. NoMA highlights that this is by no means an accurate prediction, but rather a rough guide for curve selection.

Table 13 Benchmarking EFS extrapolations in the SOC arm of ZUMA-7 with external study results from studies for primary r/r DLBCL followed by ASCT in responders.

External study	Relevant to ZUMA-7 population	Outcome in the external study (estimated from KM curves)	ZUMA-7 EFS SOC extrapolation with spline models and standard Gompertz	ZUMA-7 EFS SOC extrapolation with MCMs
ORCHARRD study - Phase III RCT designed to compare the efficacy and safety of ofatumumab-based vs rituximab-based re-induction therapy for r/r DLBCL followed by auto-SCT in responders (N = 447) Source: (25)	Subpopulation of patients with CR ≤12 months, PR, SD, or PD response to first-line therapy (N = 316)	PFS (defined as time from random assignment until SD after cycle 2, progression, or death from any cause: ~17 % at 3 years (pooled across arms)	3k hazard (best fit): 3-year EFS: 14 % 10-year EFS: 9 % 3k odds (2nd best fit): 3-year EFS: 14 % 10-year EFS: 9 % Standard Gompertz: 3-year EFS: 16 % 10-year EFS: 14 %	MCM exponential (Gilead's base case): 3-year EFS: 16 % 10-year EFS: 14 % MCM loglogistic (NoMA's base case): 3-year EFS: 15 % 10-year EFS: 13 %
CORAL study Phase III RCT designed to compare the efficacy and safety of R-ICE vs RDHAP re-induction therapy for r/r B-cell NHL followed by ASCT ± rituximab maintenance in responders (N = 396; treated N = 388). Only 13 patients did not have DLBCL Sources: (6, 26)	Subpopulation of primary refractory /early relapse patients who received prior rituximab (N = 187)	EFS was defined as the time from the start of treatment to progression, relapse, new treatment, or death (irrespective of cause) 2-year EFS: ~16 % 3-year EFS: ~13 % 4-year EFS: ~13 %		

For the mixture cure modelling, Gilead applied general population mortality to the cured fraction with a standardized mortality ratio (SMR) of 1.09, essentially implying that even a statistically cured fraction experiences excess mortality over the time horizon in the economic model. This assumption seems plausible. According to the literature, excess mortality is still present in the cohort of event-free patients,

but it decreases over time. A national Norwegian study on conditional survival after HDT with ASCT for DLBCL showed that SMRs were 14.2 (95 % CI 11.7–17.3), 4.3 (95 % CI 3–6.1), 1.7 (95 % CI 0.9–3.1) and 0.2 (95 % CI 0.03–1.7) for the entire cohort and for patients having survived 2, 5 and 10 years after HDT-ASCT, respectively (27). Danish Lymphoma Registry data from DLBCL patients in first remission show that excess mortality was present but reduced for patients achieving post-treatment event-free survival for 24 months (SMR of 1.27) and for 48 months (SMR of 1.32) (28). A recent study by Assouline et al. (2020) showed that in patients who received ASCT in the second-line treatment for DLBCL, the SMR in patients who are event-free at 12 months is already low (between 4.6 and 7.4, depending on the cohort) and declines to 2.3-4.5 in patients who are event-free at 5 years (29). Although patients in those studies were mainly respondents to the first-line treatment or late relapsers (and cannot be directly compared to the refractory/early relapsed population of ZUMA-7), the consistent trend in SMRs gives support for Gilead's assumption that the excess mortality diminishes over time and that a proportion of patients is cured from the disease. The Norwegian clinical experts that NoMA consulted confirmed that a second-line treatment with HDT-ASCT has a curative potential and that being event-free at 2-3 years is a good indication of a cure. Patients are, however, still at risk for excess mortality due to, for example, heart disease and secondary cancers, as explained by one of the clinicians.

Selection of the parametric curves – NoMA's analysis 1

- EFS

MCMs, best fitting spline models and standard Gompertz produce similar long-term EFS projections for SOC that are aligned with the KM curves from ORCHARRD and CORAL at year 3 and 4 (see Table 13). NoMA accepts modelling with MCMs, but notes that MCM exponential has a poor fit to KM data. MCM loglogistic has a better visual fit and is preferred.

For the axi-cel arm, the selection of the MCM loglogistic is acceptable as it generates a 10-year event-free proportion of 35% which is more optimistic than with best fitting spline models; 28% with 3 knot hazard and 30% with 3 knot odds. Although the application of spline models had good internal validity, their acceptance would result in a lower EFS at ten years than previously accepted for PFS in the axi-cel evaluation in the third line, i.e., 35% (23). Due to this inconsistency, NoMA chose not to run a scenario analysis where EFS is extrapolated with spline models.

- OS

NoMA supports the choice of MCM generalized gamma for the OS extrapolation in the SOC arm. MCM generalized gamma produces 10- and 20- year survivor proportions of 40% and 32% which are in line with the ≥3-line axi-cel extrapolations based on ZUMA-1, i.e., 39% and 33% (23, 24). The most optimistic spline model, 1 knot hazard, produces 10- and 20- year survivor proportions of 35% and 27% which are below the MCM projections. Although the use of the spline models cannot be completely excluded due to internal validity, NoMA chooses MCM generalized gamma in line with Gilead's base case due to lack of a better estimate.

The choice of a parametric model for OS extrapolation in the axi-cel arm could not be externally validated in the same way as the SOC arm. For internal consistency, the cure fraction had to be greater than the 38% cure fraction used for EFS extrapolation which excluded MCM exponential and MCM lognormal. For consistency with the SOC arm, MCM generalized gamma is accepted. Although it does not provide the best mathematical fit among MCMs, the best mathematical fitting curves result in crossing of OS curves which has not been observed in ZUMA-7 and would be considered an over conservative assumption given a large benefit of axi-cel on response. Different MCM functions per arm could alternatively be considered, but a difference in long term hazard pattern would have to be demonstrated.

Overall, the choice of the extrapolation function for OS is highly uncertain due to the short follow-up time and high censoring rate in ZUMA-7. NoMA accepts MCMs, but notes that the data is too immature for MCMs to accurately predict the cure fraction.

Due to theoretical limitations of fitting MCMs, NoMA has considered spline models although their external validity was poorer. NoMA explored a scenario with spline models that gave one of the most optimistic estimates; the 3 knot odds spline model for axi-cel and 1 knot odds for SOC. In addition, the 3 knot odds for axi-cel was chosen as it is on the same scale (i.e. odds) as for SOC, and the benefit of axi-cel is maintained (i.e., the curves do not cross) over most of the follow-up time. A comparison with SOC KM data from the latest DCO 25 January 2023 gives support to both MCM generalized gamma and one knot odds model as the empirical survival at Month 57 of 43% is aligned with survival extrapolated with both models. However, at Month 60, the empirical survival in the axi-cel arm of 53% was similar to extrapolation via MCM generalized gamma (i.e 51%) but was underestimated with 3 odds spline model (i.e. 47%). Given validation with the updated data, NoMA chose not to present the result of this scenario analysis in the result section.

- TTNT

Gilead chose MCM loglogistic to extrapolate TTNT in both arms. The choice of an MCM is consistent with the EFS and OS modelling. However, MCM loglogistic for TTNT crossed with Gilead's preferred MCM exponential for EFS in the SOC arm which was deemed implausible. NoMA chooses MCM generalized gamma in the SOC arm as it avoids crossing and gives better visual fit to KM data. MCM loglogistic is acceptable for the axi-cel arm.

For a comparison of Gilead's parametrization curves and NoMA's parametrization curves in NoMA's analysis 1, see Table 14 and the figures below.

Table 14: Comparison of parametrization curves.

	Gilead's main analysis	NoMA's analysis 1
EFS	Axi-cel: MCM loglogistic SOC: MCM exponential	Axi-cel: MCM loglogistic SOC: MCM loglogistic
OS	Axi-cel: MCM generalized gamma SOC: MCM generalized gamma	Axi-cel: MCM generalized gamma SOC: MCM generalized gamma
TTNT	Axi-cel: MCM loglogistic SOC: MCM loglogistic	Axi-cel: MCM loglogistic SOC: MCM generalized gamma

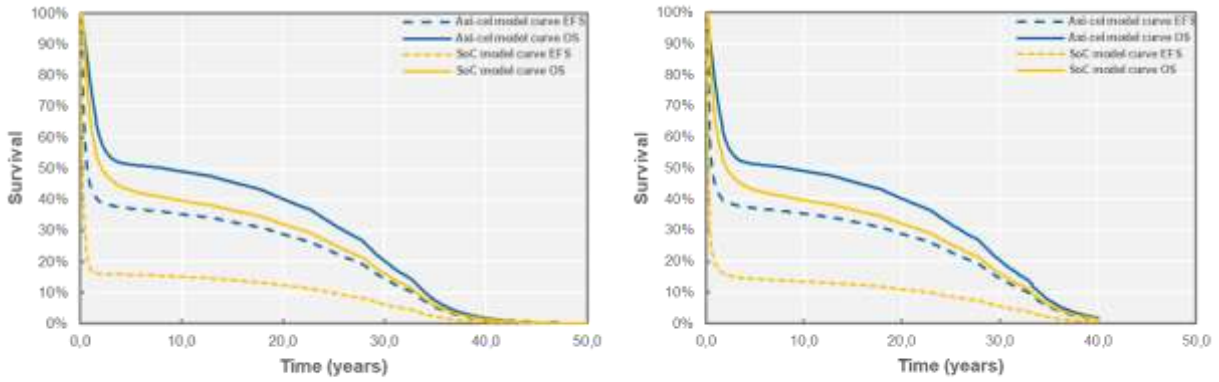


Figure 11: Gilead's base case extrapolations (left) and NoMA's base case extrapolations in NoMA's analysis 1 (right). The graphs show a relative position of parametric curves for EFS and OS in both arms.

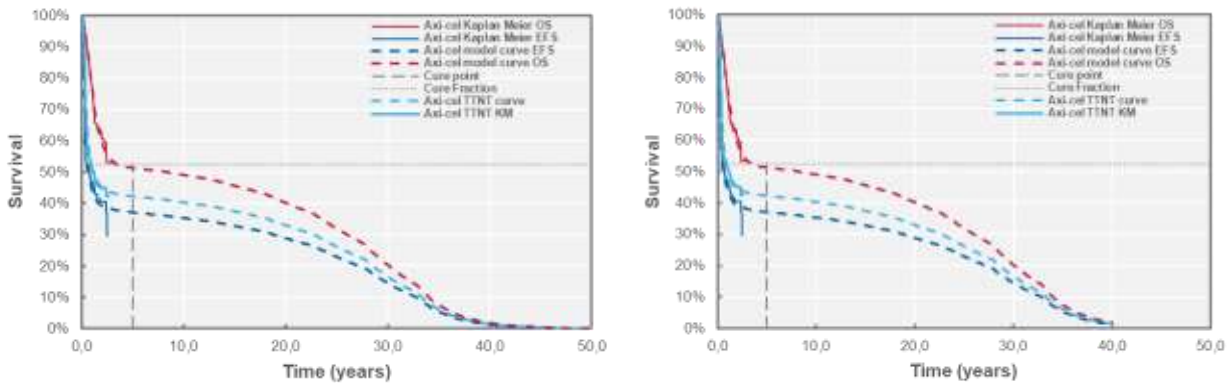


Figure 12: Gilead's base case extrapolations (left) and NoMA's base case extrapolations in NoMA's analysis 1 (right) for the axi-cel arm. The graphs show a relative position of parametric curves for EFS, OS and TTNT for axi-cel together with their fit to the KM curves from ZUMA-7.

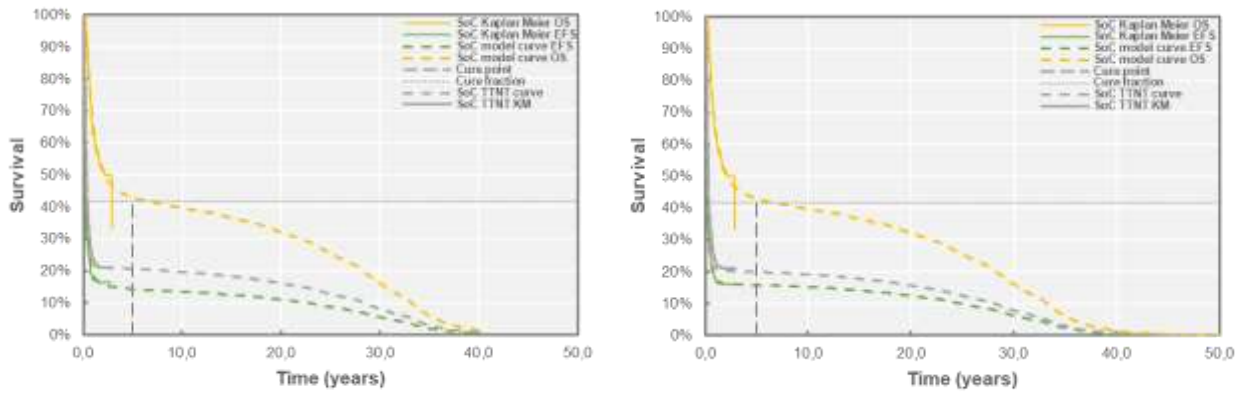


Figure 13: Gilead's base case extrapolations (left) and NoMA's base case extrapolations in NoMA's analysis 1 (right) for the SoC arm. The graphs show a relative position of parametric curves for EFS, OS and TTNT for SOC together with their fit to the KM curves from ZUMA-7.

3.5.3 Extrapolation of efficacy (EFS based on FDA's sensitivity analysis) – NoMA's analysis 2

In section 3.5.1, NoMA concluded that the EFS results based on the primary definition are biased in favour of axi-cel and that the receipt of NALT prior to disease progression as defined by IRC, after 1 cycle SD or without any disease evaluation should not be treated as an event. NoMA has requested an analysis where patients without disease progression or who had SD after 1 cycle and received NALT are followed until disease progression, but Gilead refused to send such an analysis stating that it was not defined in the protocol. A sensitivity analysis based on NoMA's preferred EFS definition was previously conducted by FDA (8). NoMA has digitalised KM curves from FDA's analysis of EFS and selected best fitting parametric functions (in what we refer to as *NoMA's analysis 2*). The results of the digitalization and parametric curve fitting are presented in Appendix 4 and 5. The survival analysis was performed in Stata 16.1 using the *stsreg* command for fitting six standard parametric functions, and *strsmix* for fitting MCMs.

Selection of the parametric curves – NoMA's analysis 2

The PH diagnostics showed that the PH assumption did not hold. Consequently, NoMA fitted individual standard parametric functions and MCM Weibull, lognormal or generalized gamma to the SOC arm for EFS. The fit of standard parametric functions was poor, except for the Gompertz function. The Gompertz function had also the best mathematical fit and it supports a monotonically decreasing hazard, which is the case here. Among MCMs, the generalized gamma provided the best visual fit with the curve almost identical to standard Gompertz. For parsimony, and in order to avoid additional assumptions, NoMA chose the standard Gompertz function to extrapolate EFS in the SOC arm for this analysis (see Figure 14).

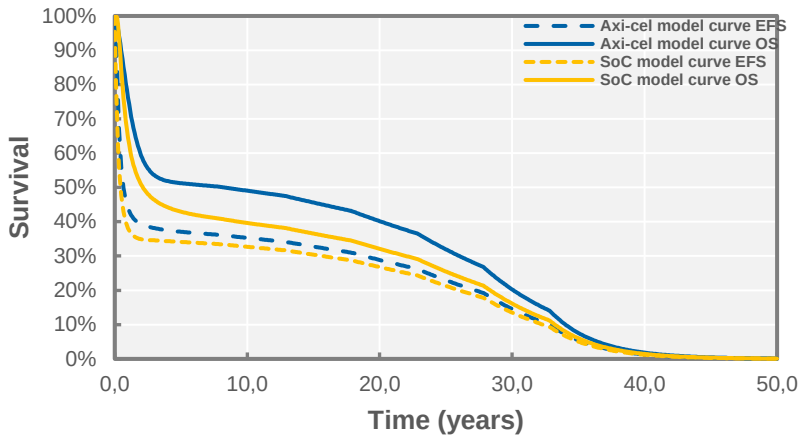


Figure 14: NoMA's choice of extrapolation functions (NoMA's analysis 2); standard Gompertz for EFS in the SOC arm and MCM loglogistic for the axi-cel arm, and MCM generalized gamma for OS in both arms. The hazard from the parametric curves could not be lower than the general population mortality hazard specific for age and sex distribution in the CUA model and multiplied by an SMR of 1.09 (i.e., correction for background mortality). Parameterization based on FDA's sensitivity analysis for EFS. ITT population.

Fitting standard Gompertz to EFS for SOC without changing parametrization for TTNT in the SOC arm leads to an implausible result where TTNT is lower than EFS. This means that third-line treatment costs in the health economic model are being generated even though patients have not yet progressed and are still in EFS. NoMA has therefore set TTNT equal to EFS. This change leads to third-line treatment being initiated as patients move from pre-event to post-event in the health economic model. This change needed to be implemented in order for analysis 2 to be plausible and to make sure that the FDA definition of EFS and the way third-line treatment costs are being modelled match and correctly reflect clinical practice.

The efficacy data for EFS and TTNT in the axi-cel arm, as well as for OS in both arms, remain as per NoMA's analysis 1. Hence, the choice of preferred parametric functions for EFS and TTNT in the axi-cel arm and for OS in both arms remains unchanged.

Compared to CORAL and ORCHARRD, the long-term EFS of 34 % in the SOC arm (as extrapolated with standard Gompertz or MCM generalized gamma) is more than doubled. This is likely due to the receipt of CAR-T as NALT and continued follow-up of those patients for progression/stable disease in the FDA sensitivity analysis of EFS in ZUMA-7. Although NoMA has not received specific information about the type of NALT received per EFS event category (despite requesting it from Gilead), 80 % of patients who received a subsequent therapy received CAR-T. Therefore, external validation of the selected parametric curves is not deemed feasible.

3.5.4 Safety

Submitted clinical documentation

Among patients in the safety analysis set (i.e., all randomised subjects who received at least one dose of protocol therapy), all subjects in both treatment groups had at least one treatment emergent adverse event (TEAE). A total of 155 subjects (91 %) in the axi-cel arm and 140 subjects (83 %) in the SOC arm had a grade 3 or higher TEAE, whereas 85 subjects (50 %) in the axi-cel arm and 77 subjects (46 %) in the SOC arm had at least one serious adverse event (SAE). The most common adverse events reported in the ZUMA-7 study by study arm are presented in Table 15.

Table 15: Most common adverse events of any grade and of grade ≥ in the ZUMA-7 study (Safety Analysis Set). Source: (3).

Event	Axi-cel (N=170)		Standard Care (N=168)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any adverse event — no. (%)	170 (100)	155 (91)	168 (100)	140 (83)
Pyrexia	158 (93)	15 (9)	43 (26)	1 (1)
Neutropenia†	121 (71)	118 (69)	70 (42)	69 (41)
Hypotension	75 (44)	19 (11)	25 (15)	5 (3)
Fatigue	71 (42)	11 (6)	87 (52)	4 (2)
Anemia	71 (42)	51 (30)	91 (54)	65 (39)
Diarrhea	71 (42)	4 (2)	66 (39)	7 (4)
Headache	70 (41)	5 (3)	43 (26)	2 (1)
Nausea	69 (41)	3 (2)	116 (69)	9 (5)
Sinus tachycardia	58 (34)	3 (2)	17 (10)	1 (1)
Leukopenia‡	55 (32)	50 (29)	43 (26)	37 (22)
Thrombocytopenia§	50 (29)	25 (15)	101 (60)	95 (57)
Chills	47 (28)	1 (1)	14 (8)	0
Hypokalemia	44 (26)	10 (6)	49 (29)	11 (7)
Hypophosphatemia	45 (26)	31 (18)	29 (17)	21 (12)
Cough	42 (25)	1 (1)	18 (11)	0
Decreased appetite	42 (25)	7 (4)	42 (25)	6 (4)
Hypoxia	37 (22)	16 (9)	13 (8)	7 (4)
Dizziness	36 (21)	2 (1)	21 (12)	1 (1)
Constipation	34 (20)	0	58 (35)	0
Vomiting	33 (19)	0	55 (33)	1 (1)
Febrile neutropenia	4 (2)	4 (2)	46 (27)	46 (27)
Cytokine release syndrome — no. (%)	157 (92)	11 (6)	—	—
Pyrexia — no./total no. (%)	155/157 (99)	14/157 (9)	—	—
Hypotension — no./total no. (%)	68/157 (43)	18/157 (11)	—	—
Sinus tachycardia — no./total no. (%)	49/157 (31)	3/157 (2)	—	—
Chills — no./total no. (%)	38/157 (24)	0/157	—	—
Hypoxia — no./total no. (%)	31/157 (20)	13/157 (8)	—	—
Headache — no./total no. (%)	32/157 (20)	2/157 (1)	—	—
Neurologic event — no. (%)	102 (60)	36 (21)	33 (20)¶	1 (1)
Tremor	44 (26)	2 (1)	1(1)	0
Confusional state	40 (24)	9 (5)	4 (2)	0
Aphasia	36 (21)	12 (7)	0	0
Encephalopathy	29 (17)	20 (12)	2 (1)	0
Paresthesia	8 (5)	1 (1)	14 (8)	0
Delirium	3 (2)	3 (2)	5 (3)	1 (1)

** Shown are any adverse events of any grade that occurred in at least 20% of the patients in either the axi-cel group or the standard care-group, as well as events of the cytokine release syndrome that occurred in at least 15% of the patients in the axi-cel group and neurologic events of any grade that occurred in at least 15% of the patients in the axi-cel group or at least 3% of those in the standard-care group. The severity of the*

cytokine release syndrome was graded according to Lee et al (30). Neurologic events were identified with the use of prespecified search list of preferred terms in the Medical Dictionary for Regulatory Activities, version 23.1, on the basis of known neurotoxic effects associated with anti-CD19 immunotherapy, and were specifically identified with the use of methods that were based on the phase 2 study of blinatumomab (31). The severity of all adverse events, including neurologic events and symptoms of the cytokine release syndrome, was graded with the use of the Common Terminology Criteria for Adverse Events, version 4.03, of the National Cancer Institute.

† Neutropenia refers to the combined preferred terms of neutropenia and neutrophil count decreased.
‡ Leukopenia refers to the combined preferred terms of leukopenia and white-cell count decreased.
§ Thrombocytopenia refers to the combined preferred terms of thrombocytopenia and platelet count decreased.
¶ Other preferred terms that were reported in one or two patients in the standard-care 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.

Infections
In the safety analysis set, 70 subjects (41 %) in the axi-cel arm and 51 subjects (30%) in the SOC arm had at least one treatment-emergent infection, including 24 subjects (14%) and 19 subjects (11%), respectively, with worst grade 3 or higher infections. Three subjects (2%) in the axi-cel arm and 6 subjects (4%) in the SOC arm had worst grade 4 infections. Five subjects (3%) in the axi-cel arm had a grade 5 TEAE of infection (2 subjects with COVID-19, 1 subject with PML, 1 subject with hepatitis B reactivation, and 1 subject with sepsis); whereas no subjects in the SOC arm had a grade 5 TEAE of infection.

Hypogammaglobulinemia
Among subjects in the axi-cel arm, 19 subjects (11%) had a hypogammaglobulinemia event, that were worst grade 1 (6 subjects, 4%) or grade 2 (13 subjects, 8%). Among subjects treated with SOC, one subject (1%) had at least one worst grade 1 hypogammaglobulinemia event.

Submitted health economic model
The health economic model included treatment-requiring severe AEs observed in ZUMA-7 that had a meaningful impact on costs and a difference of 5 percentage points between the axi-cel and SOC arm. A Norwegian clinical expert was consulted by Gilead to inform on which of the severe AEs from ZUMA-7 require treatment in Norway and how these AEs are typically managed in clinical practice. The AEs that are included in the model are shown in the table below.

Table 16: Incidence of included AEs in the model.

Adverse event	Axi-cel (N = 170)	SOC (N = 168)
Cytokine release syndrome (CRS)	6.47%	0.00%
Neurologic events	21.18%	0.06%

Included AE costs are described and assessed in section 4.1.2. No disutility due to AEs were applied in the model.

NoMA´s evaluation of safety
Serious side effects occur in most patients, both with axi-cel and with SOC. No new major safety concerns were identified within the new population and overall, the TEAEs and risks that are observed with axi-cel in the ZUMA-7 trial are similar to what has been described for other CAR-T cell therapies and for axi-cel in the other indications. Identified risks for axi-cel include CRS, neurotoxicity and hematotoxicity. In line with this, comparison of treatment arms in ZUMA-7, revealed a higher incidence of CRS, neurotoxicity, hypogammaglobulinaemia and infections in the axi-cel arm compared to the SOC arm.

Higher-grade CRS and neurotoxicity can be life threatening and may require admission to an intensive care unit, as may infection/sepsis, an adverse event associated with both axi-cel and SoC. Hypogammaglobulinemia due to B-cell aplasia increases the risk of infections, and some patients may need monthly supplemental treatment with intravenous infusions of immunoglobulins (IVIG). The duration of B cell aplasia is unknown but may persist as long as axi-cel is present. The safety profile is manageable with the current risk minimization measures presented in the SmPC.

The TEAEs and risks that are observed with axi-cel in the ZUMA-7 trial are similar to what has been described for other CAR-T cell therapies and for axi-cel in the other indications. NoMA accepts Gilead's modelling of AEs.

3.5.5 Health-related quality of life

Submitted documentation
In ZUMA-7, health-related quality of life (HRQoL) data was collected using both the EuroQoL 5-Dimensions (EQ-5D-5L) questionnaire and the EORTC Quality of Life of Cancer Patients (EORTC QLQ-C30) questionnaire. In the axi-cel arm, data was 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. Data was collected in the SOC arm at the day of screening, during the first cycle of salvage chemotherapy, at the time of disease assessment, the day of the transplantation for those receiving ASCT, and then at day 100 and 150 after randomisation (month 3 and 5), as well as month 9, 12, 15, 18, 21 and 24 after randomisation.

Out of 359 patients enrolled in ZUMA-7, 296 (82%, 165 patients in the axi-cel arm and 131 patients in the SOC arm) provided EQ-5D-5L baseline data and ≥1 follow-up time point and were included for analysis. Gilead describes that the collection of post-event HRQoL was not mandated in ZUMA-7, and that data collection after switching to subsequent therapy did not usually include patient-reported outcomes. Although some sites continued to collect patient-reported outcomes after EFS events, these comprised a minority of observations (< 11 % of total observations).

The mean EQ-5D-5L visual analogue scale (VAS) scores reported by evaluable subjects in the axi-cel and SOC arms were comparable at screening (72.4, 95% CI: 69.5, 75.2 and 74.4, 95% CI: 70.9, 77.9, respectively). EQ-5D-5L scores and changes from screening are provided in Figure 15 and Figure 16, respectively. From the results of mixed model with repeated measures (MMRM) models, there was a statistically significant and clinically meaningful difference in the mean change of scores 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) for the EQ-5D-5L VAS.

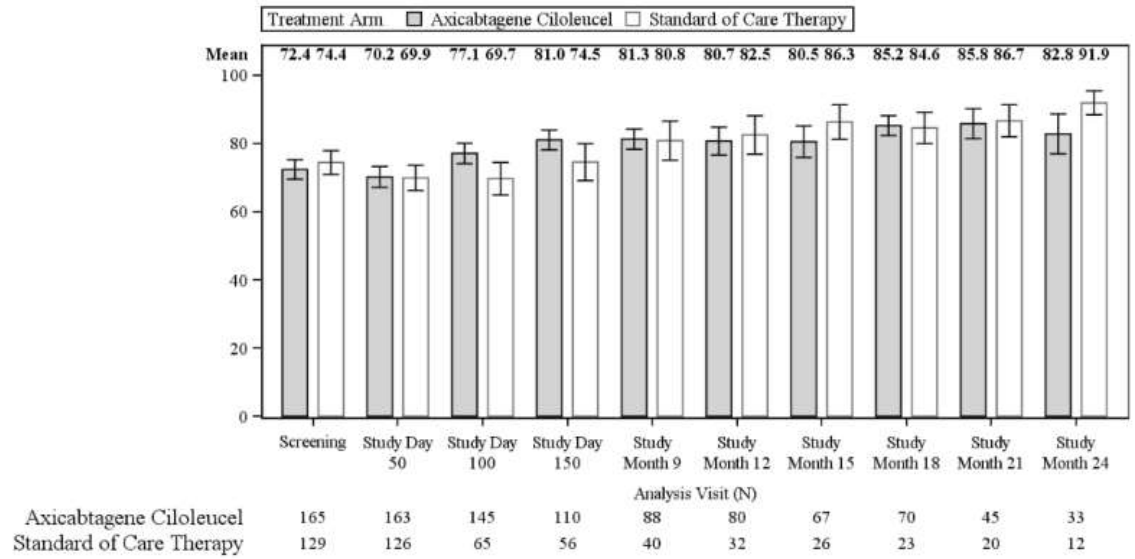


Figure 15: EQ-5D-5L VAS scores for axi-cel and SOC from the ZUMA-7 QoL analysis set. Source: (Gilead submission).

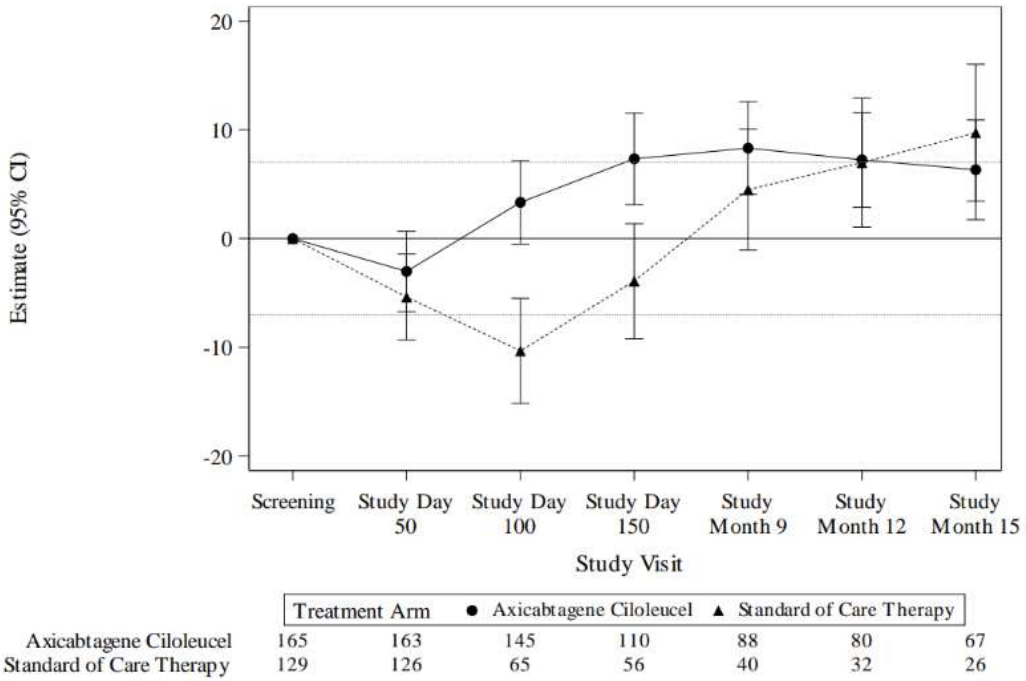


Figure 16: EQ-5D-5L VAS mixed model with repeated measures changes from screening for axi-cel and SOC, from the ZUMA-7 QoL analysis set. Source: (Gilead submission).

Submitted health economic model

In Gilead's base case, pre-event health state utility values were obtained from an analysis of the EQ-5D-5L data collected in ZUMA-7. EQ-5D-5L responses were cross-walked to EQ-5D-3L using the van Hout et al.

algorithm[2] and valued using UK general population tariffs[3] to generate the pre-event utilities. Utility data was analysed using mixed effects repeated measures models to account for multiple observations per patient. As shown in Table 17, Gilead has applied arm-specific health state utility values in the pre-event health state while patients are on treatment. For patients surviving for at least five years without an event, are utility values assumed equal to those of the age-adjusted general Norwegian population. This is based on feedback that Gilead has received from clinical experts who stated that patients who survive for five years without an event can be considered to have effectively achieved long-term response. See Table 18 for population utility values used in the model.

Given the low amount of post-event HRQoL data, the utility value in the post-event health state was based on the utility score from the ZUMA-1 trial. The progression-free utility from ZUMA-1 (third-line treatment) was assumed to reflect the post-event state in the second-line treatment.

Table 17: Health state utilities used in the model.

Health state	Utility value (SE)	Source
Pre-event, on-treatment: Axi-cel SOC	0.781 (0.016) 0.770 (0.017)	ZUMA-7
Pre-event, off-treatment	0.786 (0.011)	ZUMA-7
Post-event	0.722 (0.031)	ZUMA-1 (progression-free disease utility)

Table 18: Utility values for the general Norwegian population based on Stavem et al. (32).

Age group	Utility value	Source
19-30 years	0.906	NoMA guidelines (33).
31-40 years	0.870	
41-50 years	0.846	
51-60 years	0.811	
61-70 years	0.808	
70+ years	0.730	

The development of health state utility values in the model is adjusted for age.

[2] van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. Value Health. 2012;15(5):708-15.

[3] Dolan P. Modeling valuations for EuroQol health states. Medical care. 1997;35(11):1095-108.

No disutility values due to AEs were applied in the model. Gilead assumes that the influence of AEs on HRQoL is captured by the arm-specific utility values.

NoMA's evaluation of health-related quality of life

NoMA considers it to be a strength that the pre-event utility data in the model has been obtained directly from ZUMA-7, the same clinical study on which the efficacy data (EFS, OS and TNTT) in the health economic model is based on. Use of EQ-5D and the applied cross-walking method and tariff are also in line with NoMA's guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. After additional changes that were implemented by Gilead the method of age-adjustment is also in line with our guidelines. The implemented changes had minimal impact on the ICER.

If different arm-specific health state utility values are used for the same condition (here pre-event while on treatment), this must be fully justified and documented. For different arm-specific health state utility values to be accepted, the differences in HRQoL should be shown in clinical studies. There was a statistically significant and clinically meaningful difference in the mean change of scores from baseline to 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 $p = 0.0004$) in favour of axi-cel in ZUMA-7. These results could support the use of arm-specific health state utility values. However, the open-label trial design of ZUMA-7, a main limitation of the study, could potentially have led to bias as described in the previous chapter. This would support the use of non-arm-specific utility values. The magnitude of this potential bias is unknown. Gilead has provided the pooled utility value for pre-event from ZUMA-7 (0.779) upon request. NoMA acknowledges that the choice of approach (using arm-specific utility values or using the pooled pre-event utility value (0.779) in both arms) only affects the ICER slightly, but prefers to use a pooled utility value because of the open-label trial design and potential bias.

NoMA considers it to be plausible to assume that the longer a patient is event-free, the closer their quality of life would match with that of the general Norwegian population. However, it is unclear whether quality of life would fully return to age-adjusted general Norwegian population utility norms and whether it is appropriate to assume that this would happen after five years. In other words, it may be too optimistic to assume that there is no long-term decrement in quality of life, but we do not have evidence that suggests or proofs the opposite. A less optimistic scenario where pre-event utilities were applied for the entire model time horizon showed a small upward effect on the ICER.

NoMA agrees with Gilead on that there is a small amount of post-event HRQoL data collected in ZUMA-7 (< 11 % of total observations) and that this limits the credibility of the resulting health state utility value. The fact that the ZUMA-7 post-event utility is only slightly worse than the pre-event utility (difference of -0.005[4]) could also suggest that the ZUMA-7 post-event utility value is lacking credibility. In other HTAs on CAR-T cell therapies there was a bigger difference pre- and post-event (or progression) (34, 35). On the other hand, use of the progression-free utility from ZUMA-1 (0.772) in the post-event health state also raises concerns. NoMA has in previous HTAs pointed out that patient reported outcomes may be biased in an uncontrolled, open label trial design. Furthermore, utility scores from ZUMA-1 were only available for 34 patients, and only 49 observations informed the progression-free health state. Hence, the progression-free utility from ZUMA-1 (0.772) is also considered uncertain. In previous HTAs of axi-cel NoMA has, for

[4] Pre-event = 0.779, post-event = 0.774; submitted by Gilead as part of extra documentation upon request by NoMA.

consistency reasons, chosen to use the utility data provided in the submission for the CAR-T cell therapy tisagenlecleucel (Kymriah) for the treatment of second or later r/r DLBCL (34). The patient population in the tisagenlecleucel's pivotal JULIET study is similar to ZUMA-1. Furthermore, the data collected in JULIET is somewhat more robust than ZUMA-1 with collection of data for 105 patients. Health state utilities sourced from JULIET are as follows: 0.830 for progression-free disease and 0.710 for progressed disease. Use of a utility value of 0.830 in the post-event health state here would lead to an inconsistency where the post-event utility value is higher than the pre-event utility value. This seems clinically implausible. Therefore, the use of the progression-free utility from ZUMA-1 (0.771) in the post-event health state is accepted by NoMA.

NoMA has not evaluated (possible) utility loss related to AEs. We do not consider AE disutility to be an important driver in the model given the limited time patients are on treatment compared with the model time horizon.

NoMA accepts Gilead's HRQoL input in the submitted health economic model, but uses a pooled utility value for pre-event from ZUMA-7 (0.779) in both arms instead of arm-specific health state utility values.

4 Health economic analysis

This section presents a summary of the economic evidence submitted by Gilead in support of the use of axi-cel 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, and NoMA's assessment of the evidence. NoMA evaluates two key components in this section; the input data used not already assessed in the previous parts of this report, and the economic model used. A typical health economic model will include calculation of costs, life-years gained, and quality-adjusted-life-years (QALYs) gained.

The submitted health economic analysis is a cost-utility analysis (CUA).

4.2 The model, methods and assumptions used

Model description
Gilead used a partitioned survival (PartSA) model to assess the cost-effectiveness of axi-cel compared to SOC for adult patients with DLBCL and HGBL that relapses within 12 months from completion of, or is refractory to, first-line chemoimmunotherapy, and are intended for ASCT. The model consists of three mutually exclusive and collectively exhaustive health states that represent different disease stages of r/r DLBCL and HGBL:

- Pre-event
- Post-event
- Death

At any timepoint, the proportion of patients under the EFS curve is in the pre-event health state. The proportion of patients over the OS curve is in the state of death. The remaining patients are in the post-event health state. Event-free and post-event states were split into proportions "on treatment" and "off treatment" based on data from ZUMA-7. The post-event state was disaggregated (divided) using TTNT curves to estimate delays in initiation of third-line (3L) therapy with respect to the timing of disease progression. An illustration of the model structure is presented in Figure 17.

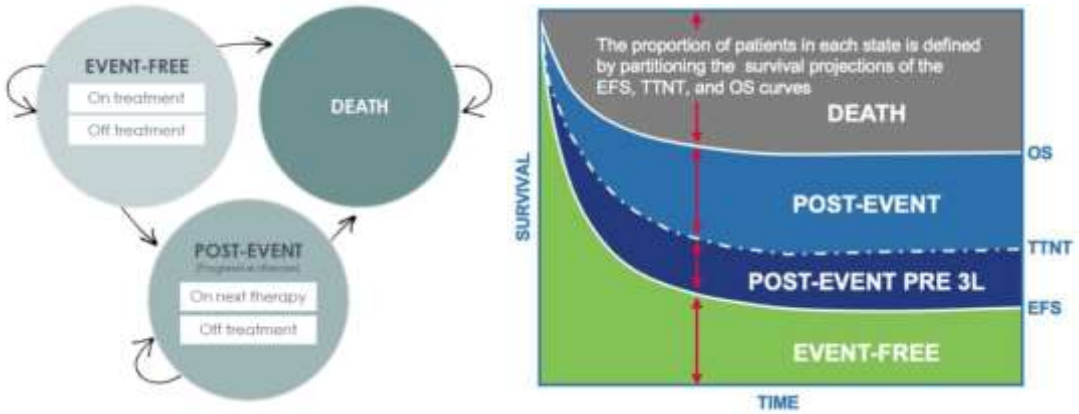


Figure 17: Model structure. Source: (Gilead submission).

The patient cohort enters the model in the pre-event health state. After each model cycle, patients can either stay in this health state, have an event and proceed to the post-event health state, or they can die. The cycle length is set to 1 month. Once patients reach 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. If patients have stable disease as best response from second-line therapy (or have progressive disease), they move to the next line of treatment.

Patients in event-free survival who live beyond 5 years revert to cost (i.e. zero costs) and utility values reflective of the general population for both the axi-cel and SoC arms.

Costs and health effects (utility values) are calculated separately for each health state and are summed up for each treatment arm with a time horizon of 50 years. Half-cycle correction is applied.

NoMA's assessment
The health economic model is well described in the submission by Gilead, and the implementation of the model in Excel is relatively transparent, making the validation easier to perform. Furthermore, important parameters and assumptions are easy to change.

The division of the pre-event health state in on- and off-treatment states based on data from the ZUMA-7 study affects only the generation of QALYs in the model slightly, not the generation of costs. TTNT curves are used to model the time at which patients receive subsequent therapy costs. As the KM for EFS and TTNT show (and the parametrisation curves estimate) there is a delay between the time point at which patients enter the post-event state and the time point for third-line treatment initiation in both arms. This way of modelling affects the generation of subsequent treatment drug- and administration costs, as well as costs related to patients' use of time and travel costs in the model. The generation of QALYs in the post-event health state is not affected by this division into on- and off-treatment. NoMA agrees with Gilead's use of TTNT curves to model the time at which patients receive subsequent therapy costs because this reflects true timing of subsequent treatment costs in the ZUMA-7 trial. However, as explained in section 3.5.3, NoMA has set TTNT equal to EFS in the SOC arm in NoMA's analysis 2 (where EFS is based on FDA's sensitivity analysis). This change was necessary to avoid implausible results.

The PartSA model structure is a common approach in oncology to estimate the effect of treatment based on data from clinical trials. This type of model together with their strengths and limitations are described in detail in the literature (36).

4.2.1 Analysis perspective

Gilead's analysis is performed from a Norwegian extended health-service perspective, including costs related to patients' use of time and travel. Health outcomes include patients' life-years (LYs) and health-related quality of life (HRQoL). Discounting of costs and effect is set to 4 % per year. The model uses a monthly cycle length, and a lifetime horizon (50 years).

NoMA's assessment
The analysis perspective is in accordance with NoMA's guidelines for the submission of documentation for single technology assessment (STA) of pharmaceuticals. The monthly cycle length is considered

appropriate to capture all meaningful differences in costs and outcomes between axi-cel and SOC. Given the starting age of 57, running the model for 50 years represents a full lifetime horizon. The lifetime horizon is considered suitable given the curative potential of treatment. However, running the model for 40 instead of 50 years also represents a lifetime horizon, and by that time there are close to zero patients alive in the model (cohort age being 97 years). So, there is no need to extend the time horizon any further. Furthermore, the discount rate should be 3 % instead of 4 % years 40+, as described in our guidelines. This is not the case in Gilead's submitted model.

NoMA accepts the analysis perspective, but changes the time horizon from 50 to 40 years.

4.2.2 Resource use and costs

Submitted documentation

The following cost components are included in the model:

- Treatment costs related to treatment with axi-cel:
  - Leukapheresis costs
  - Bridging chemotherapy costs
  - Lymphodepleting chemotherapy costs
  - Axi-cel drug and administration costs
- Treatment costs related to treatment with SOC:
  - Chemotherapy (SOC) drug and administration costs
  - Stem cell harvesting for ASCT costs
  - High-dose therapy (HDT) with BEAM costs
  - ASCT costs
- Subsequent therapy costs
- Costs related to disease management and monitoring
- Costs related to the management of adverse events
- End-of-life (terminal care) costs
- Costs related to patients' use of time and travel (transportation) costs

Package prices were sourced from NoMA's website. For drug costs, analyses must be carried out using the maximum pharmacy retail price (PRP) without value added tax (VAT). NoMA has therefore excluded VAT from the package prices.

Leukapheresis costs

The unit cost for leukapheresis (56 857 NOK per patient) is based on an estimate provided by Oslo universitetssykehus (OUS)[5] which has been adjusted to a 2022 price level by Gilead. The proportion of patients in the axi-cel arm that receives leukapheresis is set to 99 % and was based on the proportion in the ZUMA-7 trial. It was assumed that leukapheresis is performed at an outpatient visit.

Bridging chemotherapy costs

Bridging chemotherapy with glucocorticoids between leukapheresis and lymphodepleting chemotherapy was permitted in ZUMA-7 and is therefore included in the model. The model includes costs for treatment with dexamethasone (30 mg daily, taken orally for two days) for 36% of the patients in the axi-cel arm, based on the proportion of patients in ZUMA-7 that received bridging chemotherapy. Since dexamethasone is administered orally, Gilead assumed that patients receive bridging therapy at home.

Lymphodepleting chemotherapy

Patients treated with axi-cel receive lymphodepleting chemotherapy before infusion. A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/m^2 intravenous and fludarabine 30 mg/m^2 intravenous is recommended on the 5th, 4th, and 3rd day before infusion of axi-cel. Gilead included an administration cost (3 399 NOK when adjusted to a 2022 price level) for intravenous administration from NoMA's unit cost database, as well as costs related to hospitalisation (8 946 NOK per inpatient day when adjusted to a 2022 price level, based on NoMA's previous assessment, ID2019_143 (23)). Together this results in a total cost of 12 345 NOK per inpatient day while receiving intravenous medication. This total daily cost was applied for 7 days in the model. In the model, it was assumed that 96% of patients receive lymphodepleting chemotherapy based on data from ZUMA-7.

Axi-cel drug and administration costs

The unit cost of one infusion of axi-cel is set to 3 110 000 NOK (maximum pharmacy purchase price (PPP) excluding pharmacy mark-up) in the model. Gilead claims that the costs of axi-cel will only be paid by the hospital if axi-cel is administered to the patient, so the acquisition costs of axi-cel are only applied to 94% of the patients in the intervention arm in the model (based on the share of patients that received axi-cel in the ZUMA-7 trial). The infusion of axi-cel and subsequent monitoring is assumed by Gilead to incur the

[5] Cost of leukapheresis and preparation of CAR-T cells per patient at OUS, sourced from https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Yescarta_DLBCL_2019.pdf Cost of leukapheresis and preparation of CAR-T cells per patient at OUS, sourced from https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Yescarta_DLBCL_2019.pdf [5] Cost of leukapheresis and preparation of CAR-T cells per patient at OUS, sourced from https://legemiddelverket.no/Documents/Offentlig%20finansiering%20og%20pris/Metodevurderinger/K/Yescarta_DLBCL_2019.pdf

cost of hospitalisation for 5 days, admission to a patient hotel for 5 days, and the cost of cell infusion. The total cost is 52 391 NOK.

An overview of doses and cycle drug- and administration costs for drugs included in the axi-cel arm is provided in the table below.

Table 19: Doses and cycle drug- and administration costs for drugs included in the axi-cel arm.

Drug	Dose	Number of days per cycle	Cost per dose in NOK	Drug cost per cycle in NOK	Administration cost per cycle in NOK
Dexamethasone	30 mg, oral use	2	47	94	0
Fludarabine	30 mg/m^2, IV	3	1 397	4 701	86 415[6]
Cyclophosphamide	500 mg/m^2, IV	3	170		
Axi-cel	A single dose for infusion	-	3 110 000	-	52 391[7]

Chemotherapy (SOC) drug and administration costs

Gilead modelled the SOC arm as a mixed comparator, comprised of 30% R-DHAP, 20% R-ICE, 30% R-GDP, and 20% R-IME, based on input from a Norwegian clinical expert. The model applied costs for each regimen, multiplied by their distribution of use in Norway. An average of 3.5 treatment cycles with chemotherapy was applied in the model. This was based on input from a clinical expert in Norway. The mean body weight and BSA at baseline from patients in the ZUMA-7 trial were used to inform chemotherapy dosing.

Gilead included an administration cost (3 399 NOK when adjusted to a 2022 price level) for intravenous administration from the Norwegian Medicines Agency unit cost database, as well as costs related to hospitalisation (8 946 NOK per inpatient day when adjusted to a 2022 price level, based on NoMAs previous assessment, ID2019_143 (23)). Together this results in a total cost of 12 345 NOK per inpatient day while receiving intravenous SOC medication. This total daily cost was applied for 3 days per treatment cycle for the R-ICE and R-IME regimes, and for 4 days per treatment cycle for the R-DHAP and R-GDP regimes.

[6] This cost includes an administration cost for intravenous administration and costs related to hospitalisation.

[7] This cost includes costs related to hospitalisation and patient hotel admission, as well as the cost of cell infusion.

Stem cell harvesting for ASCT costs

Following R-DHAP, R-ICE, R-GDP and R-IME, patients in the SOC arm undergo stem cell harvesting before HDT with BEAM is administered. In the model, it was assumed by Gilead that patients undergo stem cell harvesting in outpatient care and the proportion of patients who undergo this procedure in the model was based on ZUMA-7, i.e., a percentage of 41% was applied. Unit costs are summarised in Table 20.

Table 20: Unit cost for stem cell harvesting.

Cost input	Cost in NOK	Source
Stem cell harvesting procedure	43 611	ID2017_105, adjusted to a 2022 price level

High-dose therapy (HDT) with BEAM costs

HDT consists of BEAM (carmustine, etoposide, cytarabine and melphalan) in the health economic model. In ZUMA-7, 36% of the patients in the SOC arm received HDT. This proportion was also applied in the model. Gilead included an administration cost (3 399 NOK when adjusted to a 2022 price level) for intravenous administration from the Norwegian Medicines Agency unit cost database, as well as costs related to hospitalisation (8 946 NOK per inpatient day when adjusted to a 2022 price level, based on NoMAs previous assessment, ID2019_143 (23)). Together this results in a total cost of 12 345 NOK per inpatient day while receiving HDT. This total daily cost was applied for 7 days, based on input from a Norwegian clinical expert.

ASCT costs

The proportion of patients in the SOC arm that received ASCT in the model was informed by the ZUMA-7 trial, where 35% completed ASCT. Unit costs are summarised in Table 21.

Table 21: Unit cost for ASCT.

Cost input	Cost in NOK	Source
ASCT	287 576	2022 DRG code 481A (annen stamcelletransplantasjon)

The Norwegian clinical expert that Gilead has consulted, informed that patients are hospitalised for three weeks after ASCT. Gilead has not included any additional costs to account for these inpatient days and explains that DRG code 481A already includes 32 inpatient days.

An overview of doses and cycle drug- and administration costs for drugs included in the SOC arm is provided in the table below.

Table 22: Doses and cycle drug- and administration costs for drugs included in the SOC arm.

Drug	Dose	Number of days per cycle	Cost per dose in NOK	Drug cost per cycle in NOK	Administration cost[8] per cycle in NOK
R-ICE:					
Rituximab	375 mg/m^2, IV	1	7 997	16 336	37 035
Etoposide	100 mg/m^2, IV	3	286		
Carboplatin	400 mg/m^2, IV	1	3 916		
Ifosfamide	5 000 mg/m^2, IV	1	3 564		
R-DHAP:					
Rituximab	375 mg/m^2, IV	1	7 997	9 668	49 380
Cisplatin	100 mg/m^2, IV	1	665		
Cytarabine	2 000 mg/m^2, IV	1	756		
Dexamethasone	40 mg, oral use	4	63		
R-GDP:					
Rituximab	375 mg/m^2, IV	1	7 997	14 318	49 380
Gemcitabine	1 000 mg/m^2, IV	2	2 786		
Dexamethasone	40 mg, oral use	4	63		
Cisplatin	75 mg/m^2, IV	1	499		
R-IME:					
Rituximab	375 mg/m^2, IV	1	7 997	14 817	37 035
Ifosfamide	2 000 mg/m^2, IV	3	1 426		
Mixantrone	8 mg/m^2, IV	1	1 685		

[8] This cost includes an administration cost for intravenous administration and costs related to hospitalisation.

Etoposide	100 mg/m^2, IV	3	286		
BEAM:					
Carmustine	300 mg/m^2, IV	1	72 653	97 938	86 415
Etoposide	200 mg/m^2, IV	4	572		
Cytarabine	200 mg/m^2, IV	4	76		
Melphalan	140 mg/m^2, IV	1	22 694		

Subsequent therapy costs

The subsequent therapies that are applied in the model are based on data from ZUMA-7. The number of subjects that received any subsequent therapy in the axi-cel and SOC arm are 70 and 120, respectively. The share of patients receiving each type of subsequent therapy and the number of cycles that patients receive are presented in the table below. It should be noted that the subsequent therapies in Table 23 are not mutually exclusive and can therefore sum up to more than 100%.

Table 23: Subsequent therapies applied in the model, based on the safety analysis set from ZUMA-7.

	Axi-cel		SOC	
Number of patients that received any subsequent therapy	70		120	
Type of subsequent therapy	Proportion of patients (%)	Number of cycles	Proportion of patients (%)	Number of cycles
Chemotherapy	97 %	3	23 %	3
Nivolumab	16 %	2	3 %	2
Pembrolizumab	7 %	5	4 %	5
Pola-BR	17 %	6	15 %	6
R-lenalidomide	9 %	4	6 %	4
Radiotherapy	29 %	3.5 fractions	28 %	3.5 fractions
Allogeneic SCT	11 %	-	5 %	-
CAR T-cell therapy:				
Yescarta	0 %	A single dose for infusion	81 %	A single dose for infusion
Breyanzi	0 %	A single dose for infusion	0 %	A single dose for infusion
Kymriah	0 %	A single dose for infusion	0 %	A single dose for infusion
ASCT	16 %	-	5 %	-

Subsequent therapy costs for CAR T-cell therapy include in addition to drug and administration costs also leukapheresis costs, bridging chemotherapy costs, and lymphodepleting chemotherapy costs.

The total drug costs for subsequent therapy (per patient) were approximately 150 000 NOK for axi-cel and 2 150 000 NOK for SOC in the CUA.

Costs related to disease management and monitoring

Resource use related to disease management and monitoring is dependent on event status (pre-event and post-event) and was based on expert consultation and Gilead's submission to NICE regarding axi-cel in the third line. The resource use in the event-free health state reverts to zero after five years, based on Gilead's assumption that patients who are still event-free after five years are effectively considered long-term responders with minimal healthcare resource use. Gilead supports their claim by referring to an article by Assouline et al. from 2020 (29). An overview of the resource use per month and associated unit costs is presented in Table 24.

Table 24: Monthly resource use related to disease management and monitoring and associated unit costs.

Type	Pre-event resource use	Post-event resource use	Unit cost in NOK	Unit cost source
GP visit	0.94	2.50	737	NoMA's unit cost database, adjusted to 2022
Cancer coordinator	1.88	1.88	489	Assumed to be similar to the cost of a nurse visit
CT scan	0.11	0.02	401	NCRP refusjonskategorier og satser offentlig radiologi 01.01.2023 (CSV)[9]
Outpatient visit (months 1 to 6)	0.69	1.00	2 479	2022 DRG code 917A (pol kons vedr lymfom, leukemi, myelomatose og visse andre benmargs-sykdommer)
Outpatient visit (months 7 to 12)	0.34	1.00	2 479	
Outpatient visit (years 2 to 3)	0.17	1.00	2 479	
Outpatient visit (years 4 to 5)	0.17	1.00	2 479	
Nurse visit	0.17	0	489	NoMA's unit cost database, adjusted to 2022
Specialist nurse visit	0.17	1.88	525	NoMA's unit cost database, adjusted to 2022
Inpatient day	0.18	0.16	8 946	ID2017_105, adjusted to a 2022 price level

[9] https://www.ehelse.no/teknisk-dokumentasjon/takster

Blood test	0.94	2.00	135	NoMA's unit cost database, adjusted to 2022
Total:				
Pre-event	Month 1-6: 5 149 NOK Month 7-12: 4 282 NOK Years 2-3: 3 860 NOK Years 4-5: 3 860 NOK			
Post-event	7 937 NOK			

Gilead has in addition to the monthly resource use mentioned in Table 24, also included resource use related specifically to follow-up after axi-cel infusion and ASCT:

Table 25: Monthly resource use related to follow-up after axi-cel infusion and ASCT and associated unit costs.

Type	Monthly resource use				Unit cost in NOK	Unit cost source
	0-6 months	6-12 months	12-24 months	3-5 years		
Outpatient visit	0,33	0,33	0,17	0,17	2 479	2022 DRG code 917A
Blood test	1,00	0,33	0,17	0,17	135	NoMA's unit cost database, adjusted to 2022
CT scan	0,17	0,17	0,00	0,00	401	NCRP refusjonskategorier og satser offentlig radiologi 01.01.2023 (CSV)[9]
GP visit	1,00	0,33	0,33	0,33	737	NoMA's unit cost database, adjusted to 2022
Total:						
0-6 months	1 758 NOK					
6-12 months	1 173 NOK					
12-24 months	6 88 NOK					
3-5 years	6 88 NOK					

Gilead points out that there might be an overlap between the pre-event resource use and the follow-up resource use.

Costs related to the management of adverse events

Costs related to the management of treatment-requiring severe AEs observed in ZUMA-7 were included. Gilead describes that the clinical expert they consulted mentions that most of the AEs can be managed within the inpatient follow-up stay after axi-cel administration and ASCT and are therefore not associated with any additional resource use. The AEs that require additional treatment are CRS, neurologic events and hypoxia.

Table 26: Resource use related to the management of adverse events and associated unit costs.

Resource use	Unit cost in NOK	Unit cost source
Management of CRS	127 380	ID2019_141
Management of neurologic events	35 784	Clinical expert input and ID2017_105 (4 x inpatient day at general ward (8 946 NOK))

No costs were included for hypoxia, as hypoxia can be a symptom of CRS, and it was therefore assumed that the cost of treating hypoxia was included in the cost of managing CRS.

End-of-life (terminal care) costs

Patients who transition to the death health state incur a one-time end-of-life cost in the model. Gilead has adjusted the unit cost that was used in the assessment of axi-cel for the third line (ID2019_143) to a 2022 price level. This resulted in a unit cost of 64 656 NOK related to terminal care.

Costs related to patients' use of time and travel (transportation) costs

Gilead has included costs related to patients' use of time, as well as transport costs linked to travel to and from treatment. A unit cost of 802 NOK, based on NoMA's unit cost database and adjusted to a 2022 price level, was applied to all hospital visits and other treatment-related activities in the model to account for travel expenses. A unit cost of 252 NOK was used for all patient hours spent on treatment-related activities. This unit cost was also sourced from NoMA's unit cost database and adjusted to a 2022 price level. The model includes patient hours spent on treatment-related activities regarding:

- Leukapheresis
- Lymphodepleting (conditioning) chemotherapy
- Axi-cel infusion

- Administration of salvage chemotherapy (SOC) regimens
- Stem cell harvesting for ASCT
- High-dose therapy (HDT) with BEAM
- ASCT
- Administration of subsequent therapies
- Disease management, monitoring and follow-up after axi-cel infusion and ASCT
- Management of AEs

The number of patient hours spent per activity was based on guidelines, input from a Norwegian clinical expert and assumptions. See Table 49 in Appendix 1 for the applied patient time in hours per treatment-related activity. In total, did patients in the axi-cel arm spent 746 hours on treatment-related activities throughout the entire model time horizon versus 870 hours for patients in the SOC arm.

NoMA's assessment

NoMA has excluded VAT from the package prices and updated some of the package prices. Regarding axi-cel, NoMA will not include the pharmacy mark-up as a part of the CUA, as explained in ID2017_105, but we will include the pharmacy mark-up in the budget analysis.

Leukapheresis costs

NoMA doesn't make any changes to Gilead's modelling of leukapheresis costs.

Bridging chemotherapy costs

Bridging chemotherapy is likely to be correlated with the treatment effect as observed in the ZUMA-7 trial. Therefore, to retain consistency between costs and effects in the analysis, the type, duration, and occurrence of bridging chemotherapy in the model should be as observed in the ZUMA-7 trial. NoMA has received the ZUMA-7 clinical study protocol and there seem to be no discrepancies between the study protocol and related costs in the model. Hence, NoMA accepts the bridging chemotherapy costs in the submitted model.

Lymphodepleting chemotherapy

Norwegian clinical experts that NoMA has consulted have estimated that patients will be hospitalised for approximately 6 days for preparation before axi-cel infusion. Therefore, we have changed the number of days hospitalised before axi-cel infusion from 7 to 6 days. We accept the unit cost for hospitalisation to ensure consistency with previous STAs of CAR-T treatments.

Axi-cel drug and administration costs

Regarding axi-cel, hospitals only pay for infused patients. So, they do not incur costs for patients that discontinue prior to axi-cel infusion. NoMA agrees with the unit cost of infusion. We have changed the number of days hospitalised after axi-cel infusion based on input from Norwegian clinical experts from 5 to 14 days. This results in a total cost of 132 905 NOK. We have left the number of overnight stays at a patient hotel unchanged. The reason for this is that we do not have data on the shares of patients that stay at a patient hotel and that live in close enough proximity to the hospital to be allowed to stay at home instead. Furthermore, a change in the number of overnight stays at a patient hotel is expected to have a minimal effect on the ICER.

Chemotherapy (SOC) drug and administration costs

NoMA has been in contact with Norwegian clinical experts about the use of different combinations of chemotherapy for treating r/r DLBCL and HGBL patients and the number of treatment cycles in Norwegian clinical practice. All four included regimens in the model are in use in Norwegian clinical practice and NoMA has received varying patient shares. In terms of drug costs per treatment, there is only little variation between them, and varying the patient shares in the model in accordance with the input received from clinical experts only has a minor impact on the ICER. Hence, NoMA accepts the distribution of treatment regimens in the SOC arm.

For the 168 subjects in the SOC arm of the safety analysis set, 152 subjects (90%) received 2 or 3 cycles of salvage chemotherapy as directed by the protocol, and 16 subjects (10%) received 1 cycle of salvage chemotherapy in ZUMA-7. The average number of cycles received was 2.3. To ensure consistency between the efficacy input and cost input in the model, NoMA has changed the average number of treatment cycles in the model from 3.5 to 2.3 in our main analyses. A scenario analysis shows the effect of including treatment costs for 3.5 cycles. An average of 3.5 cycles of salvage chemotherapy is supported by the clinical experts that NoMA has been in contact with.

Clinical experts have provided input on the number of days patients are admitted to the hospital related to salvage chemotherapy treatment in Norway. NoMA has changed the number of inpatient days according to this. The number of days is altered from 3 to 5 for R-IME, the number of days for R-DHAP is changed from 4 to 3 days, and the number of days for R-GDP is changed from 4 to 2 days.

Stem cell harvesting for ASCT costs

The unit cost for stem cell harvesting has little influence on the ICER. NoMA accepts the modelled costs for stem cell harvesting.

High-dose therapy (HDT) with BEAM costs

Norwegian clinical experts have provided input on the number of days that Norwegian patients are on average admitted to the hospital related to HDT and ASCT. Based on this has NoMA decided to remove the 7 inpatient days that Gilead included for HDT to avoid double-counting. We expect the unit cost of ASCT to cover all inpatient days related to both HDT and ASCT.

ASCT costs

NoMA agrees with using DRG code 481A (year 2022) for estimating the unit cost of ASCT. With a weight of 5.685 and a unit price of 47 742 NOK this will result in a unit cost of 271 413 NOK (not 287 576 NOK). NoMA updates the unit cost of ASCT in the model accordingly.

Subsequent therapy costs

The total drug costs for subsequent therapy (per patient) were approximately 150 000 NOK for axi-cel and 2 150 000 NOK for SOC in Gilead's main analysis. This big difference can be explained by the inclusion of axi-cel costs in the SOC arm for the majority of patients (81% of patients receiving subsequent anti-lymphoma treatment in 3rd line) compared with the inclusion of mostly chemotherapy costs (97% of patients) in the axi-cel arm. The difference has a great impact on the ICER, and subsequent therapy is one of the most influential parameters in the model.

NoMA considers it to be a strength that costs for subsequent therapy in the model are based on data from ZUMA-7 (i.e. internal validity). However, it is noted that re-treatment with axi-cel is not included among the costs of subsequent therapy for the axi-cel arm. In ZUMA-7, there were 9 out of 180 subjects retreated with axi-cel, of which 5 subjects had a response per central assessment (all 5 achieving CR). Exclusion of re-treatment costs in the model therefore impacts the internal validity of the analysis, as it underestimates the treatment costs required to deliver the modelled OS benefit. However, re-treatment with axi-cel is not expected to take place in Norwegian clinical practice and as such exclusion of re-treatment costs could be justified based on external validity. The impact of re-treatment on the efficacy estimates is uncertain. However, if the impact is considerable, the ICER could be underestimated in the main analyses, since the corresponding costs of re-treatment are not included. Taking into account feedback from the clinical experts, NoMA elected to place more emphasis on external validity in the main analyses (i.e. costs for re-treatment with axi-cel were not included). A sensitivity analysis preserving the internal validity (i.e. including re-treatment costs) is presented in Table 40.

Due to the risk of bias in the primary EFS results (as described in section 3.5.1), NoMA also presents a scenario analysis (for NoMA's analysis 1) where subsequent treatment costs in the SOC arm are altered. For patients in the ZUMA-7 SOC arm that were in response to their initial therapy but censored as an EFS event nonetheless (and hence switched to subsequent therapy too soon), third line axi-cel costs were excluded and ASCT costs were added instead. Specifically, 24 patients received new anti-lymphoma

therapy while still in BIRC assessed response. However, 4 of these patients received consolidative radiotherapy (not axi-cel) as their new anti-lymphoma therapy. So, we exclude third line axi-cel costs for 20 patients in the SOC arm. 16 out of 20 patients were in response pre-ASCT and should have proceeded to ASCT as per the study protocol. In ZUMA-7, one of these patients proceeded to ASCT off-protocol. Hence, we include ASCT costs for 15 patients in the SOC arm. In summary, a scenario analysis (Table 37) was conducted to explore the impact of bias in the primary EFS results. In this analysis axi-cel costs for 20 patients were excluded and ASCT costs for 15 patients were added for the SOC arm, reflecting a hypothetical scenario where such patients would have been treated according to the study protocol. In addition, three scenario analyses were conducted to explore the impact in reducing the proportion of patients receiving CAR-T therapy following SOC based on feedback from clinical experts (Table 39).

Costs related to disease management and monitoring

Gilead has based costs related to disease management and monitoring on input from a Norwegian clinical expert. NoMA sees that the resulting monthly pre-event and post-event costs are quite different from those used in previous HTAs (34, 35). Specifically, the pre-event costs in this HTA are much higher than in the others, whereas the post-event costs are lower in this HTA compared to the others. NoMA would like to point out that assumptions about costs related to disease management and monitoring have a negligible impact on the ICER. NoMA uses the same input as Gilead but removes the resource use that is related specifically to follow-up after axi-cel infusion and ASCT to avoid possible double-counting.

The resource use in the event-free health state reverts to zero after five years. Two out of three clinical experts that NoMA has consulted agree with this assumption and describe that there is usually no follow-up of patients that are considered cured. One clinical expert describes that Norwegian transplanted patients are being followed up as described in The European Group for Blood & Marrow Transplantation (EBMT)'s guidelines for monitoring. These guidelines include yearly check-ups at the hospital for 15 years according to the clinical expert. NoMA is aware of that monitoring of patients in clinical practice might differ from region to region and from patient to patient. Including yearly check-ups for another 10 years had a minor impact on the ICER.

Costs related to the management of adverse events

CRS is an AE that is commonly related to treatment with axi-cel and other CAR-T cell therapies and could be associated with substantial resource use. The most common adverse reactions that may be associated with CRS include pyrexia, hypotension, tachycardia, chills, and hypoxia (1). In an updated HTA from 2022 (ID2019_041), a unit cost of 127 380 NOK was applied for the treatment of CRS based on CIMBTR registry data on the mean ICU stay, ICU costs, tocilizumab use and average doses given. Gilead uses the same unit cost.

Neurologic events have also been very commonly observed in patients treated with axi-cel and other CAR-T cell therapies. Neurological events can occur concurrent with CRS, following resolution of CRS or in the absence of CRS. Norwegian clinical experts that NoMA has consulted describe that it's not uncommon for patients to be admitted to the hospital for the treatment of treatment-related AEs.

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with axi-cel. Hypogammaglobulinaemia has been very commonly observed in patients treated with axi-cel. Immunoglobulin levels should be monitored after treatment with axi-cel and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement. By the time of the 23.2 month analysis, 28 (16%) of 170 patients in ZUMA-7 received intravenous immunoglobulin therapy (1).

Clinically valid changes in the modelling of AE costs, including costs for intravenous immunoglobulin therapy, have little impact on the model result (ICER), hence NoMA has decided not to make any changes.

End-of-life (terminal care) costs

NoMA accepts the terminal care costs. This unit cost is based on Wang et al. from 2017 (37) and has been applied in several, relevant HTAs before. Wang et al. have estimated treatment costs and life expectancy of DLBCL.

Costs related to patients' use of time and travel (transportation) costs

An exclusion of costs related to use of time and transportation costs each lead to a minor increase in the ICER. Therefore, NoMA accepts these costs in the model without making any changes and evaluating their appropriateness.

Summary of changes

NoMA does the following changes in the resource use and costs input:

- *Change the time horizon from 50 to 40 years*
- *Exclude VAT from the drug package prices and update some of the package prices according to NoMA's medicine database*
- *Change the number of days patients are hospitalised before axi-cel infusion from 7 to 6 days*
- *Change the number of days hospitalised after axi-cel infusion from 5 to 14 days*
- *Change the average number of salvage chemotherapy treatment cycles from 3.5 to 2.3*
- *Change the number of inpatient days for treatment with R-IME from 3 to 5 days, for treatment with R-DHAP from 4 to 3 days, and for treatment with R-GDP from 4 to 2 days*
- *Remove the 7 inpatient days that are included for HDT with BEAM*
- *Update the unit cost of ASCT according to DRG code 481A (year 2022)*
- *Remove the resource use that is related specifically to follow-up after axi-cel infusion and ASCT*

4.3 Results

4.3.1 Gilead´s main analysis

The results from Gilead's main analysis are presented in the table below. Gilead's analysis is based on the primary definition of EFS (parameterised with MCM loglogistic in the axi-cel arm and MCM exponential in the SOC arm), OS in the FAS population (parameterised with MCM generalised gamma in both arms) and TTNT in the FAS population (parameterised with MCM loglogistic in both arms). NoMA has excluded VAT from the package prices in accordance to our guidelines and updated some of the package prices. Results are reported per patient and discounted at a discount rate of 4 %.

Table 27: Results from Gilead's main analysis. Based on maximum PRPs without VAT. Per patient. Discounted.

	Axi-cel	SOC	Difference
Total costs	4 317 061	3 762 174	554 887
Total QALYs Total life years	6.95 8.91	5.58 7.39	1.38 1.51
Incremental cost per QALY gained Incremental cost per life year gained			403 151 366 548

A more detailed overview of the costs is presented below. This overview shows that drug costs (in both second- and third line) and the difference between arms is substantial. This has a big impact on the ICER.

Table 28: Overview of the results from Gilead's main analysis by costs per category.

Discounted Costs	Axi-cel	SoC	Incremental
Drug cost	**3 060 758**	**2 234 031**	**826 727**
2L	2 907 841	81 555	2 826 286
3L	152 916	2 152 475	-1 999 559
Hospital costs	**682 854**	**869 083**	**-186 230**
2L treatment admin. (inc. Follow-up	206 390	313 064	-106 674
3L treatment admin.	208 147	233 690	-25 543
Health state resource use	225 369	275 505	-50 135
End of life cost	42 947	46 825	-3 878
Primary costs	**84 702**	**115 080**	**-30 378**
2L treatment admin. (inc. Follow-up	10 480	4 877	5 602
Health state resource use	74 222	110 202	-35 980
Adverse events costs	**15 712**	**211**	**15 501**
Indirect costs	**473 036**	**543 770**	**-70 734**
Patient time-use	170 625	199 392	-28 768
Transport	302 411	344 378	-41 966
Total	4 317 061	3 762 174	554 887

4.3.2 NoMA´s main analyses

Given that substantial uncertainty remains regarding the true magnitude of the axi-cel effect size (see section 3.5.1 for more information), NoMA has conducted two main analyses:

- *Analysis 1* is based on the primary definition of EFS and OS results as per randomised population (as per Gilead's main analysis). This analysis is considered anti-conservative as the benefit of axi-cel is driven by the higher number of premature NALT events in the SOC arm, rather than the progression-/death- events.
- *Analysis 2* is based on an alternative definition of EFS (as per FDA's sensitivity analysis). In this analysis, patients in the SOC arm who received NALT prematurely (i.e. while still in response as defined by the blinded independent review committee, in SD following only one salvage chemotherapy cycle, or who never received the randomized treatment) were followed until progression/stable disease occurred. This analysis is considered conservative as it generates over-optimistic EFS in the SOC arm, due to the added benefit of a second salvage therapy (likely primarily axi-cel) being included in the EFS event time.

NoMA has assessed the analysis and the assumptions used in the economic model submitted by Gilead. NoMA has based their two main analyses on the same assumptions as in Gilead's main analysis, except for the following changes:

- Change in the average number of salvage chemotherapy treatment cycles from 3.5 to 2.3 (see section 3.3 for explanation)
- Use a pooled utility value for pre-event from ZUMA-7 (0.779) in both arms instead of arm-specific health state utility values (see section 3.4.6 for explanation)
- Change in the time horizon from 50 to 40 years (see section 4.1.1 for explanation)

- Change in the number of days patients are hospitalised before axi-cel infusion from 7 to 6 days (see section 4.1.2 for explanation)
- Change in the number of days hospitalised after axi-cel infusion from 5 to 14 days (see section 4.1.2 for explanation)
- Change in the number of inpatient days for treatment with R-IME from 3 to 5 days, for treatment with R-DHAP from 4 to 3 days, and for treatment with R-GDP from 4 to 2 days (see section 4.1.2 for explanation)
- Remove the 7 inpatient days that are included for HDT with BEAM (see section 4.1.2 for explanation)
- Update the unit cost of ASCT according to DRG code 481A (year 2022) (see section 4.1.2 for explanation)
- Remove the resource use that is related specifically to follow-up after axi-cel infusion and ASCT (see section 4.1.2 for explanation)

In addition to these changes that are implemented in both of NoMA's main analyses, we have done the following changes in NoMA's analysis 1 and 2, respectively.

Table 29: Changes implemented by NoMA that are not common to both of NoMA's main analyses.

	Gilead's main analysis	NoMA's analysis 1	NoMA's analysis 2
Definitions	EFS, OS and TTNT: based on the primary definitions from ZUMA-7	EFS, OS and TTNT: based on the primary definitions from ZUMA-7	EFS: based on FDA's sensitivity analysis OS and TTNT: based on the primary definitions from ZUMA-7
EFS	Axi-cel: MCM loglogistic SOC: MCM exponential	Axi-cel: MCM loglogistic SOC: MCM loglogistic	Axi-cel: MCM loglogistic SOC: standard Gompertz
OS	Axi-cel: MCM generalized gamma SOC: MCM generalized gamma	Axi-cel: MCM generalized gamma SOC: MCM generalized gamma	Axi-cel: MCM generalized gamma SOC: MCM generalized gamma
TTNT	Axi-cel: MCM loglogistic SOC: MCM loglogistic	Axi-cel: MCM loglogistic SOC: MCM generalized gamma	Axi-cel: MCM loglogistic SOC: TTNT is set equal to EFS in the SOC arm

The tables below present the influence of each change that is being implemented by NoMA on the ICER in Gilead's main analysis.

Table 30: Changes implemented by NoMA, and their influence on Gilead's ICER.

Parameter	Main analysis Gilead	Main analyses NoMA	ICER (± change in ICER)
ICER in Gilead's main analysis	-	-	**403 151**
No. of salvage chemotherapy cycles	3.5	2.3	465 899 (+ appr. 63 000)
Utility value pre-event	Arm-specific utility values while on treatment	Pooled utility value in pre-event (0.779)	405 935 (+ appr. 3 000)
Time horizon in years	50	40	403 967 (+ appr. 1 000)
No. of days patients are hospitalised before axi-cel infusion	7	6	400 434 (- appr. 3 000)
No. of days patients are hospitalised after axi-cel infusion	5	14	419 943 (+ appr. 17 000)
No. of inpatient days for treatment with R-IME, R-DHAP and R-GDP	R-IME: 3 R-DHAP: 4 R-GDP: 4	R-IME: 5 R-DHAP: 3 R-GDP: 2	415 950 (+ appr. 13 000)
No. of inpatient days for HDT with BEAM	7	0	422 465 (+ appr. 19 000)
Unit cost of ASCT	287 576 NOK	271 413 NOK	406 633 (+ appr. 3 000)
Resource use that is related specifically to follow-up after axi-cel infusion and ASCT	Included	Excluded	379 262 (- appr. 24 000)

Table 31: Changes implemented by NoMA, and their influence on Gilead's ICER.

Parameter	Main analysis Gilead	NoMA's analysis 1	ICER (± change in ICER)
ICER in Gilead's main analysis	-	-	**403 151**
Parametrization functions	EFS: Axi-cel: MCM loglogistic SOC: MCM exponential OS: Axi-cel: MCM generalized gamma SOC: MCM generalized gamma TTNT: Axi-cel: MCM loglogistic SOC: MCM loglogistic	EFS: Axi-cel: MCM loglogistic SOC: MCM loglogistic OS: Axi-cel: MCM generalized gamma SOC: MCM generalized gamma TTNT: Axi-cel: MCM loglogistic SOC: MCM generalized gamma	393 098 (- appr. 10 000)

Table 32: Changes implemented by NoMA, and their influence on Gilead's ICER.

Parameter	Main analysis Gilead	NoMA's analysis 2	ICER (± change in ICER)
ICER in Gilead's main analysis	-	-	**403 151**
EFS definition + parametrization functions	EFS, OS and TTNT: based on the primary definitions from ZUMA-7 EFS: Axi-cel: MCM loglogistic SOC: MCM exponential OS: Axi-cel: MCM generalized gamma SOC: MCM generalized gamma TTNT: Axi-cel: MCM loglogistic SOC: MCM loglogistic	EFS: based on FDA's sensitivity analysis OS and TTNT: based on the primary definitions from ZUMA-7 EFS: Axi-cel: MCM loglogistic SOC: standard Gompertz OS: Axi-cel: MCM generalized gamma SOC: MCM generalized gamma TTNT: Axi-cel: MCM loglogistic SOC: TTNT is set equal to EFS in the SOC arm	1 174 173 (+ appr. 770 000)

The results from NoMA's main analyses are shown in the tables below.

Table 33: Results from NoMA's main analysis 1 (primary definition of EFS). Based on maximum PRPs without VAT. Per patient. Discounted.

	NoMA's analysis 1 – primary definition of EFS		
	Axi-cel	SOC	Difference
Total costs	4 309 734	3 646 583	663 150
Total QALYs Total life years	6,93 8,90	5,55 7,39	1,38 1,51
Incremental cost per QALY gained Incremental cost per life year gained			480 150 438 698

Table 34: Results from NoMA's main analysis 2 (alternative definition of EFS, as per FDA's sensitivity analysis). Based on maximum PRPs without VAT. Per patient. Discounted

	NoMA analysis 2 – alternative definition of EFS (as per FDA's sensitivity analysis)		
	Axi-cel	SOC	Difference
Total costs	4 309 734	2 834 002	1 475 732
Total QALYs Total life years	6,93 8,90	5,78 7,39	1,15 1,51
Incremental cost per QALY gained Incremental cost per life year gained			1 286 026 976 250

Table 35: Overview of the results per cost category in NoMA's analysis 1 to the left and NoMA's analysis 2 to the right

Discounted Costs	Axi-cel	SoC	Incremental
Drug cost	**3 060 375**	**2 200 152**	**860 223**
2L	2 907 841	65 829	2 842 012
3L	152 533	2 134 323	-1 981 790
Hospital costs	**710 038**	**799 612**	**-89 574**
2L treatment admin. (inc. Follow-up c	250 245	200 058	50 187
3L treatment admin.	191 806	268 997	-77 191
Health state resource use	225 239	283 890	-58 651
End of life cost	42 748	46 667	-3 919
Primary costs	**74 156**	**114 726**	**-40 570**
Health state resource use	74 156	114 726	-40 570
Adverse events costs	**15 712**	**213**	**15 499**
Indirect costs	**449 454**	**531 881**	**-82 428**
Patient time-use	166 840	180 616	-13 776
Transport	282 613	351 265	-68 652
Total	4 309 734	3 646 583	663 150

Discounted Costs	Axi-cel	SoC	Incremental
Drug cost	**3 060 375**	**1 831 852**	**1 228 522**
2L	2 907 841	65 829	2 842 012
3L	152 533	1 766 023	-1 613 490
Hospital costs	**710 038**	**633 917**	**76 121**
2L treatment admin. (inc. Follow-up c	250 245	200 058	50 187
3L treatment admin.	191 806	222 579	-30 773
Health state resource use	225 239	164 614	60 625
End of life cost	42 748	46 667	-3 919
Primary costs	**74 156**	**50 884**	**23 271**
Health state resource use	74 156	50 884	23 271
Adverse events costs	**15 712**	**213**	**15 499**
Indirect costs	**449 454**	**317 136**	**132 318**
Patient time-use	166 840	143 049	23 791
Transport	282 613	174 086	108 527
Total	4 309 734	2 834 002	1 475 732

Taking into consideration NoMA's anti-conservative analysis 1 and NoMA's conservative analysis 2, the ICER is believed to lie between 480 000 and 1 290 000 NOK. The difference in the ICERs is driven to a small extent by a reduced EFS treatment effect (i.e. decreased QALY incremental benefit) but mainly by the reduced costs for subsequent treatment, and reduced healthcare cost in the SOC arm (i.e. increased cost increment). The bias associated with these estimates is presented in the table below.

Table 36 Key uncertainties around NoMA's analyses 1 and 2

Parameter	Source of Bias	Effect on ICER in NoMA's analysis 1	Effect on ICER in NoMA's analysis 2
EFS	**NoMA's analysis 1** is based on the primary definition of EFS, where NALT was given prematurely in 35/63 patients (56%) in the SOC arm. **NoMA's analysis 2** ignores the 35 premature EFS events and follows patients until progression/stable disease at D150. Patients receiving NALT without having received randomized SOC treatment are censored. In analysis 1 axi-cel is associated with a QALY gain of 1.38 compared to 1.15 in analysis 2. The main impact of changing EFS input is on incremental costs in 3L.	Incremental QALYs are overestimated (EFS events are recorded prematurely, leading to poorer benefit in the SOC arm). Incremental costs are underestimated (due to higher costs of SOC, secondary to premature initiation of axi-cel in 3L in ZUMA-7). **True ICER is expected to be higher.**	Incremental QALYs are underestimated (as the added benefit of a second salvage therapy (mainly axi-cel) is included in the EFS event time for SOC). Incremental costs are overestimated (due to lower costs in the SOC arm, secondary to a higher proportion of patients being event-free (i.e. not in need of a 3L treatment). **True ICER is expected to be lower.**

OS	In ZUMA-7, 35/63 patients in the SOC arm who received NALT prematurely (mainly CAR-Ts) would otherwise be treated with SOC salvage chemotherapy followed by ASCT in responding patients. Fifteen (15) of the 35 patients were in response pre-ASCT and should have proceeded to transplant.	Incremental QALYs could be somewhat underestimated although the impact on OS is uncertain. Incremental costs are not affected by potential bias in OS. True ICER could be slightly lower.	
Re-treatment with axi-cel	In ZUMA-7 a total of 9 patients in the axi-cel arm were re-treated with aci-cel. Five of these patients achieved a CR to re-treatment. The costs of re-treatment were removed in both analyses, but the effect was not adjusted for resulting in misalignment between costs and effects.	Incremental QALYs could be somewhat overestimated. True ICER would be slightly higher.	
Overall direction of bias		**The ICER of 480 000 is likely too low**	**The ICER of 1 290 000 is likely too high**

4.3.3 Sensitivity and scenario analyses

Gilead has performed a one-way sensitivity analysis, several scenario analyses, and a probabilistic sensitivity analysis (PSA). The key drivers (parameters) that affect the ICER were the proportion of patients receiving subsequent treatment with axi-cel in the SOC arm, axi-cel acquisition costs, and the proportion of patients receiving axi-cel in the axi-cel arm.

NoMA's scenario analyses are presented in the tables below.

Table 37: Scenario analysis on subsequent treatment in SOC arm.

	NoMA's analysis 1 ICER (± change in ICER)
Subsequent treatment shares as observed in ZUMA-7 **(NoMA's analysis)**	480 150
Exclude axi-cel costs for 20 patients who received NALT while in BIRC assessed ongoing response. Of these, 15 patients were in response pre-ASCT and had the cost of ASCT added (these patients should have proceeded to ASCT as per the study protocol) - **(Scenario) - adjustment of costs only***	772 378 (+ appr. 290 000)

** In this scenario only costs are adjusted for. The impact on EFS and OS is the SOC arm (by replacing axi-cel with ASCT) is difficult to predict. If such replacement would decrease the EFS and OS in the SOC arm, the ICER increase would not be so dramatic.*

Table 38: Scenario analysis on the number of salvage chemotherapy cycles.

No. of salvage chemotherapy cycles	NoMA's analysis 1 ICER (± change in ICER)	NoMA's analysis 2 ICER (± change in ICER)
2.3 cycles **(NoMA's analyses)**	480 150	1 286 026
3.5 cycles **(Scenario)**	422 583 (- appr. 58 000)	1 216 814 (- appr. 70 000)

Table 39: Scenario analysis on the proportion of patients receiving axi-cel treatment in the third-line, in the SOC arm.

Proportion of patients receiving axi-cel treatment in third-line, SOC arm	NoMA's analysis 1 ICER (± change in ICER)	NoMA's analysis 2 ICER (± change in ICER)
81 % (based on ZUMA-7) **(NoMA's analyses)**	480 150	1 286 026
70 % (based on input from Norwegian clinical experts) **(Scenario) – adjustment of costs only***	694 734 (+ appr. 215 000)	1 499 728 (+ appr. 214 000)
60 % (based on input from Norwegian clinical experts) **(Scenario) – adjustment of costs only***	892 811 (+ appr. 413 000)	1 696 992 (+ appr. 411 000)
0% and adjusted OS based on treatment-switch adjustment analysis by Gilead: HR of 1,72 for SOC relative to axi-cel for OS **(Scenario)- adjustment of costs and effects****	813 901 (+ appr. 337 000)	NA***

For these scenarios NoMA has only adjusted the costs of the 3L treatment in the SOC arm. The effects were not adjusted. The increase in ICER of appr. 413 000 (scenario with 60%) is therefore an overestimation as the incremental benefit would also increase. This could be demonstrated in scenario ** where the effect and costs of 3L axi-cel were removed from the SOC arm, and the slope in the increase in ICER (as a function of % of patients who received axi-cel in 3L in the SOC arm) is much more gentle between NoMA's analysis 1 and the 0% scenario (ICER increased from 480 150 to 813 901) than between NoMA's analysis 1 and the 60% scenario. * Treatment-switch adjustment analysis (RPSFTM) for NoMA's analysis 2 has not been conducted as it is illogical. The FDA's definition requires that patients are followed for evidence of progression/stable disease after receiving NALT (including axi-cel), whereas treatment-switch adjustment analysis assumes that SOC patients did not cross to axi-cel in 3L.*

Table 40: Scenario analysis on the proportion of patients receiving re-treatment with CAR-T therapy in the axi-cel arm

Proportion of patients receiving re-treatment with CAR-T therapy in the axi-cel arm	NoMA's analysis 1 ICER (± change in ICER)	NoMA's analysis 2 ICER (± change in ICER)
0 % (based on clinical plausibility) **(NoMA's analyses)**	480 150	1 286 026
5 % (based on ZUMA-7) **(Scenario)***	551 597 (+ appr. 70 000)	1 372 019 (+ appr. 90 000)

**This scenario reflects internal validity as 5 % received re-treatment with CAR-T therapy in ZUMA-7. However, the scenario does not reflect external validity as the Norwegian clinical experts NoMA has contacted stated that patients will not receive re-treatment with CAR-T therapy in clinical practice.*

Table 41: Scenario analysis on drug cost of axi-cel

Drug cost	NoMA's analysis 1 ICER (± change in ICER)	NoMA's analysis 2 ICER (± change in ICER)
Maximum pharmacy purchase price (PPP) excluding pharmacy mark-up and VAT **(NoMA's analyses)**	480 150	1 286 026
Maximum pharmacy purchase price (PPP) including pharmacy mark-up, excluding VAT **(Scenario)**	496 621 (+ appr. 16 000)	1 313 348 (+ appr. 27 000)

The main issue in this assessment is the imbalance in NALT events across the study arms (6% for axi-cel vs. 35% for SOC) in ZUMA-7. For one thing, this imbalance was the key driver of EFS benefit for axi-cel. There was no plausible way to adjust for this imbalance, and the uncertainty related to the benefit in EFS of axi-cel compared to SOC is demonstrated by presenting two main analyses (Table 36 presents the biases in the two main analyses). Furthermore, costs of the subsequent treatment in the SOC arm are also a source of uncertainty as a result of "premature" initiation of NALT. For the main analyses, NoMA accepts the exclusion of axi-cel re-treatment costs as it is unlikely that patients will be re-treated in the Norwegian clinical practice. This results in a discordance between costs and effects of re-treatment in the axi-cel arm. The exclusion of axi-cel re-treatment costs decreased the incremental costs and, consequently, the ICER. At the same time, NoMA accepts the proportion of subsequent CAR-T therapy in the SOC arm as per ZUMA-7, even though this might be lower in the Norwegian clinical practice. High treatment-switch rate to CAR-Ts (81%) as a subsequent therapy in 3rd line increased the costs in the SOC arm, decreased the incremental costs and, consequently, the ICER. An important scenario analysis, in which axi-cel costs for ZUMA-7 SOC patients that switched to subsequent therapy too soon, instead of proceeding to ASCT as per study protocol, were replaced with ASCT costs, increased the ICER by 290 000 in NoMA's analysis 1. Similarly, scenario analyses in which the proportion of patient receiving axi-cel as a subsequent treatment in 3rd line in the SOC arm decreased from 81% (based on ZUMA-7) to 70% and 60% (based on the input from Norwegian clinical experts) increased the ICER by appr. 200 000 and 400 000 NOK, respectively. These scenarios decreased the costs in the SOC arm, hence increasing the cost increment and subsequently the ICER. However, in these scenarios the OS in the SOC arm has not been accordingly adjusted and if that was possible, the increase in the ICER would likely not be so dramatic.

4.4 NoMA´s conclusion on the incremental cost-effectiveness ratio (ICER)

The incremental cost (estimated using maximum PRPs without VAT) of axi-cel compared with standard of care (SOC) is:

- 480 000 NOK per QALY gained in NoMA's analysis 1 (primary definition of EFS)
- 1 290 000 NOK per QALY gained in NoMA's analysis 2 (alternative definition of EFS, as per FDA's sensitivity analysis)

Taking into consideration NoMA's anti-conservative analysis 1 and NoMA's conservative analysis 2, the ICER is believed to lie between 480 000 and 1 290 000 NOK. The difference in the ICERs is driven by a reduced EFS treatment effect (i.e. decreased QALY incremental benefit) and reduced costs for subsequent treatment in the SOC arm (i.e. increased cost increment).

The costs of the subsequent treatment in the SOC arm have a large impact on the ICER. A scenario analysis shows that excluding axi-cel costs for ZUMA-7 SOC patients that switched to subsequent therapy too soon and assuming that patients would have proceeded to ASCT as per the study protocol, increased the ICER from 480 000 to 772 378 in NoMA's analysis 1. Similarly, a scenario analysis in which the proportion of patient receiving axi-cel as a subsequent treatment in 3rd line in the SOC arm decreased from 81% (based on ZUMA-7) to 60% or 70% (based on the input from Norwegian clinical experts) increased the ICER.

Axi-cel and some of the other drugs that are included in the analyses have a discounted price. These prices are confidential and not available to the general public. The confidential ICERs and budget impact are presented in a separate attachment (not included here).

5 BUDGET IMPACT ANALYSIS

The budget impact for year 1-5 after introduction is based on the assumption that the intervention will be recommended for use in clinical practice by the four regional health authorities and possibly implemented in the guidelines of the Directorate of Health. Two scenarios are considered:

A) The technology is recommended for use in clinical practice by the regional health authorities for the eligible patient population as described in this STA.
B) The technology is not recommended for use in clinical practice.

The total budget impact is the difference between the budget impact in the two scenarios.

5.2 Estimation of the number of patients potentially eligible for treatment

Clinical experts recruited by the regional health authorities have estimated that around 20 - 25 Norwegian adult patients will be eligible for treatment with Yescarta (within the relevant indication) each year. They explain that, initially, the patient population that is considered eligible will be in line with those eligible for ASCT today. They anticipate, however, that the population eligible for CAR-T therapy may become somewhat broader in terms of age, ECOG and/or co-morbidities in the future. Broadening the population in line with the approved indication (i.e., to also include patients that may be CAR-T eligible but ASCT ineligible), is anticipated to somewhat increase patient numbers, although the populations are expected to be largely overlapping.

The number of patients expected to be treated in the first 5 years if Yescarta is recommended for use in clinical practice is presented in Table 42. The number of patients expected to be treated if Yescarta is not recommended is presented in Table 43.

Table 42: The annual number of new patients expected to initiate treatment with Yescarta (axi-cel) and SOC in the next 5 years – scenario where Yescarta (axi-cel) is recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	25	25	25	25	25
SOC	0	0	0	0	0
Total	**25**	**25**	**25**	**25**	**25**

Table 43: The annual number of new patients expected to initiate treatment with Yescarta (axi-cel) and SOC in the next 5 years – scenario where Yescarta (axi-cel) is not recommended

	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	0	0	0	0	0
SOC	25	25	25	25	25
Total	**25**	**25**	**25**	**25**	**25**

5.3 Cost estimates

NoMA has calculated the budget impact for two scenarios:

1) Drug costs for Yescarta and SOC in the second line. All other costs are excluded. This scenario is the same for NoMA's analysis 1 and 2.
2) All healthcare related costs and assumptions considered in the cost-effectiveness model: treatment costs related to treatment with Yescarta and SOC, subsequent therapy costs, costs related to disease management and monitoring, costs related to the management of adverse events, and terminal care costs. Costs related to patients' use of time and travel (transportation) costs are not included in the budget impact analysis. Therefore, this scenario is slightly different from NoMA's analysis 1 and 2, and reflects NoMA's guidelines.

In both scenarios all changes done by NoMA as described in section 4.1.2 are incorporated. The pharmacy mark-up for Yescarta is not included in the CUA, but it is part of the budget analysis.

Annual drug costs per patient according to scenario 1 are presented in Table 44.

Table 44: Drug costs (in NOK) for Yescarta and SOC in the second line per patient per year. Based on maximum pharmacy retail prices (PRPs) including VAT, undiscounted.

NoMA's analysis 1 and 2	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	3 725 565	0	0	0	0
SOC	82 286	0	0	0	0

Annual healthcare related costs per patient according to scenario 2 are presented in Table 45.

Table 45: Healthcare related costs (in NOK) for Yescarta and SOC per patient per year. Based on maximum pharmacy retail prices (PRPs) including VAT, undiscounted.

NoMA's analysis 1	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	4 395 505	96 878	46 792	37 013	34 190
SOC	3 274 077	138 094	45 596	41 527	39 466
NoMA's analysis 2	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel)	4 395 505	96 878	46 792	37 013	34 190
SOC	2 687 513	182 397	44 174	35 939	33 868

Scenario 2 (budget impact for the total budget of specialist health services) does not include re-treatment with Yescarta. There is limited data available on re-treatment with CAR-T cell therapy, and the clinical experts consulted by NoMA did not expect re-treatment to be implemented in Norwegian clinical practice.

5.4 Budget impact

Budget impact for the pharmaceutical budget for specialist health services:

The estimated budget impact based on the estimated drug costs for Yescarta and SOC in the second line only (scenario 1) is presented in Table 46. Since treatment with Yescarta is currently being reimbursed in the third line, there will be a shift from third to second line (if Yescarta ends up being implemented in the second line as well). This means that today's third line costs for treatment with Yescarta will most likely disappear (if approved in second line). Reimbursement in the second line, however, would at the same time also lead to a somewhat bigger share of patients being treated with Yescarta. The pharmaceutical budget impact does not take potential cost-savings in the third line into account. It does show how much an implementation of treatment with Yescarta in the second line would cost compared to a scenario where patients receive SOC in the second line and Yescarta in the third line.

Table 46: Estimated budget impact (in NOK) as a result of drug costs for Yescarta and SOC in the second line only (scenario 1). Based on maximum pharmacy retail prices (PRPs) including VAT, undiscounted. Rounded up to the nearest 1 000 000 NOK.

NoMA's analysis 1 and 2	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	93 000 000	93 000 000	93 000 000	93 000 000	93 000 000
Yescarta (axi-cel) NOT recommended for use	2 000 000	2 000 000	2 000 000	2 000 000	2 000 000
Budget impact of Yescarta (axi-cel) being recommended for use	**91 000 000**	**91 000 000**	**91 000 000**	**91 000 000**	**91 000 000**

Budget impact for the total budget of specialist health services:

The estimated budget impact for all healthcare related costs considered in the cost-effectiveness model (scenario 2) is presented in Table 47 and Table 48. The total budget impact reflects the savings due to moving Yescarta from third to second line per patient, but does not account for a bigger share of patients treated with Yescarta in second line.

Table 47: Estimated budget impact (in NOK) as a result of all healthcare related costs considered in the cost-effectiveness model (scenario 2). Based on NoMA's analysis 1. Based on maximum pharmacy retail prices (PRPs) including VAT, undiscounted. Rounded up to the nearest 1 000 000 NOK.

NoMA's analysis 1	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	110 000 000	112 000 000	113 000 000	114 000 000	115 000 000
Yescarta (axi-cel) NOT recommended for use	82 000 000	85 000 000	86 000 000	87 000 000	88 000 000
Budget impact of Yescarta (axi-cel) being recommended for use	**28 000 000**	**27 000 000**	**27 000 000**	**27 000 000**	**27 000 000**

Table 48: Estimated budget impact (in NOK) as a result of all healthcare related costs considered in the cost-effectiveness model (scenario 2). Based on NoMA's analysis 2. Based on maximum pharmacy retail prices (PRPs) including VAT, undiscounted. Rounded up to the nearest 1 000 000 NOK.

NoMA's analysis 2	Year 1	Year 2	Year 3	Year 4	Year 5
Yescarta (axi-cel) recommended for use	110 000 000	112 000 000	113 000 000	114 000 000	115 000 000
Yescarta (axi-cel) NOT recommended for use	67 000 000	72 000 000	73 000 000	74 000 000	75 000 000
Budget impact of Yescarta (axi-cel) being recommended for use	**43 000 000**	**40 000 000**	**40 000 000**	**40 000 000**	**40 000 000**

Conclusion:

The total budget impact for the specialist health services of a positive recommendation for Yescarta for the eligible patient population as described in this STA is estimated to be around 28 – 43 million NOK including VAT in the year with the largest budget impact after introduction. The calculations are uncertain and based on simplifications.

6 Summary and conclusions

Health service interventions are to be evaluated against three prioritisation criteria – the benefit criterion, the resource criterion and the severity criterion. The priority-setting criteria are to be assessed and weighed against one another. The more severe the condition or the more extensive the benefit of the intervention, the higher resource use will be acceptable. Quality and uncertainty associated with the documentation and the budget impact are to be included in the overall assessment of interventions.

NoMA has assessed the criteria for priority-setting when using axi-cel in accordance with the request from Ordering Forum (Bestillerforum, request number ID2022_020: *En hurtig metodevurdering med en kostnad-nytte vurdering (løp C) gjennomføres ved Statens legemiddelverk for axicabtagene ciloleucel (Yescarta) til behandling av voksne pasienter med diffust storcellet B-cellelymfom (DLBCL) og høygradig B-cellelymfom (HGBL) som får tilbakefall innen 12 måneder etter fullføring av, eller som er refraktære overfor, førstelinje kjemoimmunterapi*, and the approved summary of product characteristics (SmPC). NoMAs´s assessment is primarily, but not exclusively, based on the documentation presented by Gilead.

<u>NoMA's assessment of the benefit criterion:</u>
The efficacy and safety of axi-cel in adult patients with r/r DLBCL/HGBL was demonstrated in a phase 3 randomised, open-label, multicentre study (ZUMA-7). The data cut-off used for the efficacy analysis was 18 March 2021, with a median follow-up time of 24.9 months. In total, 359 patients were randomised in a 1:1 ratio to receive a single infusion of axi-cel or SOC (2 to 3 cycles of standard chemoimmunotherapy followed by HDT-ASCT in those with disease response).

Axi-cel was superior to SOC with respect to the primary endpoint, event-free survival (EFS), with a median EFS time of 8.3 months (95 % CI: 4.5, 15.8 months) vs. 2.0 months (95 % CI: 1.6, 2.8 months), respectively (stratified HR of 0.398 (95 % CI: 0.308, 0.514)). The secondary endpoint of ORR was supportive of the primary outcome measure, with an overall response rate (ORR) of 83% in the axi-cel arm compared to 50% in the SOC arm. Overall survival (OS) was also a secondary endpoint in the trial, but data were not mature at the time of the primary data-cut off. Updated OS data using a data cut-off date of 25 January 2023 became available during the procedure, demonstrating a statistically significant OS benefit in favour of axi-cel (median OS not reached for Yescarta vs. 31.1 months for SOC, HR = 0.73 (95% CI: 0.54, 0.98).

In the SOC arm, the majority of patients who went on to receive a third-line therapy switched to CAR-T as their subsequent treatment (81 %). Treatment-switch adjusted analyses of OS were submitted and presented (Figure 6). However, in Norway axi-cel is reimbursed in the third line and treatment-switch adjustment for OS is therefore not considered appropriate. NoMA explored the treatment-switch adjustment in one scenario analysis.

<u>NoMA's assessment of quality and uncertainty associated with submitted documentation:</u>
Overall, the ZUMA-7 randomized controlled trial is considered appropriate for defining the relative benefit of axi-cel over SOC. Nevertheless, substantial uncertainty remains regarding the true magnitude of the axi-cel relative effect size, due to the EFS definition (allowing new anti-lymphoma therapy (NALT) at the discretion of the investigator) in the context of the open-label design.

In an open-label study, initiation of new anti-cancer therapy prior to adjudicated disease progression is likely to be informative. In the current trial, there was a large imbalance in NALT events across the study arms (6% for axi-cel vs. 35% for SOC) and this imbalance was the key driver of EFS benefit for axi-cel. A

closer examination of NALT events conducted by the FDA (8), established that 35/63 events in the SOC arm were due to "premature" initiation of NALT (i.e. initiation of NALT in responding patients (n=22), patients who had stable disease following only 1 cycle of salvage chemotherapy as opposed to the protocol specified 2-3 cycles (n=7) and patients who received a new therapy without ever having received the randomized treatment (n=6)). Thus, an apparent perceived lack of efficacy for SOC in the context of the open-label trial design, is considered to have biased the primary outcome measure.

To explore the impact of such bias, an EFS sensitivity analysis was requested by NoMA, where the "premature" NALT events were to be followed until disease progression. Gilead declined to send the requested analysis stating that it was not defined in the protocol. A similar sensitivity analysis was previously conducted by the FDA (8). This sensitivity analysis resulted in a HR for EFS of 0.7 (95%CI: 0.535-0.916), compared to the original HR of 0.4 (95% CI: 0.308- 0.514) (Figure 9 and Figure 3), illustrating that bias introduced by the open-label trial design could have had a rather large impact on the magnitude of the EFS effect size. There is no satisfactory way to correct for this bias, which ideally should have been minimized by adequate study design and conduct.

Due to this substantial uncertainty in the EFS effect-size. NoMA conducted two main analyses:

- *Analysis 1* is based on the primary definition of EFS and OS results as per randomised population (as per Gilead's main analysis). This analysis is considered anti-conservative as the benefit of axi-cel is driven by the higher number of premature NALT events in the SOC arm, rather than the progression-/death- events. In this analysis, treatment witch axi-cel was associated with 1,38 additional QALYs compared to today's SOC.
- *Analysis 2* is based on an alternative definition of EFS (as per FDA's sensitivity analysis). In this analysis, patients in the SOC arm who received NALT before progression/stable disease at day 150 as defined by the blinded independent review committee were followed until progression occurred. This analysis is considered conservative, as the receipt of CAR-Ts as NALT would likely generate over-optimistic EFS result for the SOC arm. In this analysis, treatment witch axi-cel was associated with 1,15 additional QALYs compared to today's SOC.

NoMA therefore anticipates that the true magnitude of the axi-cel relative effect size lies somewhere in between the two analyses.

The OS analysis is also biased due to the early initiation of NALT. Nevertheless, the impact of bias on OS results may be less pronounced, as premature initiation of NALT (mostly CAR-T) pre-progression may be less likely to have substantially altered the overall clinical course. It is therefore anticipated that the OS outcome may more closely reflect the true effect size of axi-cel in the 2nd line. In both analyses, the OS result is the same, where treatment with axi-cel results in a life year gain of 1,51 compared to SOC. There is still a lack of evidence for the long-term effect, and therefore the proportion of patients for which axi-cel may lead to a cure cannot be verified.

In ZUMA-7, there were 9 subjects retreated with axi-cel, of which 5 subjects had a response per central assessment, with all 5 subjects achieving a complete response (CR). This re-treatment may therefore have contributed to the OS estimates applied in the model. However, the health economic analyses (both Gilead's and NoMA's) do not include costs for re-treatment since re-treatment with axi-cel is not included in the approved SmPC or expected to take place in clinical practice. This is in favour of axi-cel. Subsequent therapy is one of the most influential parameters in the model, and an inclusion of re-treatment costs in the axi-cel arm would lead to an increase in the ICER. Note also that ZUMA-7 patients in the comparator

arm switched to subsequent therapy too soon, resulting in shorter EFS and less benefit being modelled in the comparator arm in the model, as well as resulting in higher costs for subsequent therapy in the comparator arm. Less effect and higher costs in the comparator arm is also in favour of axi-cel. Therefore, NoMA presents a scenario analysis (for NoMA's analysis 1) where subsequent treatment costs in the SOC arm are altered (see Table 37). Excluding axi-cel costs for ZUMA-7 SOC patients that switched to subsequent therapy too soon and assuming that patients would have proceeded to ASCT as per the study protocol, had a big impact on the ICER (i.e. +290 000 NOK).

Considering post-progression treatment with CAR-T therapy following SOC, this is in line with Norwegian clinical practice where axi-cel is available from the 3rd line. However, it is acknowledged that there is uncertainty regarding the proportion of 3rd line patients that would eventually be offered CAR-T in Norwegian clinical practice. Two scenario analyses considering lower proportion receiving third line CAR-T therapy and a scenario analysis removing both costs and effects attributed to CAR-T therapy all resulted in higher ICERs (see Table 39).

NoMA's assessment of the resource criterion:
There are significant drug costs associated with axi-cel compared to today's standard of care (SOC) which consists of salvage chemotherapy, followed by HDT and ASCT for those who are eligible. The total drug costs (per patient) for treatment in the second line were 2 907 841 NOK for patients treated with axi-cel and 65 829 NOK for patients treated with SOC in NoMA's analyses.

There is limited data available on re-treatment with CAR-T cell therapy, and the clinical experts consulted by NoMA did not expect re-treatment to be implemented in Norwegian clinical practice. Since treatment with axi-cel is currently being reimbursed in the third line, there will be a shift from third to second line (if axi-cel ends up being implemented in the second line as well). This means that today's third line costs for treatment with axi-cel would be reduced (if approved in second line). Reimbursement in the second line, however, would at the same time also lead to a somewhat bigger share of patients being treated with axi-cel.

NoMA's assessment of the severity criterion:
NoMA estimates the absolute shortfall based on current standard care with chemotherapy to be approximately 13 QALYs (in both analysis 1 and analysis 2).

NoMA's conclusion on cost-effectiveness
NoMA has estimated an incremental cost (using maximum PRP without VAT) of axi-cel compared with SOC of:

- 480 000 NOK per QALY gained in NoMA's analysis 1 (primary definition of EFS)
- 1 290 000 NOK per QALY gained in NoMA's analysis 2 (alternative definition of EFS, as per FDA's sensitivity analysis)

There is a rather large difference in the ICER produced by the two analyses. Partly this is explained by a small decline in the incremental QALY benefit in analysis 2 compared to analysis 1 (1,15 vs 1,38 QALYs). The main driver of the difference in ICER, however, is related to the cost of subsequent treatment, as the time patients spend in EFS has impact on the proportion of patients receiving subsequent CAR-T therapy in the SoC arm. The time the patients spend in EFS also impacts other healthcare costs.

Taking into consideration NoMA's anti-conservative analysis 1 and NoMA's conservative analysis 2, the ICER is believed to lie somewhere between 480 000 and 1 290 000 NOK.

Axi-cel and some of the other drugs that are included in the analyses have a discounted price. These prices are confidential and not available to the general public. The confidential ICERs and budget impact are presented in a separate attachment (not included here).

NoMA's assessment of budget impact:

- Budget impact for the pharmaceutical budget for specialist health services:

NoMA estimates the annual budget impact of introducing Yescarta (axi-cel) for the eligible patient population as described in this STA to be around 91 million NOK including VAT in year 5. The budget impact for the pharmaceutical budget for specialist health services is based on drug costs for Yescarta and SOC in the second line only.

- Budget impact for the total budget of specialist health services:

NoMA estimates the total annual budget impact of introducing Yescarta (axi-cel) for the eligible patient population as described in this STA to be around 28 – 43 million NOK including VAT in the year with the largest budget impact after introduction. These calculations include subsequent therapy costs (for third-line CAR-T treatment, after SOC), costs related to disease management and monitoring, costs related to the management of adverse events, and terminal care costs.

The presented budget impact estimates are uncertain and simplified.

Statens legemiddelverk, 30-06-2023

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Appendix 1 Overview of treatment-related activities and patient time in hours

Table 49: Treatment-related activities and patient time in hours spent on each activity.

Treatment-related activities	Patient time in hours
Leukapheresis	3
Lymphodepleting chemotherapy	112
Axi-cel infusion and post-infusion monitoring	160
Administration of salvage chemotherapy (SOC) regimens:	
R-ICE infusion	48
R-DHAP infusion	48
R-GDP infusion	48
R-IME infusion	80
Stem cell harvesting for ASCT	3
HDT with BEAM	112
ASCT	336
Administration of subsequent therapies:	
Chemotherapy	48
Nivolumab	0.5
Pembrolizumab	0.5
Radiotherapy (per fraction)	0.5
ASCT	448
Allogeneic SCT	448
CAR-T cell therapy	160
R-lenalidomide	4.5

Pola-BR	32
Disease management and monitoring:	
Nurse visit	0.5
Specialist nurse visit	0.5
Inpatient day	16
Blood test	0.5
CT scan	1.0
Outpatient visit (months 1 to 6)	0.5
Outpatient visit (months 7 to 24)	0.5
Outpatient visit (years 2 to 3)	0.5
Outpatient visit (years 4 to 5)	0.5
Cancer coordinator	0.5
GP visit	0.25
Follow-up after axi-cel infusion and ASCT:	
Follow-up 0-6 months	1.09
Follow-up 6-12 months	0.58
Follow-up 12-24 months	0.25
Follow-up 2-5 years	0.25
Management of CRS	75
Management of neurologic events	64

Appendix 2 Severity and shortfall

NoMA has quantified the severity of relapsed and refractory DLBCL and HGBL using absolute shortfall. Absolute shortfall is the number of future quality-adjusted life years (QALYs) an average patient in the patient group will lose because of his/her disease, compared to the average in the population of the same age. Absolute shortfall is the same as the reduction in expected future QALYs without the treatment under consideration.

The calculation of absolute shortfall is done in stages:

1) The mean age at start of treatment for the relevant Norwegian patient group which is being considered for the new treatment is defined. We refer to the age as A. A = 57. The source for the age of 57 years is ZUMA-7, the same clinical study on which the efficacy data in the model is based on. The median age of 59 years in ZUMA-7 (mean age 57.2 years) is younger than the median age of DLBCL/HGBL patients in Norwegian clinical practice (70 years) but reflects the expected age in a transplant eligible population.
2) The number of remaining QALYs (undiscounted) for an average person from the general population with the age A is estimated. We refer to this as $QALYs_A$. We use mortality data for the Norwegian population from Statistics Norway (2019) in calculating expected remaining lifetime at different ages[10]. This is combined with age-specific quality of life data to calculate quality adjusted remaining lifetime for different ages. We have used Norwegian age-specific quality of life data for an average population, with value sets based on UK general population available for EQ-5D, based on Stavem et al (2018)[11]. Table 51 shows the expected remaining quality adjusted life years according to age in the average population.
3) The prognosis for the relevant Norwegian patient group is calculated. The prognosis is the average number of remaining QALYs (undiscounted) for the patient group with the current standard treatment. We refer to this as P_A. We calculate the prognosis from the number of QALYs the patients can expect with the comparator treatment in the health economic analysis.
4) The absolute shortfall (AS) is the difference between the estimated number of remaining QALYs for the general population at the same age (point 2) and the expected number of remaining QALYs for the patient group with the comparator treatment (point 3).

Absolute shortfall (AS) = $QALYs_A - P_A$.

NoMA estimates the absolute shortfall based on current standard care to be approximately 13 QALYs (see Table 50 below).

[10] SSB. Dødelighetstabeller, 2019. Available from: https://www.ssb.no/befolkning/statistikker/dode.

[11] Stavem K, Augestad LA, Kristiansen IS, Rand K. General population norms for the EQ-5D-3 L in Norway: comparison of postal and web surveys. Health and quality of life outcomes. 2018;16(1):204.

Table 50: Calculation of severity

Age	A	57	
Expected QALYs without disease (undiscounted)	$QALYs_A$	22.00	
Expected number of QALYs with disease (undiscounted)	P_A	8.76 (NoMA analysis 1)	9.16 (NoMA analysis 2)
Number of lost QALYs with disease (absolute shortfall)	**AS**	**13.24**	**12.84**

Expected remaining QALYs in the general population

Table 51 (below) shows the expected remaining QALYs and (health-related) health state utility values (HSUV) respectively, by age for the general population. Expected remaining QALYs are based on mortality data for the Norwegian population from Statistics Norway[12] and the age-specific HSUV in the right hand column.

Stavem et al[13] covers the age group from 19 to 97. HSUV (values in parentheses) for the age groups 19-50 years in 10-year brackets are directly incorporated from Stavem et al[13]: 19-30 (0.906), 31-40 (0.870), 41-50 (0.846). Using the raw data[14] from Stavem et al[13], we have calculated a simplified weighted average[15] for the age groups 51-70[16] (0.811) and 71-80 (0.808). The raw data is also used for the HSUV for the age group above 80 (0.730). This sharper decrease in HSUV after age 80 compared with the decrease between ages 50 and 80 is supported by findings in the Tromsø Study (T7, unpublished) and in European health status surveys (38-40). Furthermore, NoMA assumes that HSUV are somewhat higher in the younger age group (0-19) and uses the same increment as before (0.02) yielding a HSUV of 0.926.

[12] SSB. Dødelighetstabeller, 2019. Available from: .

[13] Stavem K, Augestad LA, Kristiansen IS, Rand K. General population norms for the EQ-5D-3 L in Norway: comparison of postal and web surveys. Health and quality of life outcomes. 2018;16(1):204.

[14] Stavem – Personal communication.

[15] The raw data were available for the groups 71-75 and 76-80; the average is weighted by the fraction of responders in each of the two age groups.

[16] Stavem et al reported lower utility values in the age bracket 51-60 compared with 61-70 years. Such fluctuations are not reported in other comparable studies, and NoMA chose to smooth the HSUV by weighting an average for the pooled 51-70 group.

Table 51: Expected remaining QALYs and HSUV in the general population.

Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV	Age	Expected remaining QALYs	HSUV
0	70,9	0,926	36	38,8	0,870	72	11,6	0,808
1	70,2	0,926	37	37,9	0,870	73	11,0	0,808
2	69,2	0,926	38	37,1	0,870	74	10,4	0,808
3	68,3	0,926	39	36,2	0,870	75	9,8	0,808
4	67,4	0,926	40	35,4	0,870	76	9,2	0,808
5	66,5	0,926	41	34,6	0,846	77	8,7	0,808
6	65,6	0,926	42	33,7	0,846	78	8,1	0,808
7	64,6	0,926	43	32,9	0,846	79	7,5	0,808
8	63,7	0,926	44	32,1	0,846	80	7,0	0,808
9	62,8	0,926	45	31,3	0,846	81	6,5	0,730
10	61,9	0,926	46	30,5	0,846	82	6,0	0,730
11	61,0	0,926	47	29,7	0,846	83	5,6	0,730
12	60,0	0,926	48	28,9	0,846	84	5,2	0,730
13	59,1	0,926	49	28,1	0,846	85	4,9	0,730
14	58,2	0,926	50	27,3	0,846	86	4,5	0,730
15	57,3	0,926	51	26,5	0,811	87	4,1	0,730
16	56,4	0,926	52	25,7	0,811	88	3,8	0,730
17	55,4	0,926	53	25,0	0,811	89	3,5	0,730
18	54,5	0,926	54	24,2	0,811	90	3,2	0,730
19	53,6	0,906	55	23,5	0,811	91	3,0	0,730
20	52,7	0,906	56	22,7	0,811	92	2,8	0,730
21	51,9	0,906	57	22,0	0,811	93	2,6	0,730
22	51,0	0,906	58	21,2	0,811	94	2,4	0,730

23	50,1	0,906	59	20,5	0,811	95	2,2	0,730
24	49,2	0,906	60	19,8	0,811	96	2,0	0,730
25	48,3	0,906	61	19,1	0,811	97	1,8	0,730
26	47,4	0,906	62	18,3	0,811	98	1,8	0,730
27	46,6	0,906	63	17,7	0,811	99	1,6	0,730
28	45,7	0,906	64	17,0	0,811	100	1,5	0,730
29	44,8	0,906	65	16,3	0,811	101	1,5	0,730
30	43,9	0,906	66	15,6	0,811	102	1,4	0,730
31	43,0	0,870	67	14,9	0,811	103	1,3	0,730
32	42,2	0,870	68	14,2	0,811	104	1,0	0,730
33	41,3	0,870	69	13,6	0,811	105	0,8	0,730
34	40,5	0,870	70	12,9	0,811			
35	39,6	0,870	71	12,3	0,808			

Appendix 3 Gilead's base case selection of parametric functions

Extrapolation of EFS

The log cumulative hazard plot for EFS showed parallel curves that converged at the end of the follow-up time (Figure 18). Based on that Gilead concluded that the proportional hazard (PH) assumption is not fulfilled and chose to fit independent survival curves per arm. A Schoenfeld residuals plot showed a sinusoidal wave pattern (not shown here) and the global PH test was significant indicating that the PH assumption may not hold.

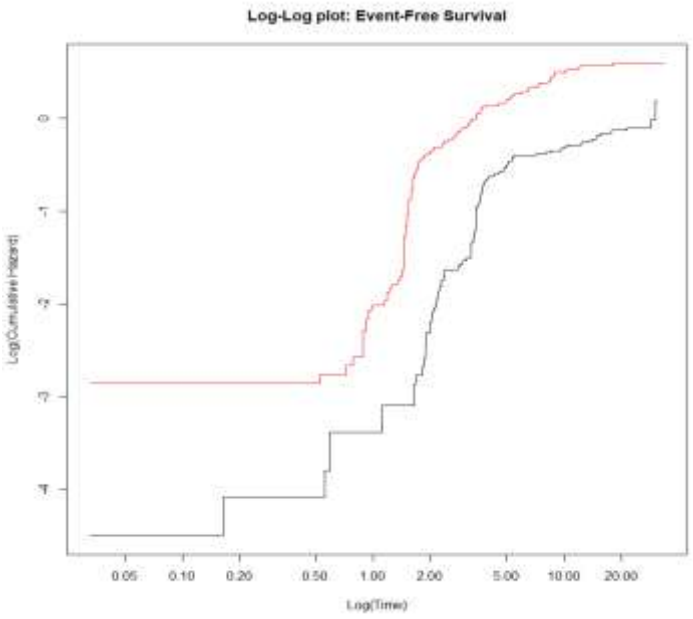

Figure 18: Log cumulative hazard plot for EFS. Source: (Gilead submission).

Seven standard parametric models, seven MCMs and nine 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 52, and the extrapolations of EFS up to 180 months are presented in Figure 19 and Figure 20. 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 the exponential model for SOC. The cure fractions from the MCMs are presented in Table 53.

Table 52: Statistical goodness-of-fit for EFS extrapolation with standard parametric models and MCMs. Source: (Gilead submission).

	Axi-cel		SoC	
	AIC	BIC	AIC	BIC
Standard parametric models				
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

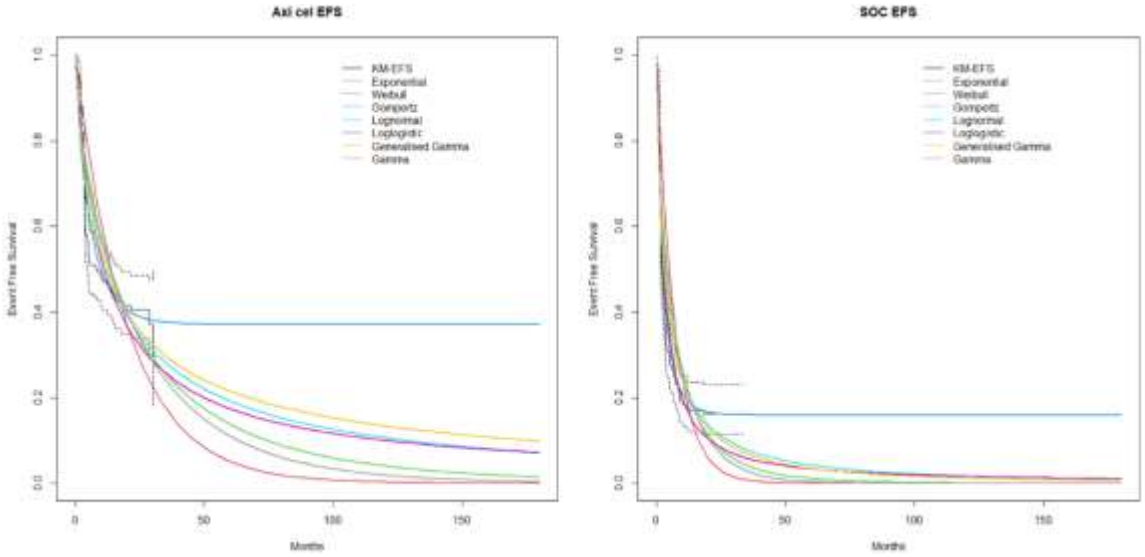

Figure 19: Standard parametric models of partitioned survival: non-proportional hazard models of EFS for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM EFS. Source: (Gilead submission).

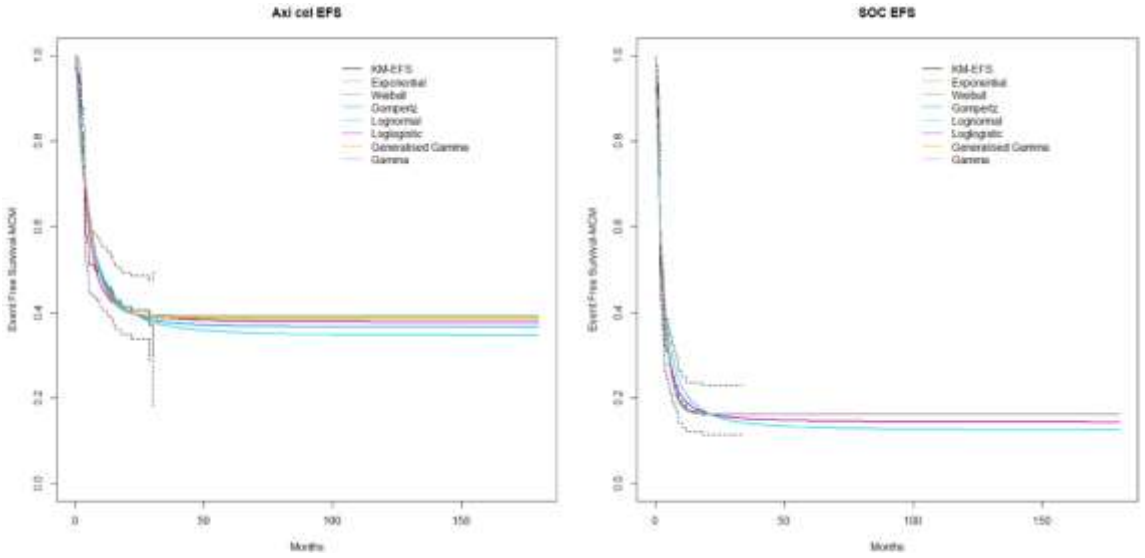

Figure 20: MCMs of partitioned survival: non-proportional hazard models of EFS for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM EFS. Source: (Gilead submission).

Table 53: Cure fractions from the MCMs for EFS and OS. Source: (Gilead submission).

Distribution	Axi-cel		SOC	
	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 %
Generalized gamma	39 %	53 %	16 %	42 %

The EFS curves for the one-, two- and three-knot spline models using hazard, odds and normal scales are provided in Figure 21. According to the goodness-of fit statistics, the 3 best fitting spline models were 3 knot hazard (AIC 771), 3 knot odds (AIC 773) and 3 knot normal (AIC 790) for axi-cel, and 3 knot hazard (AIC 699), 3 knot odds (AIC 704) and 2 knot odds (AIC 714) for SOC.

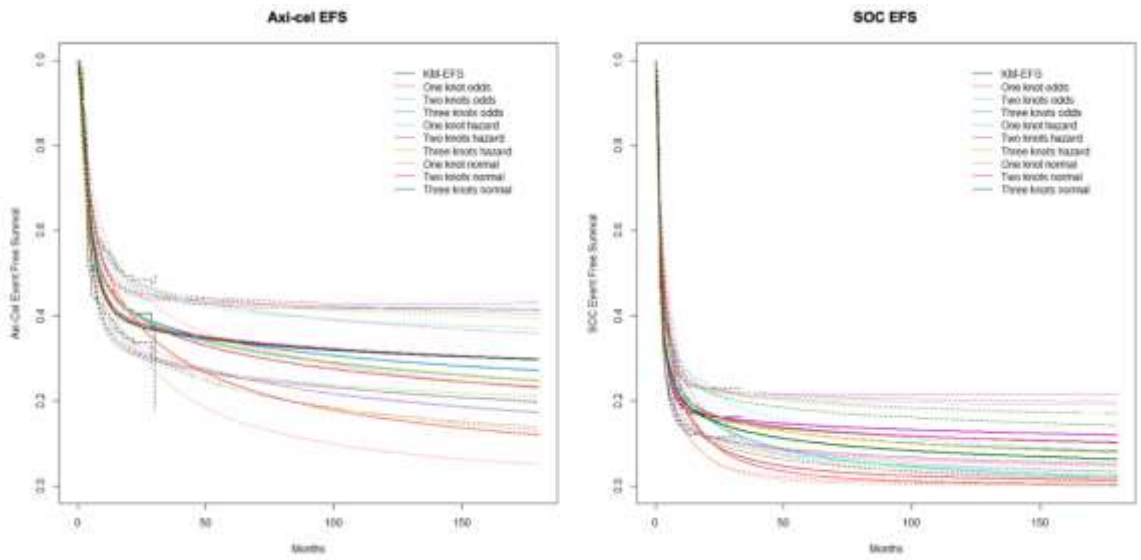

Figure 21: EFS curves from restricted cubic spline models for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM EFS. Source: (Gilead submission).

Gilead chose MCM loglogistic to extrapolate EFS for axi-cel and MCM exponential for SOC based on the clinical plausibility of the cure models and the best statistical fit.

Extrapolation of OS

The log cumulative hazard plot for OS showed crossing curves (Figure 22). However, a Schoenfeld residuals plot showed a sinusoidal wave pattern (not shown here) and the global PH test wasn't significant indicating that the PH assumption may hold. Due to clear lack of parallelism in the log cumulative hazard curves, Gilead chose to fit individual parametric curves to each treatment arm.

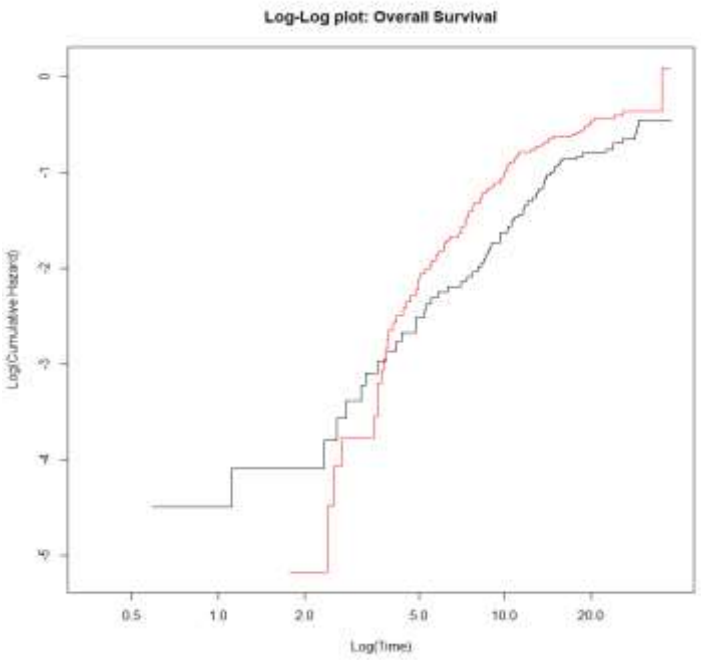

Figure 22: Log cumulative hazard plot for OS. Source: (Gilead submission).

Statistical goodness-of fit for OS for standard parametric functions and MCMs is presented in Table 54. 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 extrapolations of OS with the standard parametric models and MCMs up to 180 months are presented in Figure 23 and Figure 24, respectively.

Table 54: Statistical goodness-of-fit for OS extrapolation with standard parametric models and MCMs. Source: (Gilead submission).

	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

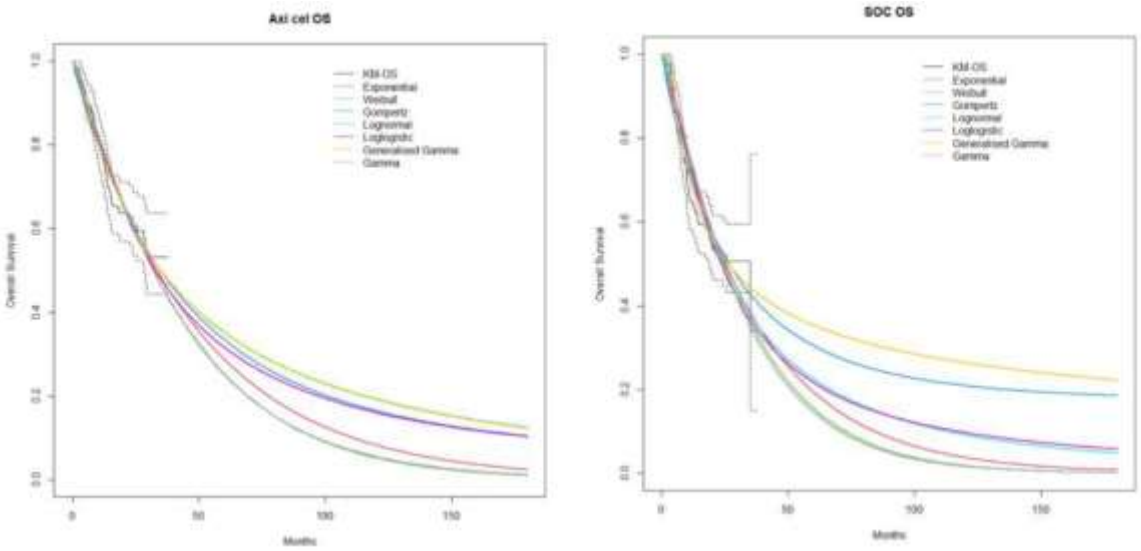

Figure 23: Standard distribution models of partitioned survival: non-proportional hazard models of OS for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM OS. Source: (Gilead submission).

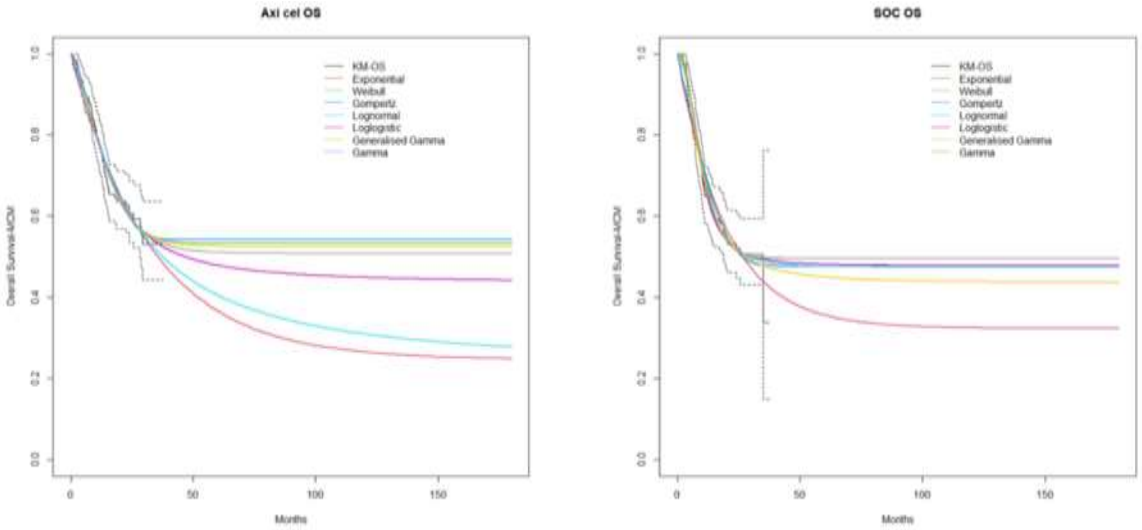

Figure 24: MCMs of partitioned survival: non-proportional hazard models of OS for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM OS. Source: (Gilead submission).

The OS curves for the one-, two-, and three-knot spline models using hazard, odds and normal scales are provided in Figure 25. All fitted spline models had a similar mathematical fit to axi-cel KM data (AIC between 699 to 702) as well as to SOC KM data (AIC between 743 and 747).

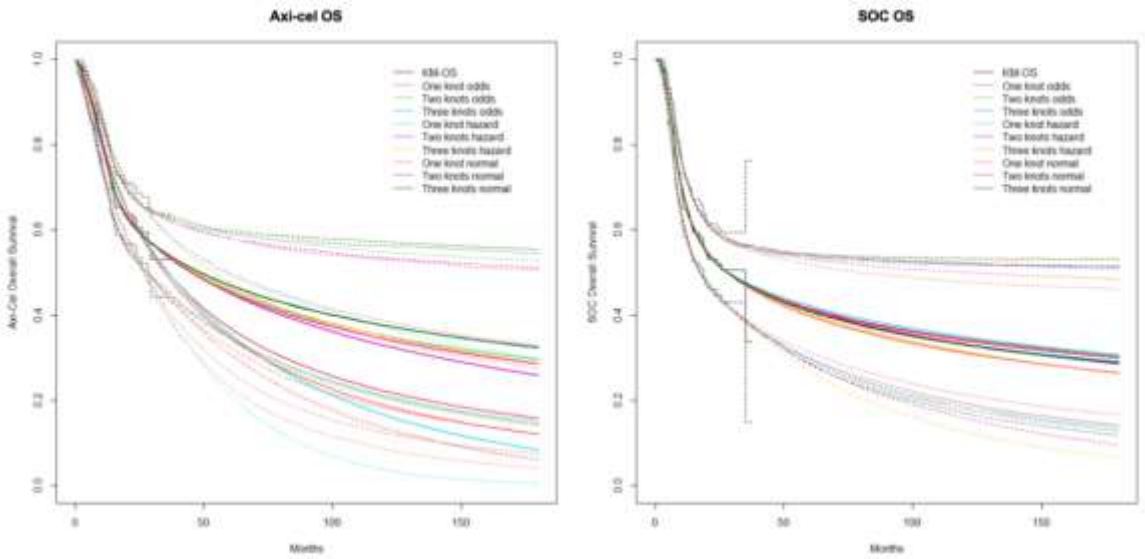

Figure 25: OS curves from restricted cubic spline models for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM OS. Source: (Gilead submission).

Gilead aimed at selecting the same MCM for both arms, as it was assumed that a 'cured' population would be observed at the end of the survival curve (as only cured populations would remain) and therefore follow the same hazard in the long-term independent of treatment arm. The best fitting MCM loglogistic would result in long-term crossing of the curves which was deemed implausible. Subsequently, Gilead chose MCM generalized gamma for their base case due to good mathematical fit and long-term benefit of axi-cel on survival.

Extrapolation of time to next treatment (TTNT)

The log cumulative hazard plot for TTNT showed crossing curves at the beginning and parallel lines for the most of follow-up time (Figure 26). A Schoenfeld residuals plot showed a sinusoidal wave pattern (not shown here) and the global PH test was significant indicating that the PH assumption may not hold. Gilead chose to fit independent functions.

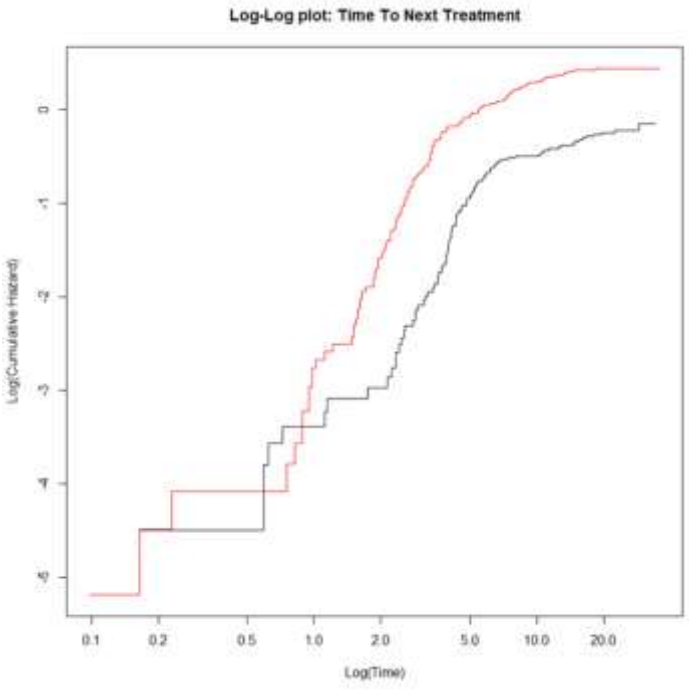

Figure 26: Log cumulative hazard plot for TTNT. Source: (Gilead submission).

Of the standard parametric models, the Gompertz model provided the best statistical fit for both axi-cel and SOC (Table 55). 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. Gilead discussed the clinical plausibility of the curves in Figure 28 with the consulted Norwegian clinical expert, who informed that all curves were clinically plausible for axi-cel. For SOC, the clinical expert informed that the Weibull

curve could be excluded. Thus, the loglogistic curve was selected based on the best statistical fit. The fit of spline models was not discussed in the documentation.

Table 55: Statistical goodness-of-fit for TTNT extrapolations. Source: (Gilead submission).

	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

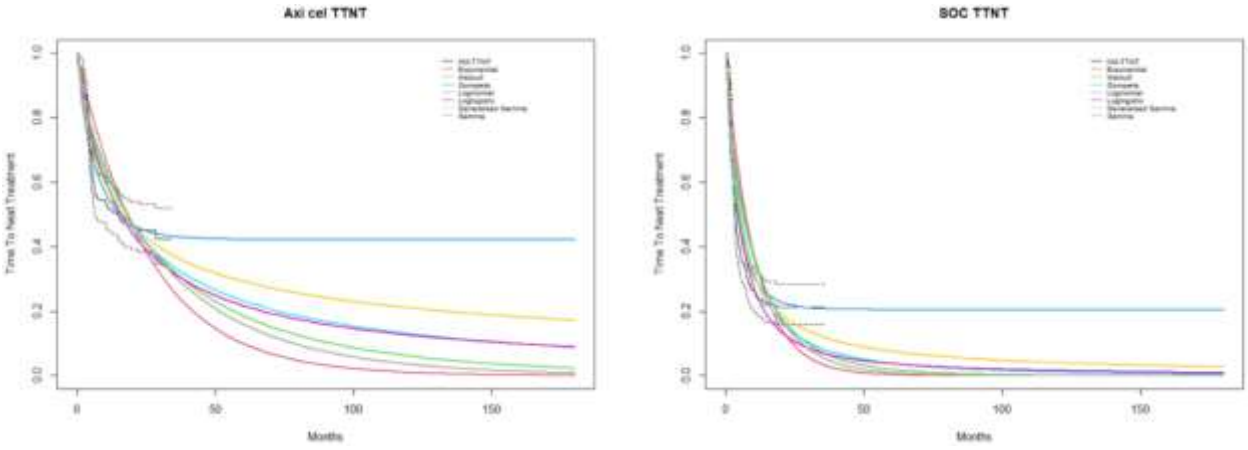

Figure 27: Standard parametric models of partitioned survival: non-proportional hazard models of TTNT for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM TTNT. Source: (Gilead submission).

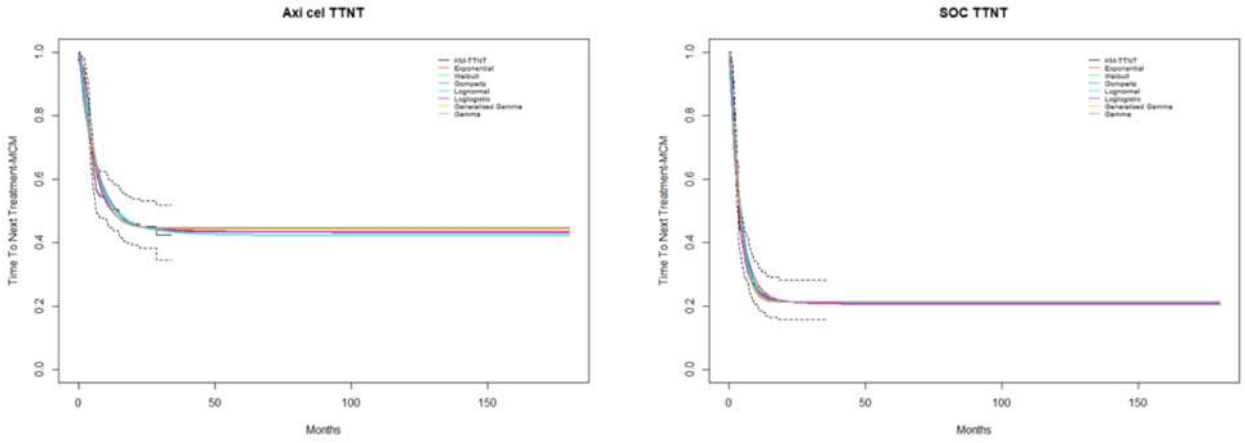

Figure 28: MCMs of partitioned survival: non-proportional hazard models of TTNT for axi-cel and SOC. Background mortality not applied. The dotted lines represent 95 % CI for KM TTNT. Source: (Gilead submission).

Appendix 4 Reconstruction of individual patient data from published survival curves using the IPDfromKM Shiny Application

Individual patient data (IPD) were reconstructed from a published curve of FDA's sensitivity analysis of EFS from ZUMA-7 (8).

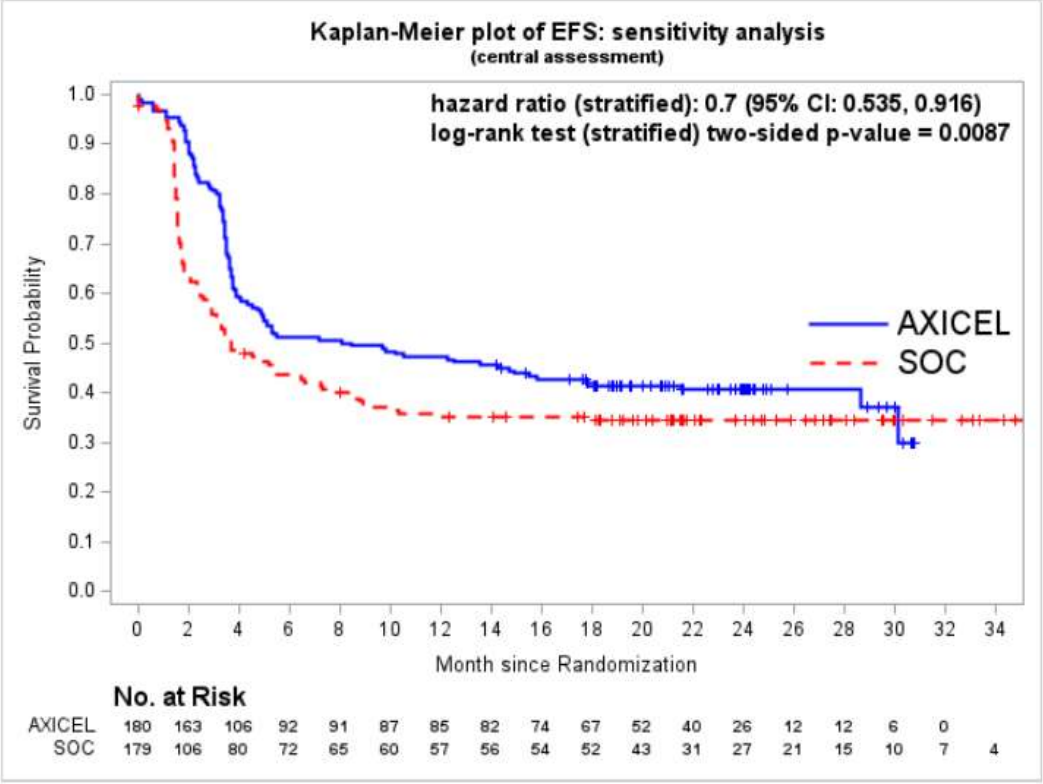

Figure 29: FDA KM-plot of EFS, sensitivity analysis. Source: (8).

The curve reconstruction was done using the Shiny app based on the Liu, Zhou and Lee (2021) method (41). The IPDfromKM Shiny app adapts the R package *IPDfromKM* to reconstruct IPD from published Kaplan-Meier (KM) survival curves.

Accuracy of reconstruction
The SOC arm:

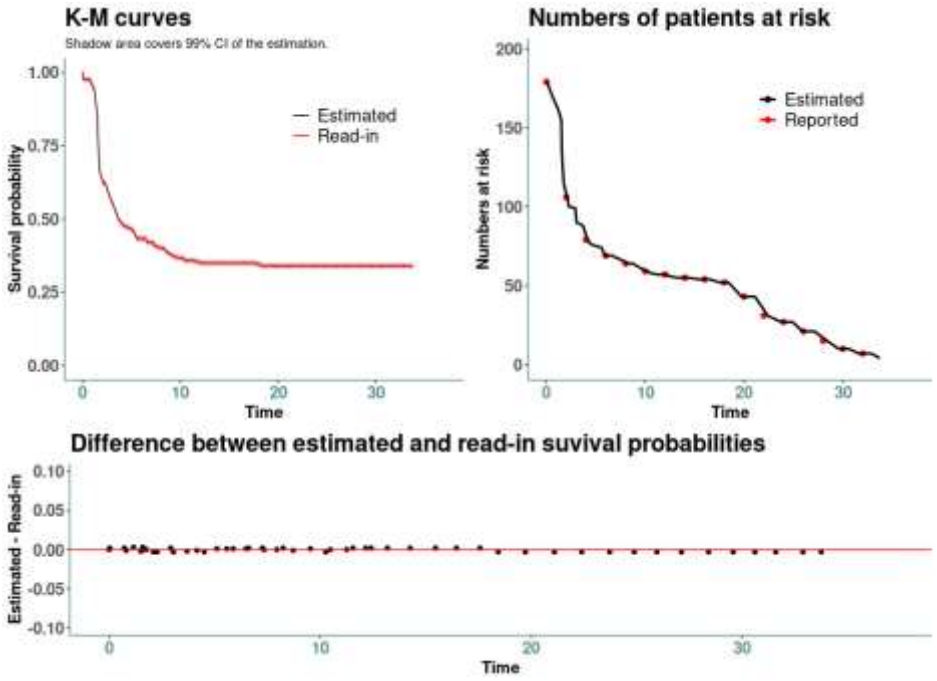

Figure 30: Survival probability for SOC.

The axi-cel arm:

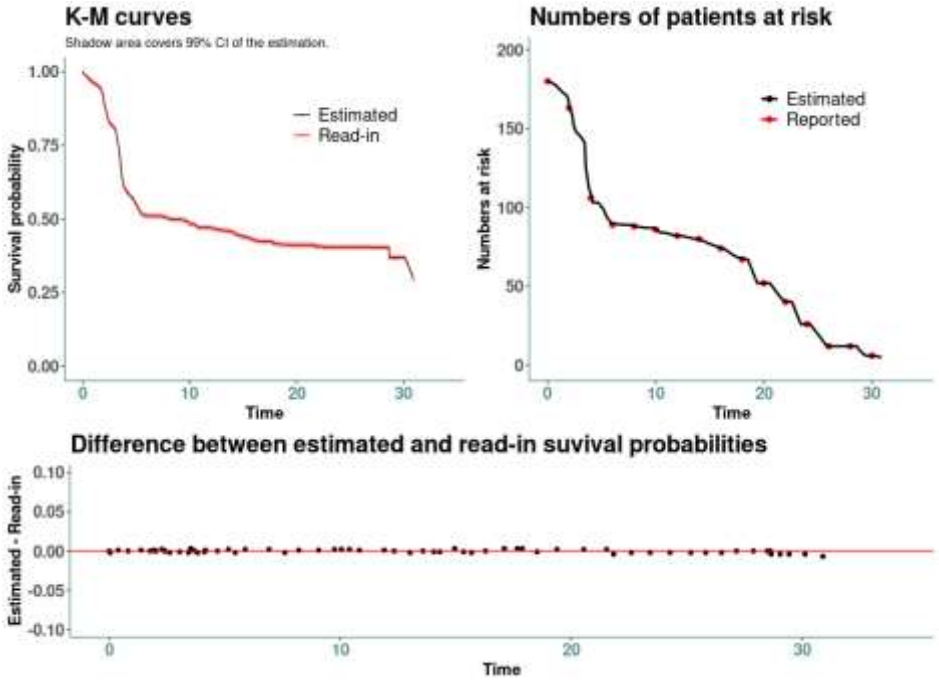

Figure 31: Survival probability for axi-cel.

Table 56 shows the summary statistics that are used to evaluate the accuracy of the IPD reconstruction for the two groups.

Table 56: Summary statistics of accuracy assessment.

Summary statistics	Treatment 1 (SOC)	Treatment 2 (axi-cel)
Root mean square error (RMSE)	0.002	0.002
Mean absolute error	0.002	0.002
Max absolute error	0.003	0.003
Kolmogorov-Smirnov test statistics (p-value)	0.26(0.0495)	0.11(0.8316)

Secondary analysis on the reconstructed IPD

Figure 32 shows the KM curve and cumulative risk.

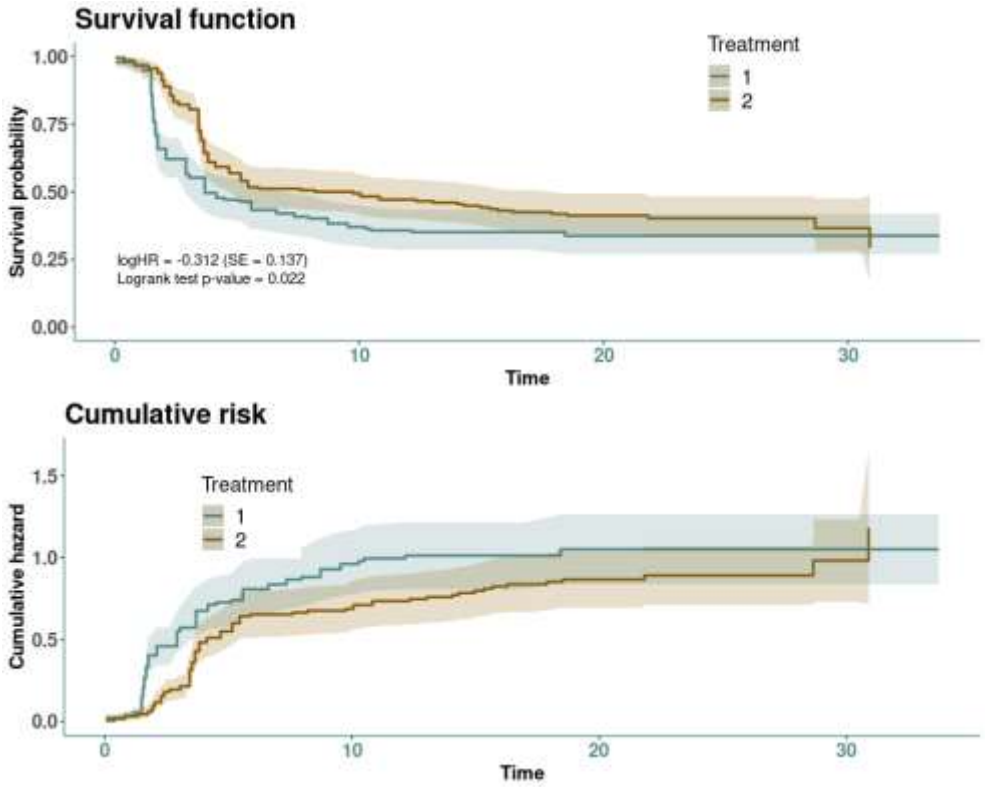

Figure 32: KM curve and cumulative risk.

Table 57 shows the landmark survival probabilities, standard error (SE), and 95% confidence intervals (CIs), given specified survival times, while Table 58 shows the reported survival times and corresponding 95% CIs given specified survival probabilities.

Table 57: Survival probabilities, standard error (SE), and 95% CIs.

Time	Survival probability	SE	95% lower CI	95% upper CI
Treatment 1 (SOC)				
2	0.6587	0.0371	0.5898	0.7356
4	0.4958	0.0393	0.4244	0.5793
6	0.4331	0.0391	0.3629	0.5168
8	0.4017	0.0387	0.3326	0.4851
10	0.3703	0.0381	0.3027	0.4531
12	0.3578	0.0378	0.2908	0.4402
14	0.3515	0.0377	0.2849	0.4337
16	0.3515	0.0377	0.2849	0.4337
18	0.3515	0.0377	0.2849	0.4337
20	0.338	0.0374	0.272	0.4199
22	0.338	0.0374	0.272	0.4199
24	0.338	0.0374	0.272	0.4199
26	0.338	0.0374	0.272	0.4199
28	0.338	0.0374	0.272	0.4199
30	0.338	0.0374	0.272	0.4199
32	0.338	0.0374	0.272	0.4199
Treatment 2 (axi-cel)				
2	0.9108	0.0213	0.87	0.9535
4	0.6094	0.0368	0.5414	0.6859
6	0.5116	0.0378	0.4427	0.5912
8	0.5059	0.0378	0.437	0.5856
10	0.4944	0.0378	0.4256	0.5742
12	0.4714	0.0377	0.403	0.5514
14	0.4599	0.0377	0.3917	0.54
16	0.4309	0.0375	0.3634	0.511
18	0.4188	0.0374	0.3517	0.4989
20	0.4126	0.0373	0.3456	0.4927
22	0.4025	0.0378	0.3349	0.4838

24	0.4025	0.0378	0.3349	0.4838
26	0.4025	0.0378	0.3349	0.4838
28	0.4025	0.0378	0.3349	0.4838
30	0.3659	0.0489	0.2816	0.4756

Table 58: Survival times and 95% CIs.

Survival probability	Survival time	95% lower CI	95% upper CI
Treatment 1 (SOC)			
0.75	1.6764	1.5474	1.7623
0.5	3.6966	2.9229	7.3502
0.25	NA	NA	NA
Treatment 2 (axi-cel)			
0.75	3.4387	3.0518	3.6536
0.5	9.7573	5.158	17.8812
0.25	NA	NA	NA

Appendix 5 NoMA's analysis 2 based on FDA's sensitivity analysis of EFS

In section 3.5.1, NoMA concluded that the EFS results based on the primary definition are biased in favour of axi-cel and that the receipt of NALT prior to disease progression as defined by IRC, after 1 cycle SD or without any disease evaluation should not be treated as an event. NoMA has requested an analysis where patients without disease progression or who had SD after 1 cycle and received NALT are followed until disease progression, but Gilead refused to send such an analysis stating that it was not defined in the protocol. A sensitivity analysis based on NoMA's preferred EFS definition was previously conducted by FDA (8). NoMA has therefore digitalised KM curves from the FDA's analysis of EFS and selected best fitting parametric functions (*NoMA's analysis 2*). The survival analysis was performed in Stata 16.1 using the *stsreg* command for fitting six standard parametric functions, and *strsmix* for fitting MCMs.

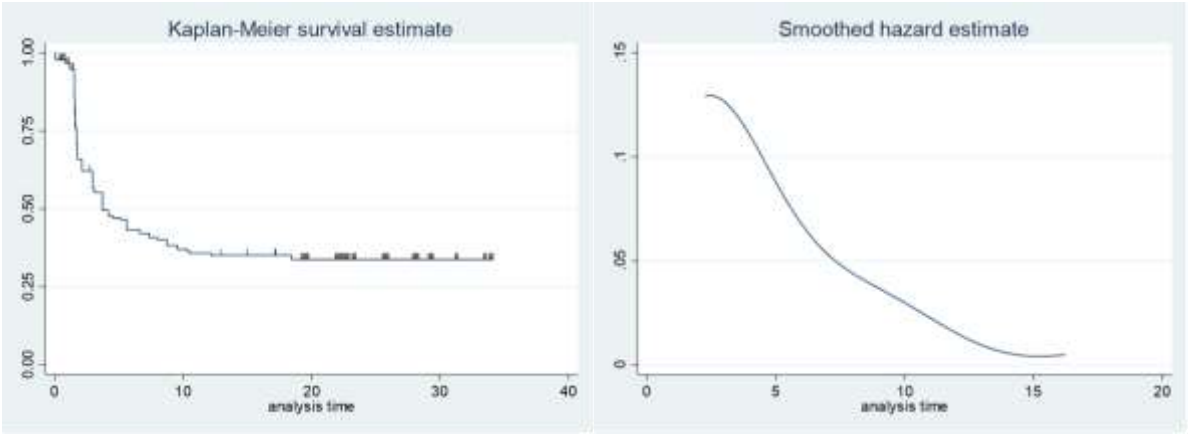

Figure 33: Digitalised KM SOC curve from the FDA's analysis of EFS (8) (left) and Kernel smoothed hazard rates (right). Digitalization based on the Liu, Zhou and Lee (2021) method (41). NoMA's analysis using Stata 16.1.

The PH diagnostics showed that the PH assumption did not hold, i.e., the log cumulative hazard plot did not show parallel lines, the Schoenfeld residuals did not show a horizontal line (Figure 34), and the global test p-value was 0.0006. Consequently, NoMA fitted individual standard parametric functions and MCM Weibull, lognormal or generalized gamma to the SOC arm for EFS.

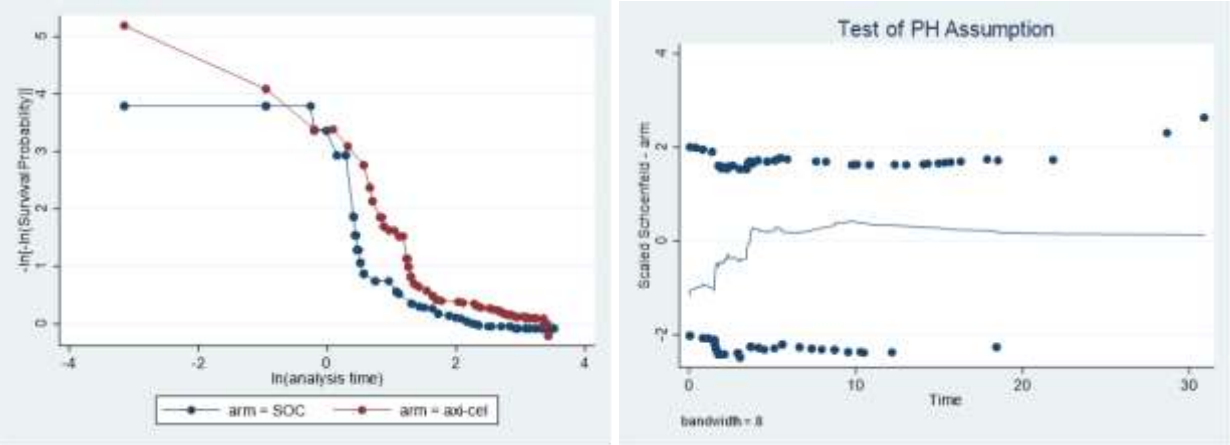

Figure 34: Log cumulative hazard plot, left, and Schoenfeld residuals, right, of EFS as per FDA analysis. NoMA's analysis using Stata 16.1.

The fit of standard parametric functions was poor, except for the Gompertz function (Figure 35). The Gompertz function had also the best mathematical fit (Table 59). The Gompertz function supports monotonically decreasing hazard which is the case here (Figure 33). Consequently, and in order to avoid additional assumptions, NoMA chose the Gompertz function to extrapolate EFS in the SOC arm for this analysis.

Fitting standard Gompertz to EFS for SOC without changing parametrization for TTNT in the SOC arm leads to an implausible result where TTNT is lower than EFS. This means that third-line treatment costs in the health economic model are being generated even though patients have not yet progressed and are still in EFS. NoMA has therefore set TTNT equal to EFS. This change leads to third-line treatment being initiated as patients move from pre-event to post-event in the health economic model. This change needed to be implemented in order for analysis 2 to be plausible and to make sure that the FDA definition of EFS and the way third-line treatment costs are being modelled match and correctly reflect clinical practice.

The efficacy data for EFS and TTNT in the axi-cel arm, as well as for OS in both arms, remain as per NoMA's analysis 1. Hence, the choice of preferred parametric functions for EFS and TTNT in the axi-cel arm and for OS in both arms remains unchanged.

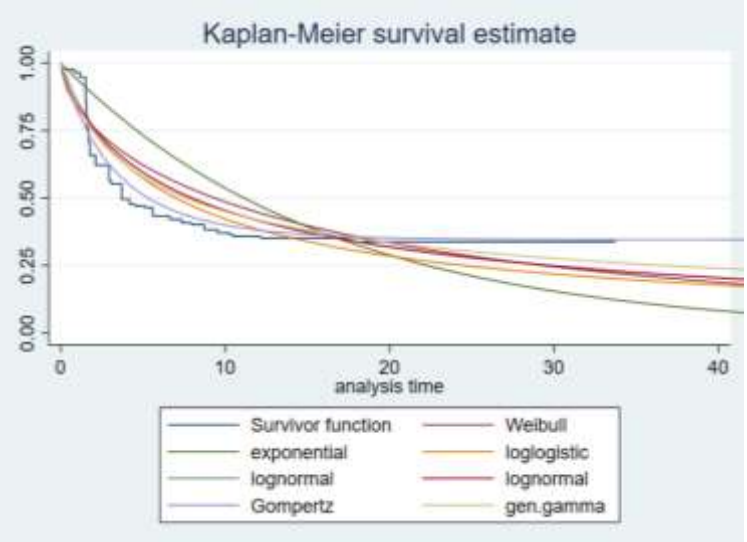

Figure 35: Fit of standard parametric functions to SOC for EFS as per FDA analysis. NoMA's analysis using Stata 16.1. Background mortality not applied.

Table 59: Mathematical fit of standard parametric functions and MCMs (no background mortality) to SOC for EFS as per FDA analysis. NoMA's analysis using Stata 16.1.

Parametric function	AIC	BIC
Weibull	587	594
Exponential	635	638
Loglogistic	561	567
Lognormal	560	566
Gompertz	519	525
Gen.gamma	556	566
MCM Weibull	667	676
MCM lognormal	654	663
MCM gen.gamma	621	634

NoMA has also explored the option of fitting MCMs with the *strsmix* command with or without background mortality. The background mortality was selected based on the mean age and sex distribution in the model. The lack of patient-level data (and patient characteristics per patient) is a natural limitation of digitalised group level data and even more for MCMs that require background mortality for validity.

NoMA found that the fit of MCM available in the *strsmix* command was poor, but surprisingly providing better fit when background mortality (i.e., set to zero) was not used in the estimation (Figure 36).

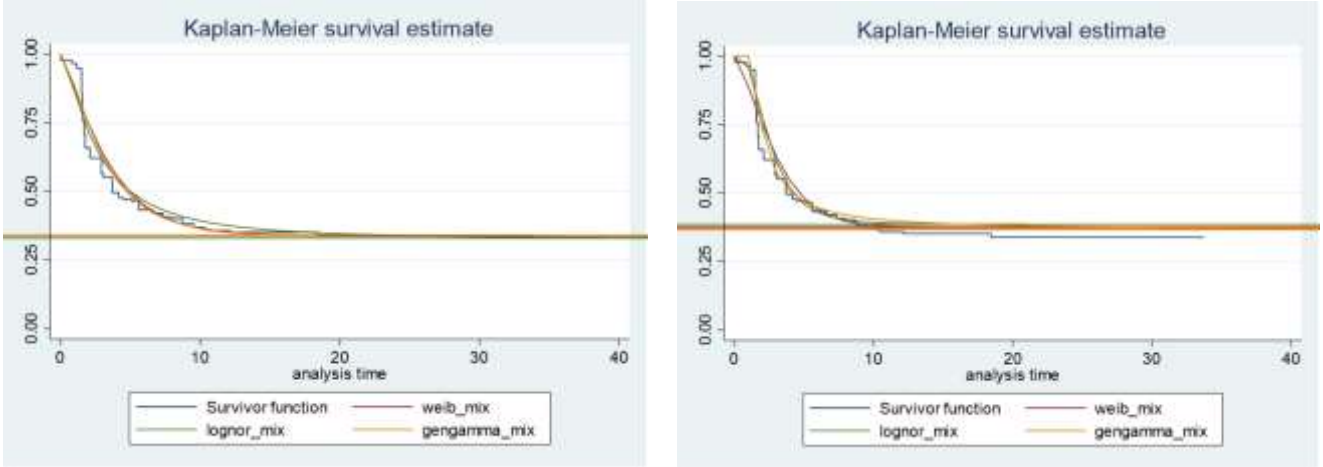

Figure 36: Fit of MCMs to SOC for EFS as per FDA analysis; no background mortality (left) and with background mortality (right) used for estimation. The horizontal line shows cure fractions. Based on KM graphs digitalized by NoMA. NoMA's analysis using Stata 16.1.

The produced cure fractions for MCM Weibull, lognormal and generalized gamma were 38 %, 39 % and 37 %, respectively when background mortality was used in the estimation vs. 34 %, 33 % and 34 %, respectively, when background mortality was not used in the estimation. The MCM generalized gamma (no background mortality) provided the best visual and mathematical fit (Figure 37). MCM generalized gamma is not tested in a scenario analysis as the curve is almost identical to standard Gompertz.

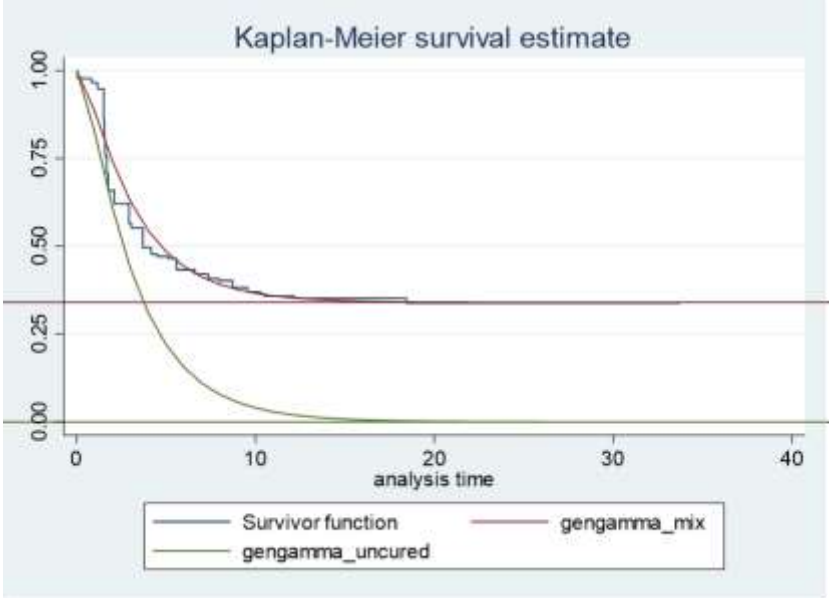

Figure 37: Extrapolation of EFS in the SOC arm (as per FDA analysis) with MCM generalized gamma (with no background mortality used for the estimation). Red curve- extrapolation in the whole population, green line- extrapolation in the uncured fraction, horizontal lines- cure fractions. NoMA's analysis using Stata 16.1.

Compared to CORAL and ORCHARRD, the long-term EFS of 34 % in the SOC arm (as extrapolated with standard Gompertz or MCM generalized gamma) is more than doubled. This is likely due to the receipt of CAR-T as NALT and continued follow-up of those patients for progression/stable disease in the FDA sensitivity analysis of EFS in ZUMA-7. Although NoMA has not received specific information about the type of NALT received per EFS event category (despite requesting it from Gilead), 80 % of patients who received a subsequent therapy received CAR-T. Therefore, external validation of the selected parametric curves is not deemed feasible.

Vedlegg 1 Kommentarer fra produsent

GILEAD
Creating Possible

12.06.2023

This document contains both Gilead´s input to NOMA´s draft report and views on the report from clinician Alexander Fosså. The comments were originally four and a half pages, but following request from NOMA both comments have been shortened to three pages alltogether.

Gilead's input to the Norwegian Medicines Agency's health technology assessment of Yescarta in 2nd line DLBCL
Overall, we think that the report has been thoroughly prepared, well-written and with many good assessments. In two areas, however, we would like to give our feedback to the understanding, description and assessments.

(1) NOMA is questioning the data quality from ZUMA-7. Gilead considers there to be robust, long-term evidence on the comparative efficacy of Yescarta in 2L DLBCL; the efficacy and safety of Yescarta has been evaluated in ZUMA-7, the largest (N=359) Phase 3 randomised controlled trial comparing CAR T-cell therapy to SoC, with a long median follow-up of over 4 years (Westin et al., 2023). Furthermore, Yescarta is the only commercially available CAR T with a 5-year follow-up of the clinical trial ZUMA-1 in 3L+ DLBCL, suggesting the curative potential in an aggressive and fast-progressing disease (Neelapu et al, 2023).

EFS endpoint in ZUMA-7: In this refractory and rapidly relapsing population, new lymphoma therapy is an important event for identifying the necessity for a change in therapeutic intervention where a response other than a complete response (or possibly 'good' partial response) to prior therapy is a treatment failure. For instance, attainment of stable disease (SD) is inadequate for patients to proceed to HDT-ASCT, as it has been established in the literature that HDT-ASCT is futile in patients with SD following salvage chemotherapy. Referring patients immediately upon failure to respond to 2L treatment is crucial to optimise patient outcomes as it ensures that patients maintain sufficient functional status to be candidates for subsequent lines of therapy (e.g. with a CAR-T therapy). Therefore, commencement of new lymphoma therapy is indeed a clinically meaningful event even in the absence of objective measures of progressive disease (PD), as suboptimal responses (e.g. patients achieving less than PR) are predictors of imminent disease progression. For this reason, EFS is widely accepted by the clinical community as a valid endpoint in these high-risk patients. Further, worldwide regulatory and reimbursement authorities have accepted EFS as being an appropriate endpoint for assessing the efficacy of axi-cel in ZUMA-7. Though EFS is the designated primary endpoint in ZUMA-7, the recently published primary analysis of Overall Survival demonstrates that the gold standard outcome of patient benefit unequivocally favors 2L axi-cel over current SoC. The positive OS benefit (data cut off January 2023) further validates the use of EFS as the primary endpoint in ZUMA-7 that had a positive read out earlier (data cut off March 2021).

Open label RCT: Gilead acknowledges that the trial is unblinded due to the nature of the interventions used in each arm. However, the claim about reduced quality of the data due to inability to blind investigators to the allocated intervention is not valid. This is because an independent blinded radiologic review was used as the basis for analysis of disease response. This approach was used to minimise the potential for bias and ensures that the results reported for the ZUMA-7 trial are as unbiased as possible given that the nature of therapy delivered in each arm of the trial made it unfeasible to blind investigators and patients to the allocated interventionOS is an objective outcome by nature.

OS uncertainty: The Primary OS results from ZUMA-7 (data cut January 2023) favoring 2L axi-cel over SoC provide greater certainty that the incremental benefit is long term since the data are based on median follow-up times of 47.0 months (axi-cel) and 45.8 months (SoC) in the Full Analysis set. Even though a large proportion of patients (56%) in the SoC arm received 3L CAR-T therapies as subsequent treatment after 2L failure, the primary OS benefit remains significantly in favor of 2L axi-cel (HR 0.726 [95% CI 0.540, 0.977]). It is important to emphasize that Yescarta has demonstrated an OS plateau in long-term follow up of ZUMA-1 trial (in 3L+ DLBCL). There is remarkable consistency in the shape and plateauing of OS K-M curves for both ZUMA-7 (2L axi-cel) and ZUMA-1 (3L+ axi-cel) based on the most up to date follow-up, with clear additional OS improvement in 2L compared to 3L+

setting. Therefore, NOMA's view that long-term relative benefit of axi-cel remains highly uncertain is unreasonable, given the substantive accumulated clinical evidence to date, mature follow-up duration of ZUMA-7 and ZUMA-1, and the available real-world data.

(2) The Norwegian Medicines Agency presents a budgetary impact by introducing Yescarta in the second line at an estimated NOK 91 million NOK per year, while the report states that 20-25 patients annually are estimated to receive the treatment in the second line and that the treatment in the third line is displaced. When Yescarta was introduced in third line, it was assumed that 20 patients annually would receive Yescarta. Thus, it follows from the Norwegian Medicines Agency's report and previous assessments that 0-5 patients extra will receive Yescarta annually. It is obvious that 0-5 patients extra per year will not lead to such large budgetary effects as presented by NOMA for hospitals.

Alexander Fossås comments:

"The report from Noma evaluating the effect of Axi-cel in 2nd line for transplant-eligible patients with refractory and early relapsed DLBCL has been shown to me by Gilead. I have been involved as an advisor to Gilead in the preparation of the application, mostly to aid in translating the results of the trial to Norwegian practice. I have not been able to read all details due to short notice and competing activities. I have read more thoroughly the pages dealing with estimates of effect size of the benefit of Axi-cel over SOC, mostly pages 52-55. I have not had time to discuss with Gilead details that I believe would have been relevant to the analysis presented by Noma.

In general, I find the analysis presented in table 11 and concerning the OS benefit interesting from a formal point of view, but overly scholastic and conservative when considering this is a trial done in real patients with DLBCL. NOMA seems to forget that the Zuma-7 trial is done in an aggressive lymphoma with heterogeneous clinical presentation. These patients may have needs that sometimes compete with formal details of an academic trial, even the best doctors participating in the best trials may struggle. We know that from our own participation in the similar trial with Tisa-cel in 2nd line DLBCL. Also, summarizing data in groups and response categories, may not pay justice to variations that necessarily will influence treatment decisions and results. If taken apart and criticized for every detail, any trial in small patient groups may be difficult to interpret. Furthermore, Noma seems also to pay little attention to the aggressiveness of DLBCL, where progression or failure to respond may be an imminent threat to patients' lives. Lastly, in those parts of the report that I have read, I see no acknowledgement of the fact that the Zuma-7 trial is the largest randomized trial in R/R DLBCL performed in recent yearsAs such, Noma's evaluation of the details of effects would fit better in a much larger randomized trial in a common and less aggressive cancer. Here, their expectations may be met to higher level rather than in rare and aggressive hematological malignancies. The Parma trial introduced, without Rituximab and without PET response criteria, the concept of an auto-transplant (auto-Tx) in 2nd line for responding patients. However, with PET-CT available, most clinicians now consider a metabolic PR a poor response when aiming for cure with an auto-Tx. Most clinicians will also, in the setting of progressive or early relapsing DLBCL, consider a failure to achieve at least PR after one or a good PR after two cycles of salvage treatment as sign of immanent failure, justifying concern as to continue with the same regimen for a second or third cycle. Similarly, SD a broad category that encompasses patients with failure to shrink by 50 %, or even a beginning growth, will prompt many enlightened patients to worry and clinicians to recommend change of treatment, at least if no sign of shrinkage is seen. These considerations are in line with Norwegian clinical practice. Therefore, the aggregated numbers presented in Table 11 deserve some comments. Responses classified as SD after one cycle and PR after two is sufficiently poor to alarm patients and clinicians. In real world, very few of these will become transplant candidates, and for many patients, NALT may be justified, despite the protocol stating otherwise. One has to remember that many patients themselves are aware of options available for NALT when their response is suboptimal. Only a split into how many metabolic CR patients after 2 cycles of SOC received NALT would in my opinion be a relevant source of bias, neither PR after two or SD after one deserves to get too much attention in terms of polluting the SOC arm in a negative direction.

The aggressive nature of the disease may also explain the numbers who did not start or could not tolerate any treatment, be it Axi-cel or SOC treatment. Deterioration of patients' condition may be a reason to withdraw from

the allocated treatment. This may explain the initiating of NALT in 6 patients in the SOC arm and 2 in the Axi-cel arm. In general, second line chemotherapy and auto-Tx is a more toxic approach, and the difference here may reflect doctors anticipating failure to tolerate SOC therapy. In addition, initiation of NALT in patients where response could not be adequate assessed, to me as a clinician more likely reflects the aggressiveness of the disease and lack of possibility to conduct a formal response assessment in all cases. I would hope that Noma would refrain from introducing additional doubt in rare and heterogeneous patient groups where innovation is hampered for other reasons already. To me, having been part of similar trial with Tisa-cel, excluding patients as proposed in Table 11 without further details seems overly conservative and does not pay justice to the patient group, available number patients in real-life and the disease biology. Details of the kind needed to address these issues are often difficult to capture in trials where categories must be used for summarizing data. Noma also seems to cast doubt on the input to their analysis given by Norwegian experts in their report, but does not comment on doubts these same experts may have on the clinical relevance of Noma's conclusions. This is a bias, especially as more clinical relevant input has been an aim for these evaluation processes in recent years and the academic community has been invited to a more formal involvement. Noma seems to forget that Norwegian clinicians used as experts have no personal experience with CAR-T treatment, at least not in second line, and we as a country, have been unable to gather the real-world experience, as have other countries. We are still struggling to catch up on the experience gap in 3rd line. Any estimates on how many will be candidates for CAR-T in second line are still a matter of opinion. We do not have neither experience nor detailed data from our registries to estimate this with any confidence. Therefore, these figures should be interpreted with care, but not be used to cast unnecessary doubt on the procedure as such. Real-world data in Sweden in 3rd line, about to be published, reveal fewer treated patients than expected but better results than published phase 2 data from trials (Jerkeman, M, personal communication), showing that experience in patient selection may matter.

As in previous analyses of CAR-T methods in DLBCL, Noma seems to doubt the maturity of data after 24-36 months as to the durability of responses and actual cure rates. Failure to accept PFS data at 24-36 months was one explanation why Axi-cel was not accepted for reimbursement in 3rd line for many years. I seriously hope our authorities will not repeat this mistake. I believe the clinical community of lymphoma clinicians will seriously doubt this conclusion, and I challenge to Noma provide expert support for their assumption. Concerning OS, the main weakness of the trial is the cross-over design, a feature that makes academic analyzes more difficult for Noma. Alternatives would however not be considered ethical by the community where 3rd line CAR-T is available. In the absence of pure OS data for the SOC arm not contaminated by CAR-, I believe the patients with DLBCL deserve the benefit of more doubt.

In summary, as a clinical expert, I seriously doubt the conclusion and the wording of NoMAs report:

1. I see some uncertainty about individual patients and the initiation of NALT, but no substantial uncertainty as to the true magnitude of the Axi-cel relative effect size. Noma overestimates the uncertainties introduced by individual patient decisions without having access to the details behind.

2. I agree that details on EFS events would be of benefit. As a clinical researcher, I know that any larger post-hoc analysis of EFS events as requested by Noma will be difficult to do. Data are only captured in a categorized fashion in modern trials and details may be lost in the process.

3. I believe the EFS definition (allowing new anti-lymphoma therapy (NALT) at the discretion of the investigator) and the open-label design is the only way to perform such a trial in an aggressive disease like DLBCL. Noma may ask for a trial design that would have been scientifically more stringent, but difficult to do in real-life. Such a trial would probably have left us with no clearer results.

4. I would caution the authorities from repeating the mistake of placing too much doubt on the maturity of progression-free and overall survival curves showing a benefit of Axi-cel both in the original Zuma-7 report and in later long-term results. These are regarded as mature for the biology of DLBCL by most clinicians I like to trust. I recommend Noma to provide and cite expert clinical advice on this specific concern."